

Relationship Between Serum Uric Acid Levels and Cognitive Functions in Bipolar Disorder

Ozlem Bas Uluyol^a , Ozge Sahmelikoglu Onur^b , Ajda Ekinci^b , Oya Guclu^c 

^aSancaktepe Sehit Prof. Dr. Ilhan Varank Research & Training Hospital, Department of Psychiatry, Istanbul, Turkey, ^b3rd Psychiatry Clinic, Bakirkoy Research & Training Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey, ^c4th Psychiatry Clinic, Bakirkoy Research & Training Hospital for Psychiatry, Neurology and Neurosurgery, Istanbul, Turkey

Abstract

Background: Many studies have shown that cognitive impairment persists during the remission period in bipolar disorder type 1 (BPD1). Uric acid, the end product of purine catabolism, is a natural antioxidant. The purinergic system has a role in the regulation of mood, sleep, energy, cognitive function and behaviour. Previous studies have indicated that a malfunction of the purinergic system might have an impact on the pathophysiology of BPD1. In this study, we aimed to compare differences in cognitive functions and serum urate levels between patients with BPD1 and healthy controls (HC) and to evaluate the relationship between serum uric acid levels and cognitive functions in the patient group.

Methods: This study included 75 euthymic patients with BPD1 and 75 healthy age- and sex-matched individuals. All participants completed a sociodemographic form, the Beck Anxiety Inventory (BAI), the Beck Depression Inventory (BDI) and the Montreal Cognitive Assessment scale (MoCA). All also underwent a neuropsychometric battery and measurement of blood serum uric acid levels. The researchers conducted clinical interviews using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Structured Clinical Interview for DSM Disorders (SCID-I) and obtained Young Mania Rating Scale (YMRS) scores for the patients; the HC group was investigated using the non-patient version of the SCID.

Results: In all neurocognitive domains, patients demonstrated worse performance than the healthy controls ($p < 0.05$). Serum uric acid levels were significantly lower in the BPD1 group than in the HC group ($p < 0.05$) and highlighted a statistically significant effect for the differentiation of BPD1 from HC in the regression analysis ($p < 0.05$). Participants displayed no statistically significant correlation between uric acid levels and the neurocognitive domains of attention, executive functions and visual memory ($p > 0.05$). However, a statistically significant negative correlation was observable between uric acid levels and the neurocognitive domain of verbal memory ($p < 0.05$).

Conclusion: Study results revealed a relationship between the rise in serum uric acid levels and impairment in verbal memory functions in patients with BPD1. Our study is the first to report the relationship between serum uric acid levels and all areas of cognitive functions, including executive functions, verbal and visual memory and attention, as assessed using neurocognitive batteries in patients with euthymic BPD1. Uric acid may therefore present a target in the treatment of BPD1, especially in the presence of various cognitive dysfunctions.

ARTICLE HISTORY

Received: May 21, 2020

Accepted: Apr 25, 2020

KEYWORDS: bipolar disorder, cognitive function, uric acid level, biomarker

INTRODUCTION

Many studies have identified prominent cognitive deficits, assessed using neuropsychological tests, in patients diagnosed with bipolar disorder type 1 (BPD1) [1-4]. Although low performance on cognitive tests (1,4) is related to depressive and manic symptoms, these deficits persist in the remission period in patients with BPD1 [2]. The most recent meta-analyses declared that the most affected areas were attention, executive functions, verbal learning and memory [1,2]. Factors known to affect cognitive

functions include mood symptoms, number of mood episodes, number of hospitalizations, age at onset of the disease, duration of illness and disease periods, presence of psychotic symptoms, suicide attempts and medications used. However, information remains limited regarding the deterministic causal relationship and the progression of cognitive dysfunction in patients with BPD1 [5].

Several studies have indicated that malfunction of the purinergic system might have an impact on the

Corresponding author: Ozge Sahmelikoglu Onur, E-Mail: ozge_sahmelikoglu@hotmail.com

To cite this article: Uluyol Bas O, Onur Sahmelikoglu O, Ajda Ekinci A, Guclu O. Relationship Between Serum Uric Acid Levels and Cognitive Functions in Bipolar Disorder. Psychiatry and Clinical Psychopharmacology 2020;30(2):165-174, DOI: 110.5455/PCP.20200321090156

pathophysiology of BPD1 [6,7]. The purinergic system has a known role in the regulation of mood, sleep, energy, cognitive function and behaviour [8]. The end-product of purine catabolism is uric acid, a natural antioxidant [9]; escalated uric acid levels have been associated with impulsivity, along with hyperthymic and irritable temperamental characteristics, in individuals with no psychiatric diagnoses [8]. Historically, Carl Lange made the first mention of a 'uric acid diathesis' in the pathogenesis of depression [10]. Emil Kraepelin was the first to suggest a relationship between uric acid excretion, hyperuricemia, gout and manic symptoms [11]. John Cade also suggested a role for uric acid in manic patients' 'psychotic excitement'. [12]. Increasing evidence currently suggests that purinergic system disturbances contribute to the pathogenesis and treatment of BPD1 [6,7]. Oliveira et al. suggested that depressed patients with higher levels of serum uric acid are at greater risk of a subsequent manic or hypomanic episode. The researchers further noted that the purinergic system may have a key role concerning therapeutic options, mostly by identifying diagnostic, prognostic and therapeutic biomarkers [13]. The antioxidative properties of uric acid may also mask the worsening of cognitive function associated with vascular pathology [14]. Some studies have indicated that uric acid is protective against Alzheimer's disease due to its strong antioxidant properties in the central nervous system [15]. For example, Euser et al. reported protective characteristics of high uric acid levels against the progression of dementia, when considered apart from cardiovascular risk factors, and linked high urate levels to the promotion of superior cognitive functions at older ages [14]. One potential problem of the process that produces uric acid is that it can also cause oxidative stress [16]. Nevertheless, the protective effect of urate observed in patients with dementia may also occur in patients with BPD1.

Cognitive impairment associated with BPD1 may cause psychosocial dysfunction by itself, independent of mood irregularities; therefore, this impairment may belong to a distinct category in the functioning of patients with BPD1 [17]. Impairment of cognitive functions, especially verbal memory and executive function, adversely affects patients' life quality and psychosocial functions [18]. Previous literature has reported the most affected areas in cognitive functions of patients with BPD1 as attention, executive functions and memory [1,2]; thus, identifying risk factors for these cognitive dysfunctions in BPD1 becomes vital to gaining an understanding of patients within this group that is already at increased risk of illness. Patients with BPD1, even in the euthymic period, can show cognitive impairment and purinergic system dysfunction. However, no study has yet explored any relationship between urate levels and cognitive functions in patients with BPD1. Consequently, understanding the link between cognitive functions and urate levels may contribute to an understanding of the treatment of cognitive impairment, key to the healthy functioning of patients with BPD1. In this study, patients with BPD1 and healthy controls were

administered a neuropsychometric battery evaluating executive functions, attention and verbal and visual memory.

The study had two aims: first, to perform a comparative determination of cognitive functions and urate levels in euthymic patients with BPD1 and healthy controls (HCs). The second aim was to assess the relationship between serum uric acid levels and cognitive functions in patients with BPD1 in the euthymic period. We hypothesized that subjects suffering from BPD1 in this period would differ in terms of serum uric acid levels and cognitive functions in comparison to HCs. Our second hypothesis was that the levels of serum uric acid would be associated with cognitive functionality in the domains of attention, executive function and memory in BPD1 patients.

METHODS

Sample

The patient cohort consisted of 136 patients aged 18-65 years with a diagnosis of euthymic BPD1 based on a Young Mania Rating Scale (YMRS) score <8 and a Beck Depression Inventory (BDI) score <10. The patients were recruited from Bakirkoy Training and Research Hospital outpatient clinic between July 2017 and December 2017. Diagnoses were ascertained using the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*-based SCID interview (19). Exclusion criteria included uncooperativeness, individuals with cognitive impairment due to mental retardation, Montreal Cognitive Assessment scale (MoCA) <21, neurologic disease, electroconvulsive therapy in the last 6 months, a history of psychosurgery or other brain surgery, head trauma, alcohol/drug addiction, comorbid psychiatric disease other than specific phobia, presentation with psychotic symptoms, treatment with medicines that could impact serum uric acid levels, diabetes mellitus, hypertension, cardiovascular disease, hyperlipidemia, peripheral vascular disease, atrial fibrillation and renal failure. In checking hypertension, after 5 min rest, the blood pressure was measured twice using a sphygmomanometer. The average of the two blood pressure measurements was used in the analyses. The serum levels of mood stabilizers were measured in all patients, and they were confirmed to fall within the therapeutic spectrum (0.6-1 mEq/L for lithium; 60-100 mg/L for valproic acid and 6-10 mg/L for carbamazepine). We assessed 136 patients with BPD1. Participants with diabetes mellitus (n=10), hypertension (n=8), cardiovascular disease (n=2), drug use (n=6), hyperlipidemia (n=24), or MoCA scores <21 (n=11) were excluded as shown in Figure 1. This resulted in a sample of 75 patients with BPD1 available for the study (Figure 1).

The control group consisted of 75 HCs with no psychiatric disease (except specific phobia) based on the *DSM-IV*, assessed using the SCID Non-patient Edition (20) and having no neurologic disease, alcohol/drug use or any condition that could affect serum uric acid level. The control group was matched with the BPD1 group in terms of sex, age

and education. Written consent was obtained from the participants prior to enrolment. The study protocol was approved by the Committee for Ethics at the Bakirkoy Training and Research Hospital (June 6th, 2017, protocol number 2017-06-47).

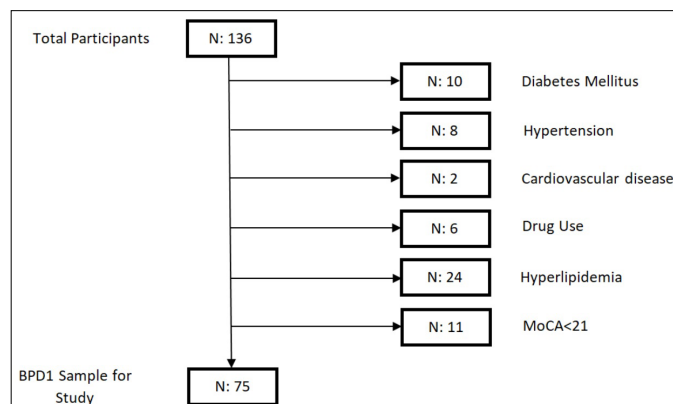


Figure 1. Assessment of patient group for inclusion. 136 patients with BPD1 were interviewed. 10 were with diabetes mellitus (a fasting glucose level of ≥ 106 mg/dl or participant receiving medication for diabetes). 8 were with hypertension (blood pressure of $\geq 130/85$ mmHg, or participant receiving medication for hypertension), 2 were with cardiovascular disease (coronary artery disease and heart failure), 6 were drug users (alcohol and substance abuse), 24 were with hyperlipidemia (fasting serum triglyceride levels of ≥ 150 mg/dl, fasting low-density lipoprotein cholesterol levels of ≥ 130 mg/dl, total cholesterol ≥ 200 mg/dl or participant receiving medication for hyperlipidemia), 11 were MOCA < 21. These patients were excluded from the study. As a result, 75 patients with BPD1 were available for the study.

Instruments

Serum uric acid levels were assessed from venous blood samples drawn around 09:00 after a 12-hour fast. We also noted values that could potentially influence serum uric acid levels, such as total cholesterol, triglycerides, glycemia, creatinine and urea parameters. Vacutainer tubes were used to take blood samples, and uric acid was assayed using a direct enzymatic method by oxidation with uricase coupled with peroxidase. The oxidation product was measured with an AutoAnalyzer. The normal range of serum uric acid values in our clinic were 3.5-7.2 mg/dL in men and 2.6-6.0 mg/dL in women.

Sociodemographic Data Form

The researchers prepared this form to assess the participants' sociodemographic and clinical characteristics. The form, which researchers completed while interviewing the participants, comprised questions about the participants' age, gender, marital status, education and employment status as well as personal and family history. Clinical data such as age of onset of disease, number of hospitalizations and treatment were also included on the form.

Structured clinical interview for DSM-IV (SCID-I)

This is a diagnostic instrument that a professional interviewer used to determine DSM-IV Axis I disorders. Validity and reliability studies for the Turkish form were conducted by Özkürkçügil [21].

Young Mania Rating Scale (YMRS)

The YMRS, developed by Young et al., consists of 11 items, each measuring the severity of a symptom on a scale of 0-4 [22]. Seven of these items are graded on a five-point Likert scale, while the remaining four items are graded on a nine-point Likert scale. The total score varies between 0 and 60. A score of < 8 indicates a remission of manic symptoms. Assessment is based on an interview concerning the patient's state over the previous 48-hour period, along with observations made during the interview. In this study, the YMRS was used to determine whether the patient was euthymic. The Turkish validity and reliability study was conducted by Karadag et al. [23].

Beck Depression Inventory (BDI)

The BDI is a self-report scale that measures physical, emotional and cognitive indicators of depression. The maximum score is 63; higher scores indicate more severe depression. Beck developed the BDI to determine the severity of depressive symptoms (24). In this study, the BDI was used to identify whether the patient was euthymic. Turkish validity and reliability studies were conducted by Hisli [25].

Beck Anxiety Inventory (BAI)

The BAI, developed by Beck et al. (26), is a self-report scale that measures the frequency of anxiety symptoms experienced by an individual. Turkish validity and reliability studies were conducted by Ulusoy et al. (27). Anxiety can affect cognition, making it important to control for anxiety as a variable [28].

Montreal Cognitive Assessment (MoCA)

This method was developed by Nasreddine et al. and designed as a rapid instrument especially for the detection of mild cognitive impairment [29]. The MoCA assesses the different cognitive dimensions of attention and concentration, executive functions, memory, language, visual-spatial skills, abstract thinking, calculation and orientation. Currently, this assessment is being successfully used as a screening method with evidence-based validity and reliability [30]. The maximum total score is 30; a score of 21 points and above is considered normal. This test provides information about participants' general cognitive status.

Neuropsychometric Battery

Neuropsychological assessment was administered at around 14:00 for each participant after assessing the blood sample results, lasting approximately 60 min. Before the test, the participants were asked whether

they wore glasses or hearing aids, and those that answered affirmatively wore their aids throughout the assessment process. Participants who reported insomnia the night before the application were not tested. All participants were asked to refrain from the use of stimulant substances, such as cigarettes, tea and coffee for 2 hours before the tests. The same directions were given to all participants.

A battery testing neurocognitive functions was designed to assess the following domains: attention, verbal memory, visual memory and executive functions. Attention was assessed with the Stroop Color and Word Test, the Wechsler Memory Scale-Revised Digit Span Subtest and the Trail Making Test. Verbal memory was assessed with the Rey Auditory Verbal Learning Test. Visual memory was evaluated using the Wechsler Memory Scale-Revised Visual Memory Subtest. Executive functions were evaluated using the Wisconsin Card Sorting Test. To ensure that higher scores indicated better performance, neurocognitive test scores that had inconsistent metrics were revised. The scores on each test were converted to z-scores based on the scores of the control group. Subsequently, the following neurocognitive domains were calculated: attention, verbal memory, executive functioning and visual memory. In addition, an overall cognition score was determined based on the average of all the z-scores. This method was based on previous research [31].

The tests in the battery were as follows:

Öktem Verbal Memory Test (ÖVMT), Rey Auditory Verbal Learning Test (RVALT)

This test is a word list learning test that Rey developed for the purpose of evaluating verbal learning and memory functions [32]. Standardization research was conducted by Öktem [33]. In this test, a list of fifteen unrelated words is read to the subject, who is then asked to say the remembered words without looking at the order. The same trial is repeated ten times or until the entire list is accurately repeated. Each time, the subject's answers are recorded. Thirty minutes later, the subject is asked to say the words as memorized as a delayed self-recall attempt. An attempt is then made to recognize and remember the words that the participant cannot recall.

Wisconsin Card Sorting Test (WCST)

This test is used to evaluate the integrity of the frontal complex attention system, including conceptualization and abstraction along with the ability to maintain the subjective installation, and change this installation if necessary. The WCST was developed by Berg and modified into a handbook by Heaton et al. [34]. Valid Turkish adaptation studies have been conducted [35]. The test consists of 64 pairs of response cards and four stimulus cards. Each card has a variety of shapes and colours. In the test, the participant is asked to pair each reaction card in the deck with the stimulus card she/he thinks is correct. The correct matching category is determined

to be colour, shape and number, respectively. When the subject makes the correct match 10 times in a row, the category passes to the next. After each response, the subject is told whether his or her response is true or false, but she/he is not given any information identifying the correct match category. The test is completed when the subject completes all six categories or all cards in both decks are used.

Stroop Color Word Test (SCWT)

Since this test was first developed by J. R. Stroop, several versions of the Stroop test have been introduced. The essential assessment here is the evaluation of concentration and sustained attention based on a time period and the task that is instructed. The Stroop test is one of the best evaluations to assess the ability to withstand interfering stimuli, to block improper stimuli and to suppress inappropriate reaction tendencies. The Turkish standardization research was conducted by Karakaş et al. [36].

In the SCWT, the participant is asked to name the colour of the coloured rectangles in the first stage. In the second stage, she/he is asked to read colourful words. At the last stage, the participant is asked to read the word on the card where the colour names are written with coloured pencils and say what colour the word is. When the test is scored, errors, spontaneous corrections and time are recorded.

Wechsler Memory Scale-Revised (WMS-R) Digit Span Subtest

The WMS-R is an improved version of the original test that Wechsler first developed [37]. A valid Turkish adaptation study was conducted by Karakaş et al. [36]. This study used the WMS-R digit span subtest to evaluate simple attention. According to various sources, the straight-line range is also referred to as short-term memory. The backward span test can be highlighted under the framework of complex attention [38].

The digit span subtest consists of two parts: forward span test and backward span test. In both, random numbers are read to the subject at one-second intervals; each trial involves an increasing number of times. After hearing the numbers, the subject is asked to repeat them in the same order. The forward span test is based on how many digits subjects correctly remember and repeat in the same order. In the backward span test, the subject is asked to say the complex numbers in reverse order. For both versions, the number of digits from the previous series in which the subject fails twice in succession creates a range. In normal individuals, the lower limit is generally considered to be 6 forward and 4 backward. In the evaluation, the total scores for the numbers listed forward and backward are used. Notably, stress and anxiety significantly affect the test and shorten the range.

Wechsler Memory Scale-Revised (WMS-R) Visual Memory Subtest

Another subtest of the WMS-R is used to demonstrate learning, immediate memory and long-term memory for figures (39). First, the participant is shown cards with figures drawn on them. The first two cards are displayed for 10s, and the third card is displayed for 13s. Next, the participant is asked to draw these shapes from memory on the front side of a piece of paper. Specific points are given for each element that the subject correctly recalls and draws. The highest score from all three cards is 14. Twenty minutes after the test, the subject is asked to redraw the shapes. If the participant cannot remember all the cards, he/she will try to recognize and recall by selecting the shape that the test administrator wants her/him to remember from among similar shapes. The first application creates a short-term memory score. A total visual recognition score is generated from these answers. After 20 minutes, the subject is asked to draw the shapes as far as she/he can remember, creating the subject's long-term visual memory score.

Trail Making Test (TMT)

This is a visual attentive and task-switching test to assess domains such as visual-motor scan, motor speed, planning, inhibition of response tendency, task change, abstract thinking, concentration and inhibition tolerance (40). The Turkish standardization research was performed by Türkeş et al. (41). The Trail Making Test consists of two parts: TMT-A and TMT-B. In the TMT-A, a sheet containing 25 randomly placed numbers inside circles is given to the patient. The patient is asked to join the circles in sequence by drawing a continuous line without lifting the pen. In the TMT-B, both letters and numbers inside circles are mixed on the same page. The patient is asked to draw a line joining the circles, alternating letters and numbers (i.e. 1-A-2-B-3-C, etc.). The completion durations of the tests comprise the TMT-A and TMT-B scores.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 for Windows statistical software. Statistical significance was considered to be $p < 0.05$.

Descriptive statistical methods including mean, standard deviation, median, frequency and ratio values were used. The Kolmogorov-Smirnov test was used to assess the distribution of the variables. A chi-square test was applied for qualitative independent variables between the BPD1 and control groups including the ratios of sex, employment status, marital status and use of alcohol, drugs and smoking. The independent samples t-test was applied for quantitative independent data with normal distribution between the case and control groups, including age. The Mann-Whitney U test was used for quantitative independent variables with non-normal distribution between the case and control groups including education, cognitive functions, T-scores, BAI scores, BDI scores and levels of uric acid, urea and creatinine. Univariate and multivariate logistic regression served to determine the effect level of cognitive functions, MoCA scale scores and uric acid, urea and creatinine values in the differentiation of BPD1 participants from HCs. Spearman's test was used to evaluate correlations between serum uric acid level and cognitive functions in the BPD1 group.

RESULTS

Table 1 presents data comparing the sociodemographic characteristics of the groups. The Mann-Whitney U test, Student's t-test and chi-square test were used to compare the groups.

No statistically significant differences were evident between the BPD1 and HC groups with respect to age, sex, education level and smoking status ($p > 0.05$). The percentage of working and married individuals in the BPD1 group was significantly lower than that of the HC group ($p < 0.05$) (Table 1).

Table 1. Comparison of Sociodemographic Variables between BPD1 and HC

		BPD1			HC			p	
		Mean ± SD/n	%	Median	Mean ± SD/n	%	Median		
Age		35.4	± 8.6	36.0	34.4	± 8.4	36.0	0.455	t
Gender	Female	40	53.3		40	53.3		1.000	x ²
	Male	35	46.7		35	46.7			
Education		11	± 3.8	12.0	11.1	± 3.8	11.0	0.914	m
Employment Status	Employed	35	46.7		69	92		<0.001	x ²
	Unemployed	40	53.3		6	8			
Marital Status	Single	32	42.7		22	29.3		0.004	x ²
	Married	34	45.3		49	65.3			
	Divorced/Widow	9	12		4	5.3			

^m Mann-Whitney U test / ^t Student's t-test / x² chi-square test. BPD1: Bipolar Disorder Type 1, HC: Healthy Control, SD: standard deviation, n: number of participants. Sociodemographic data for 75 BPD1 and 75 HCs were compared. p value of <0.05 was considered statistically significant and is shown in bold.

Table 2 shows the clinical features of the BPD1 group.

Table 2. Clinical Characteristics of BPD1 Group

		Mean ± SD/n		%
Age of onset		21.7	±	6.2
Number of hospitalizations		2.2	±	2.2
YMRS score		0.8	±	1.5
Mood stabilizer of choice	Li		40	53.3
	VPA		18	24.0
	CBZ		1	1.3
	Lamotrigine		1	1.3
	Li+VPA		10	13.3
	Li+CBZ		1	1.3
	VPA+CBZ		1	1.3
	VPA+Lamotrigine		1	1.3
Additional treatment	Absent		17	22.7
	Present		58	77.3
Additional medication	AAP		49	65.3
	AD		1	1.3
	AAP+LAI		1	1.3
	AAP+AD		6	8.0
	AD+LAI		1	1.3

YMRS: Young Mania Rating Scale, Li: Lithium, VPA: Valproic acid, CBZ: Carbamazepine, AAP: Atypical antipsychotic, AD: Antidepressant, LAI: Long-acting injectable antipsychotic, n: number of patients, SD: standard deviation. Clinical data for 75 BPD1 patients.

Table 3. Comparison of Cognitive Functions, MoCA, BAI and BDI Scores and Uric Acid, Urea and Creatinine Levels Among BPD1 and HCs

	BPD1		HC		p	m
	Mean ± SD	Median	Mean ± SD	Median		
Attention ^a	-0.20 ± 0.64	-0.10	0.18 ± 0.73	0.28	0.000	m
Verbal Memory ^b	-0.23 ± 0.54	-0.13	0.23 ± 0.41	0.30	0.000	m
Executive Function ^c	-0.45 ± 1.38	-0.51	-0.45 ± 1.38	0.88	0.001	m
Visual Memory ^d	-0.26 ± 0.91	-0.17	-0.26 ± 0.91	0.42	0.000	m
MoCA	24.5 ± 2.3	24.0	24.5 ± 2.3	27.0	<0.001	m
BAI	8.1 ± 9.1	5.0	8.1 ± 9.1	6.0	0.358	m
BDI	6.1 ± 3.3	8.0	6.1 ± 3.3	5.0	0.026	m
Uric acid (mg/dl)	5.5 ± 1.3	5.5	5.5 ± 1.3	4.5	<0.001	m
Urea (mg/dl)	22.9 ± 6.7	23.0	22.9 ± 6.7	23.4	0.030	m
Creatinine (mg/dl)	0.8 ± 0.1	0.8	0.8 ± 0.1	0.70	0.038	m

^m Mann-Whitney U test. BPD1: Bipolar Disorder Type 1, HC: Healthy Control, MoCA: Montreal Cognitive Assessment scale, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, SD: standard deviation. a: Z-score of the Stroop Color Word Test, the Wechsler Memory Scale-Revised (WMS-R) Digit Span Subtest and the Trail Making Test, b: Z-score of the Rey Auditory Verbal Learning Test, c: Z-score of the Wisconsin Card Sorting Test, d: Z-score of the Wechsler Memory Scale-Revised (WMS-R) Visual Memory Subtest. p value of <0.05 was considered statistically significant and is shown in bold.

The mean age at disease onset in the BPD1 group was 21.7 ± 6.2 years. Mean YMRS score was 0.8 ± 1.5 (Table 2). The mood stabilizers of choice are also shown in Table 2.

Comparison of cognitive functions, MoCA, BAI and BDI scores and uric acid, urea and creatinine levels among groups using the Mann-Whitney U test are presented in Table 3.

In all the neurocognitive domains, BPD1 patients showed worse performance than HCs. MoCA scores were statistically significantly lower, whereas BDI scores were higher in the BPD1 group than in the HC group (p<0.05). Uric acid and creatinine levels were significantly higher (p<0.05) while serum urea levels were significantly lower in the BPD1 group than in the HC group (p<0.05) (Table 3).

Binomial logistic regression analysis was applied to determine whether the differentiation of the groups was predicted by the significant variables obtained from the analyses (MoCA, uric acid, urea, creatinine, attention, verbal memory, executive function, visual memory). Results are presented in Table 4.

Table 4. Regression Analysis of Test Scores and Blood Sample Values in the Differentiation of BPD1 from HC

	Univariate Model			Multivariate Model		
	OR	0.95	p	OR	0.95	p
MoCA	0.60	0.50 - 0.73	0.000			
Uric Acid	1.94	1.43 - 2.65	0.000	1.67	1.02 - 2.72	0.041
Urea	0.94	0.89 - 0.99	0.012			
Creatinine	15.08	1.35 - 168.18	0.027			
Attention ^a	0.39	0.22 - 0.70	0.002			
Verbal Memory ^b	0.10	0.04 - 0.26	0.000			
Executive Function ^c	0.65	0.51 - 0.83	0.000			
Visual Memory ^d	0.50	0.34 - 0.75	0.001			
Model Sum: Omnibus Test: X2:83.441, p:.000, - 2 Log Probability: 124.503, Cox & Snell R-square: .427, Nagelkerke R-square: .569						

Binomial Logistic Regression, OR: odds ratio, MoCA: Montreal Cognitive Assessment scale. a: Z-score of the Stroop Color Word Test, the Wechsler Memory Scale-Revised (WMS-R) Digit Span Subtest and the Trail Making Test, b: Z-score of the Rey Auditory Verbal Learning Test, c: Z-score of the Wisconsin Card Sorting Test, d: Z-score of the Wechsler Memory Scale-Revised (WMS-R) Visual Memory Subtest. p value of <0.05 was considered statistically significant and is shown in bold.

When all independent variables were entered in the equation, it was determined that the probability value of the logistic regression model (-2 Log) was 124.503. In addition, the value of the Nagelkerke R-square was 0.569, while the Cox & Snell R-square was 0.427. The model in this step was found to significantly explain the probability of being included in the differentiation of groups (X²:83.441, p<0.05). Regarding the regression coefficients, the univariate model revealed a statistically significant effect for the MoCA score, uric acid levels, urea levels, creatinine

levels and neurocognitive domains of attention, verbal memory, executive function and visual memory (Table 4). The multivariate model, in comparison, revealed a statistically significant effect for uric acid levels (Table 4). Spearman's correlation analysis was used to investigate the relationship between uric acid and cognitive functions in the BPD1 group. Findings are presented in Table 5.

Table 5. Relationship between Serum Uric Acid Levels and Cognitive Functions in the BPD1 Group

	Attention ^a	Verbal Memory ^b	Executive Function ^c	Visual Memory ^d
Uric acid	r -0.162	-0.290	-0.075	-0.197
	p 0.051	0.011	0.364	0.091

Spearman's Correlation. a: Z-score of the Stroop Color Word Test, the Wechsler Memory Scale-Revised (WMS-R) Digit Span Subtest and the Trail Making Test, b: Z-score of the Rey Auditory Verbal Learning Test, c: Z-score of the Wisconsin Card Sorting Test, d: Z-score of the Wechsler Memory Scale-Revised (WMS-R) Visual Memory Subtest subscale scores. p value of <0.05 was considered significant and is shown in bold.

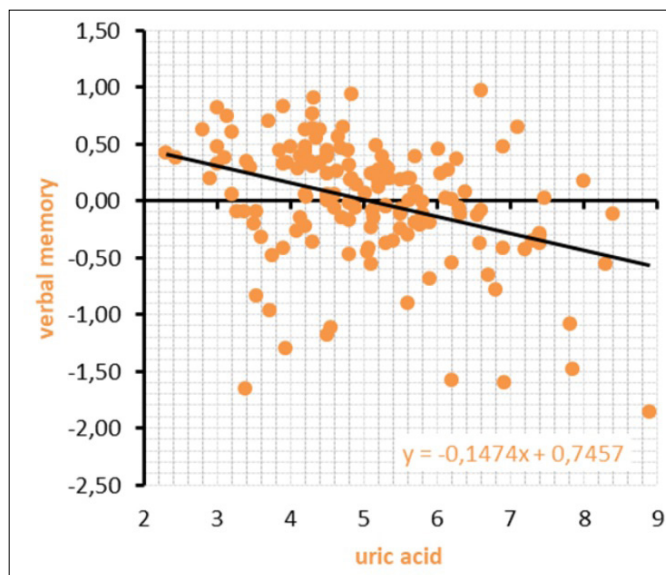


Figure 2. Relationship between uric acid and verbal memory score in the BPD1 group

No statistically significant correlation was evident between uric acid levels and the neurocognitive domains of attention, executive functions and visual memory ($p > 0.05$). A statistically significant negative correlation was observed between uric acid levels and the neurocognitive domains of verbal memory ($p < 0.05$) (Table 5) (Figure 2).

DISCUSSION

We hypothesized that uric acid, the end product of purine metabolism, may differ in patients with BPD1 and may be related to cognitive functions in the domains of attention, executive functions and memory. We tested

these hypotheses by comparing euthymic patients with BPD1 to HCs across cognitive functions and serum uric acid measures. In addition, we examined relationships between uric acid levels and cognitive functioning in patients with BPD1. We found that patients with BPD1 displayed higher serum uric acid levels and cognitive impairments across nearly all domains in comparison to the control subjects. Also, increasing uric acid levels in patients with BPD1 corresponded to impairment in memory function. These findings were in line with our hypothesis. To our knowledge, this is the first study testing the relationship between serum uric acid levels and cognitive functions in patients with BPD1.

In our study, patients with BPD1 achieved lower scores than the control group in the neurocognitive areas of executive functions, attention and verbal and visual memory. Some evidence exists for persistent cognitive impairment in BPD1 in areas related to verbal memory, attention and executive functions in the euthymic period [42]. We excluded conditions such as cardiovascular risk factors, diabetes mellitus, hypertension, hyperlipidemia, heart disease, alcohol use, medications that could affect serum urate level, metabolic and inflammatory diseases associated with hyperuricemia (e.g. gout) as well as liver and kidney failure, aiming to eliminating any confounding effects of these conditions. Despite this meticulous exclusion, our findings still linked serum uric acid levels to poorer memory functions, which is in line with the current literature. Although our study bears similarities to previous studies, it differs in terms of the relationship between cognitive functions and uric acid in patients with BPD1.

Uric acid has known associations with the pathophysiology and treatment of mood disorders, especially impulsivity and risk behaviours [43,44]. In this study, uric acid levels were significantly higher in the patient group. Gültekin et al. reported that elevation in uric acid levels might be a situational biomarker indicating a manic episode in BPD1 [6]. Additionally, Bartoli et al. had similar findings [45]. The application of allopurinol, a hypouricemic agent, showed anti-manic and anti-aggressive effects in the treatment of BPD1 and supported the relationship between mania and high uric acid levels [43]. Allopurinol added to lithium [44], and to lithium and haloperidol [46], was effective in the treatment of mania. In our study, the high levels of serum urate, even in the euthymic period of BPD1, suggest that uric acid elevation might not be specific to the manic period. Gültekin et al. found no interrelationship between urate levels and YMRS scores in patients with BPD1, which further supports our results [6]. Our finding of high uric acid levels in the euthymic period implies that allopurinol may also be an efficient treatment in this period. Future studies should address this possibility.

The interrelationship between urate and cognitive functions remains controversial. Uric acid has been considered to have neuroprotective properties because it is a potent antioxidant [14]. Some studies have shown a linkage between higher uric acid concentrations in the elderly and better cognitive functions; however, uric acid

elevation is also related to several vascular risk factors that raise the risk of dementia (47).

In our study, we found a statistically significant negative relationship between serum urate levels in the BPD1 group and verbal memory scores. On a related note, Verhaaren et al. found an association between high uric acid levels and white matter atrophy and deteriorated cognitive functions. They further stated that increased uric acid levels were primarily associated with information processing speed and, to a lesser extent, with impaired executive functions [48]. Vannorsdall et al. demonstrated a relationship between urate and hyperintense lesions in the brain white matter [49], reporting that increased urate levels were associated with impairments in verbal memory performance and fluency, working memory and processing speed. Moreover, this relationship was still present after controlling for medical and demographic variables [49]. A similar relationship was noted by Schretlen et al., who found that increased uric acid levels were associated with impaired processing speed, along with verbal and working memory [50]. Even after controlling for medical and demographic parameters, a negative correlation between uric acid levels with verbal memory and working memory performance remained [50]. Our findings linking increased levels of uric acid to related deterioration in verbal memory assessments are therefore compatible with the current literature.

Although uric acid is an antioxidant molecule having neuroprotective properties, high serum uric acid levels have been reported to accompany conditions that increase the risk of cognitive dysfunction [49]. In particular, the negative relationship between uric acid and nitric oxide may be one cause of cerebral ischemia, and increased uric acid levels may lead to structural and functional deterioration in the brain by inhibiting the activity of nitric oxide, a potent vasodilator. The level of cerebral ischemia can mediate the association between uric acid and cognitive dysfunction [49]. Our findings showed that high uric acid levels were associated with impairments in verbal memory functions. This may be related to ischemia in cerebral tissues associated with increased uric acid.

When antioxidant compounds reach abnormally high levels in the blood, they become pro-oxidant compounds [51]. During the early phase of the atherosclerotic process, uric acid behaves as an antioxidant. However, it is transformed into a pro-oxidant state in the late stages of the process. This paradoxical state depends on many environmental factors, such as the stage of the disease process, the tissue and substrate location, the oxidant environment, acidity, the reduction of other local antioxidants, oxidation agents and enzymes as well as their presence in the environment [9]. The possibility exists that uric acid may have exhibited pro-oxidant properties in our patient group because BPD1 is a chronic disease.

Our study has certain limitations. It was cross-sectional in nature. The recall factor might have led to distortion of some information about the disease due to the methods

used to obtain the information from the patients and their relatives. The level of situational anxiety experienced by the participants during neuropsychometric evaluation could also affect neurocognitive performance. Because the tester and participants were from different cultural structures, cultural factors could also have affected the test results. Dietary factors that may have affected the serum uric acid level could not be controlled among the participants. Additionally, it should be taken into account that these results cannot be generalized for all BPD subgroups of patients since only BPD1 patients in the euthymic period were included in the study. We also did not assess the body mass index of participants and the effect of lithium or valproic acid on serum uric acid levels. Furthermore, we did not make a separate analysis by gender even though gender-specific variability in uric acid levels is well-known.

CONCLUSION

A relationship was noted between the rise in serum uric acid levels and impairment in verbal memory functions in patients with BPD1. Our study is the first in this area to report a relationship between serum uric acid levels and all areas of cognitive functions, including executive functions, verbal and visual memory and attention as assessed using neurocognitive batteries in patients with euthymic BPD1. In addition, the exclusion of conditions linked to hyperuricemia such as cardiovascular risk factors, hyperlipidemia, diabetes and hypertension, is a strong point of our study. The relationship between cognitive functions and serum uric acid levels in BPD1 should be investigated through longitudinal studies on larger samples including patients in all episodes by gender-separated analysis.

Conflict of Interest: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors. The authors are responsible for the content and writing of the paper.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Acknowledgement: This paper was given as an oral presentation at the 54th National Psychiatry Congress held in Izmir on 2-6 October 2018.

REFERENCES

- [1] Kurtz MM, Gerraty RT. A Meta-analytic investigation of neurocognitive deficit in bipolar illness: profile and effects of clinical state. *Neuropsychology* 2010;23(5):551-62.
- [2] Bourne C, Aydemir O, Balanzá-Martínez V, Bora E, Brissos S, Cavanagh JTO, et al. Neuropsychological testing of cognitive impairment in euthymic bipolar disorder: an individual patient data meta-analysis. *Acta Psychiatrica Scandinavica* 2013;128(3):149-62.
- [3] Svendsen AM, Kessing LV, Munkholm K, Vinberg M,

- Miskowiak KW. Is there an association between subjective and objective measures of cognitive function in patients with affective disorders? *Nordic Journal of Psychiatry* 2012;66(4):248-53.
- [4] Doruk A, Yazihan NT, Balikci A, Erdem M, Bolu A, Ates MA. Cognitive functions in bipolar manic, depressed and remission episodes. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology* 2014;24(1):59-68. [Turkish]
- [5] Bora E, Simavi V, Akdeniz F. The role and importance of cognitive symptoms in bipolar disorder. *Türkiye Psikiyatri Dergisi-Turkish Journal of Psychiatry* 2008;19(1). [Turkish]
- [6] Gültekin BK, Kesebir S, Kabak SG, Ergün FF, Tatlıdil Yaylacı E. Are uric acid levels different from healthy subjects in bipolar affective disorder and schizoprenia?: relationship between clinical improvement and episode severity in male patients. *Nöro Psikiyatri Arşivi-Archives of Neuropsychiatry* 2014;51(3):229. [Turkish]
- [7] Bartoli F, Carrà G, Clerici M. Update on bipolar disorder biomarker candidates: what about uric acid/adenosine hypothesis? *Expert Review of Molecular Diagnostics* 2017;17(2):105-6.
- [8] Lorenzi TM, Borba DL, Dutra G, Lara DR. Association of serum uric acid levels with emotional and affective temperaments. *Journal of Affective Disorders* 2010;121(1-2):161-4.
- [9] Demir M, Bulunmaz M, Müderrisoğlu C, Köse Ş, Erdem S, Polat H. Role of uric acid in determining cardiovascular risk. *İstanbul Tıp Dergisi-Istanbul Medical Journal* 2014;15(4):203-208. [Turkish]
- [10] Felber W. Lithium prevention of depression 100 years ago—an ingenious misconception. *Fortschritte Der Neurologie-Psychiatrie* 1987;55(5):141-4.
- [11] Lord J R. Manic-depressive insanity and paranoia. By Prof. Emil Kraepelin; translated by R. Mary Barclay, MA, MB; edited by George M. Robertson, MD, FRCP Edin. Edinburgh. *Journal of Mental Science* 1921;67(278):342-6.
- [12] Shorter E. The history of lithium therapy. *Bipolar Disorders* 2009;11(2):4-9.
- [13] Dos Santos Oliveira PM, Santos V, Coroa M, Ribeiro J, Madeira N. Serum uric acid as a predictor of bipolarity in individuals with a major depressive episode. *Bipolar Disorders* 2019;21(3):235-43.
- [14] Euser SM, Hofman A, Westendorp RGJ, Breteler MMB. Serum uric acid and cognitive function and dementia. *Brain* 2009;132(2):377-82.
- [15] Chen X, Guo X, Huang R, Chen Y, Zheng Z, Shang H. Serum uric acid levels in patients with Alzheimer's disease: a meta-analysis. *PLoS One* 2014;9(4) e94084.
- [16] Dawson J, Walters M. Uric acid and xanthine oxidase: future therapeutic targets in the prevention of cardiovascular disease? *British Journal of Clinical Pharmacology* 2006;62(6):633-44.
- [17] Cipriani G, Danti S, Carlesi C, Cammisuli DM, Di Fiorino M. Bipolar disorder and cognitive dysfunction. *The Journal of Nervous and Mental Disease* 2017;205(10):743-56.
- [18] Bonnín CM, Martínez-Arán A, Torrent C, Pacchiarotti I, Rosa AR, Franco C, et al. Clinical and neurocognitive predictors of functional outcome in bipolar euthymic patients: a long-term, follow-up study. *Journal of Affective Disorders* 2010;121(1-2):156-60.
- [19] First MB, Spitzer RL, Gibbon M WJ. Structured clinical interview for DSMIV-TR Axis I disorders (SCID). Research version, patient edition. New York, 2002.
- [20] First MB, Spitzer RL, Gibbon M WJ. Structured clinical interview for DSMIV-TR Axis I disorders. Research version, non-patient edition (SCID-1/NP). New York: New York State Psychiatric Institute, Biometric Research, 2002.
- [21] Özkürçügil A, Aydemir O, Yıldız M, Danacı A, Köroğlu E. Adaptation and reliability study of Turkish structured clinical interview for DSM-IV Axis I Disorders. *İlaç ve Tedavi Dergisi* 1999;12(4):233-6. [Turkish]
- [22] Young RC, Biggs JT, Ziegler VE, Meyer DA. A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry* 1978;133:429-35.
- [23] Karadağ F, Oral ET, Aran Yalçın F, Erten E. Reliability and validity of Turkish translation of Young mania rating scale. *Türk Psikiyatri Dergisi-Turkish Journal of Psychiatry* 2002;13(2):107-14. [Turkish]
- [24] Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry* 1961;4:561-71.
- [25] Hisli N. A reliability and validity study of Beck depression inventory in a university student sample. *Türk Psikoloji Dergisi - Turkish Journal of Psychology* 1989;7:3-13. [Turkish]
- [26] Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology* 1988;56(6):893-7.
- [27] Ulusoy M, Sahin NH, Erkmen H. Turkish version of the Beck anxiety inventory: psychometric properties. *Journal of Cognitive Psychotherapy* 1998;12(2):163-72.
- [28] Park J, Moghaddam B. Impact of anxiety on prefrontal cortex encoding of cognitive flexibility. *Neuroscience* 2017;345:193-202.
- [29] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society* 2005;53(4):695-9.
- [30] Selekler K, Cangöz B, Uluç S. Power of discrimination of Montreal cognitive assessment (MOCA) scale in Turkish patients with mild cognitive impairment and Alzheimer's disease. *Türk Geriatri Dergisi - Turkish Journal of Geriatrics* 2010;13(3):166-71. [Turkish]
- [31] Van Camp L, Sabbe BGC, Oldenburg JFE. Metacognitive functioning in bipolar disorder versus controls and its correlations with neurocognitive functioning in a cross-sectional design. *Comprehensive Psychiatry* 2019;92:7-12.
- [32] Schmidt M. Rey auditory and verbal learning test: a handbook. Los Angeles, CA: Western Psychological Services;1996.
- [33] Öktem Ö. Öktem sözel bellek süreçleri testi (Öktem

- SBST). 1 Basım. Ankara: Türk Psikologlar Derneği Yayınları;2011. [Turkish]
- [34] Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtiss G. Wisconsin cardsorting test manual - revised and expanded. Florida Psychological Assessment Resources;1993;62-230.
- [35] Karakaş S. BİLNOT bataryası el kitabı: nöropsikolojik testler için araştırma ve geliştirme çalışmaları. Ankara: Dizayn Ofset; 2004. p.115-32. [Turkish]
- [36] Karakaş S, Eski R, Başar E. Türk kültürü için standardizasyonu yapılmış nöropsikolojik testler topluluğu: BİLNOT bataryası. 32. Ulusal Nöroloji Kongresi Kitabı. İstanbul: Ufuk Matbaası;1996. p.43-70. [Turkish]
- [37] Wechsler D. The Wechsler memory scale-revised. New York: Psychological Corporation;1987.
- [38] Öktem Ö. Nöropsikolojik testler ve nöropsikolojik değerlendirme. Türk Psikoloji Dergisi - Turkish Journal of Psychology 1994;9(33):33-44. [Turkish]
- [39] Wechsler D. The Wechsler memory scale. New York: Psychological Corporation; 1945.
- [40] Lezak MD. Neuropsychological assessment. 3rd edition. New York: Oxford University Press; 1995. p.381-402.
- [41] Türkerş N, Can H, Kurt M, Dikeç BE. A study to determine the norms for the trail making test for the age range of 20-49 in Turkey. Türk Psikiyatri Dergisi - Turkish Journal of Psychiatry 2015;26(3):189-96. [Turkish]
- [42] Demirel A, Demirel O, Kadak M, Duran A. Neurocognitive deficits in euthymic bipolar patients. Psikiyatride Güncel Yaklaşımlar - Current Approaches in Psychiatry 2012;4(3):381-95. [Turkish]
- [43] De Berardis D, Conti CM, Campanella D, Carano A, Di Giuseppe B, Valchera A, et al. Evaluation of plasma antioxidant levels during different phases of illness in adult patients with bipolar disorder. Journal of Biological Regulators & Homeostatic Agents 2008;22(3):195-200.
- [44] Machado-Vieira R, Soares JC, Lara DR, Luckenbaugh DA, Busnello J V, Marca G, et al. A double-blind, randomized, placebo-controlled 4-week study on the efficacy and safety of the purinergic agents allopurinol and dipyridamole adjunctive to lithium in acute bipolar mania. The Journal of Clinical Psychiatry 2008;69(8):1237-45.
- [45] Bartoli F, Crocamo C, Dakanalis A, Brosio E, Miotto A, Capuzzi E, et al. Purinergic system dysfunctions in subjects with bipolar disorder: a comparative cross-sectional study. Comprehensive Psychiatry 2017;73:1-6.
- [46] Akhondzadeh S, Milajerdi MR, Amini H, Tehrani-Doost M. Allopurinol as an adjunct to lithium and haloperidol for treatment of patients with acute mania: a double-blind, randomized, placebo-controlled trial. Bipolar Disorders 2006;8(5p1):485-9.
- [47] Vannorsdall TD, Kueider AM, Carlson MC, Schretlen DJ. Higher baseline serum uric acid is associated with poorer cognition but not rates of cognitive decline in women. Experimental Gerontology 2014;60:136-9.
- [48] Verhaaren BFJ, Vernooij MW, Dehghan A, Vrooman HA, de Boer R, Hofman A, et al. The relation of uric acid to brain atrophy and cognition: the Rotterdam scan study. Neuroepidemiology 2013;41(1):29-34.
- [49] Vannorsdall TD, Jinnah HA, Gordon B, Kraut M, Schretlen DJ. Cerebral ischemia mediates the effect of serum uric acid on cognitive function. Stroke 2008;39(12):3418-20.
- [50] Schretlen DJ, Inscore AB, Jinnah HA, Rao V, Gordon B, Pearlson GD. Serum uric acid and cognitive function in community-dwelling older adults. Neuropsychology 2007 ;21(1):136-40.
- [51] Kumar AN, Aruna P, Naidu JN, Kumar R, Srivastava AK. Review of concepts and controversies of uric acid as antioxidant and pro-oxidant. Arşiv Kaynak Tarama Dergisi - Archives Medical Review Journal 2015;24(1):19-40. [Turkish]