



Research report

Uric acid levels may be a biological marker for the differentiation of unipolar and bipolar disorder: The role of affective temperament



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ABSTRACT

Background: The aim of this study was to investigate whether uric acid levels are different between patients with remission period of bipolar disorder type I (BD) and patients with remission period of major depressive disorder (MDD).

Methods: For this aim 41 patients diagnosed with BD and 30 patients diagnosed with recurrent MDD according to DSM-IV who were in remission period for at least 8 weeks were evaluated consecutively. The median age and gender distribution of the two groups were similar. Subjects with comorbid psychiatric diagnosis and/or severe medical illnesses were excluded. Affective temperament was evaluated with TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire). Plasma uric acid levels were recorded in mg/dl.

Results: The uric acid levels of BD patients were found higher than patients with MDD and healthy controls. Additionally uric acid levels of MDD patients were lower than patients with BD and healthy subjects ($F=4.183$, $p=0.039$). A moderate correlation between hyperthymic and irritable temperament scores and uric acid levels was detected in both patient groups and in healthy controls. A negative correlation was observed between depressive temperament and uric acid levels only in MDD group.

Limitations: The measurements of temperament were estimated depending on the patient's statement. The medications that patients used were not controlled.

Conclusion: There is a purinergic dysfunction not only in BD but also in MDD patients. High uric acid levels are associated with hyperthymic and irritable temperament scores whereas low uric acid levels are associated with depressive temperament scores.

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1. Introduction

Purinergic system plays role in the regulation of mood, motor activity, cognitive function, sleep and behavior (Jinnah, 2009). The end product of purine metabolism is uric acid which is produced by xanthine dehydrogenase. Increased levels of uric acid mean accelerated purinergic transformation and decreased adenosinergic transmission (Burnstock, 2008).

Adenosinergic receptors limit cellular excitability by inhibiting neurotransmitter release in the central nervous system. Case-control studies show that a non-conservative aminoacid change from a glutamine to arginine in the P2RX7 purinergic receptor protein is associated with both bipolar and unipolar affective disorders (McQuillin et al., 2009).

Increasing evidence suggest that impairment in the function of purinergic system plays a part in the pathophysiology and treatment of mania. Preliminary studies revealed increased uric acid levels both in first and recurrent episodes of mania (Zarate and Manji, 2008, Salvadore et al., 2010). In parallel with these results, in their placebo controlled study, Machado-Vieira et al. (2008) showed that addition of xanthine dehydrogenase inhibitor allopurinol to lithium therapy is effective in the treatment of acute mania. While uric acid levels are suggested as a screening test in mania (Machado-Vieira, 2012), such an increase in uric acid levels aren't detected in depression or remission periods of bipolar disorder type I (BD) (De Berardis et al., 2008). However, in one of our recent studies, we found uric acid levels of subjects with mania, depression and remission periods of BD to be higher than healthy controls (Kesebir et al., 2013).

The function of purinergic system was investigated in patients with major depressive disorder (MDD) as well. Two studies conducted with these patients reported different serum uric acid levels than healthy controls. Chaudhari et al. (2010) suggested that uric acid levels of MDD patients are lower than healthy subjects. Additionally Wen et al. (2012) detected lower uric acid levels in patients with

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MDD than healthy subjects and reported that those levels returned to normal ranges after 5 weeks of antidepressant treatment. In the former study, a strong inverse relation was found between uric acid levels and Hamilton Depression Rating Scale scores, both at the time of diagnosis and after 12 weeks of antidepressant treatment. When results of these two studies and our study are considered together, uric acid levels may be suggested as a marker for the differentiation of unipolar depression and bipolar depression. In fact, the differentiation between unipolar and bipolar depression is a primary clinical problem. If any markers for this purpose could be established, it would be of functional and clinical importance for all depressive patients (Cardoso de Almeida and Phillips, 2013).

The aim of this study was to investigate whether uric acid levels differentiate between patients with remission period of BD and patients with remission period of MDD. Additionally it was to determine if uric acid levels are related to affective temperament.

2. Methods

2.1. Study sample

Of the individuals who were admitted to our outpatient clinic for their regular follow-up assessments and gave their informed consent, 100 patients diagnosed as BD and 100 patients diagnosed as recurrent MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) were evaluated consecutively. There weren't any patients with Bipolar Disorder type II in BD group.

The patients who had been in remission period for at least 8 weeks and who didn't have comorbid psychiatric disorders were recruited to the study. As diseases like gout, chronic inflammatory disease, hypertension, renal disease, hypertriglyceridemia are associated with hyperuricemia, subjects with those and/or other severe or unstable medical illnesses were excluded. At the end our patient sample consisted of 41 patients with BD and 30 patients with recurrent MDD who were in remission.

The control group consisted of 43 healthy staff members of our hospital without any prior psychiatric admission or treatment history who matched with the patient group in terms of age and gender.

2.2. Procedure

Approval for the study was obtained from Erenkoy Psychiatry Hospital Training and Scientific Investigations Committee. The cost of the measurement of plasma uric acid levels was met from the Investigation Budget Fund of our hospital.

Diagnostic interviews were done with the Turkish version of SCID-I at the time of recruitment to the study. A protein-rich diet was given to all subjects for 1-week if they were determined as healthy by physical and neurological examination and laboratory tests. This protein-rich diet was prepared by a dietician and no control measures were taken to determine whether subjects complied with the diet apart from their self reports.

At the end of 1-week diet, bloodsamples were obtained and plasma uric acid levels were recorded in mg/dl after being rotated for 15 min in centrifuge with 3000 rotations and kept at -80°C . At the time of laboratory testing, remission for the patients was defined as Hamilton Depression Rating Scale (HDRS) score < 8 for depression and Young Mania Rating Scale (YMRS) score < 5 for mania.

2.3. Assessment tools

2.3.1. Structured clinical interview for DSM-axis I disorders (SCID-I)

Turkish version of structured clinical interview for DSM-IV axis I disorders (Çorapçioğlu et al., 1999; First et al., 1997).

2.3.2. Hamilton Depression Rating Scale (HDRS)

It was developed to measure the level of depression and changes in its severity (Hamilton and Williams, 1978). Its reliability and validity study in Turkish was carried out by Akdemir et al. (1996).

2.3.3. Young Mania Rating Scale (YMRS)

It is used to measure the severity of manic symptoms before treatment in manic cases and to confirm the state of remission in recovery period. This scale administered by the interviewer was developed by Young et al. (1978) and its validity and reliability study in Turkish was carried out by Karadag et al. (2001).

2.3.4. Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A)

It was developed by Akiskal et al. (2005) to evaluate depressive, cyclothymic, hyperthymic, irritable and anxious temperaments. The reliability and validity study for the Turkish form was done by Vahip et al. (2005).

2.4. Statistical analysis

Analysis of variance was used to compare uric acid levels between patients and healthy controls and Bonferroni corrections were applied for postHoc analysis. Pearson correlation test was used for correlation analysis. Statistical significance was set at $p < 0.05$, all tests were two-tailed.

3. Results

Mean age of BD and MDD patient groups and healthy controls were similar ($30.6 \pm 4.2/32.3 \pm 5.7/29.1 \pm 2.9$). Gender distribution of BD patients, MDD patients and healthy controls were matched as well (F/M: 22/19, 17/13, 26/17).

As uric acid levels of patients with BD were higher than patients with MDD and healthy subjects, uric acid levels of patients with MDD were found to be lower than patients with BD and healthy subjects ($F=4.183$, $p=0.039$), (Table 1), (Fig. 1).

While the depressive and anxious temperament scores of the patients with BD and MDD were similar, both scores were higher than those of healthy individuals (Table 2). On the other hand cyclothymic and irritable temperament scores of patients with BD were higher than patients with MDD, both scores of the patient groups were higher than healthy controls. Finally hyperthymic temperament scores were similar in patients with BD and healthy controls, who in turn were higher than scores of patients with MDD.

There was a moderate relation between hyperthymic and irritable temperament scores and uric acid levels (Table 3). This relationship was less evident in patients with MDD. Being significant only for patients with MDD, an inverse relation was observed between depressive temperament and uric acid levels.

Table 1

Comparison of uric acid levels in BD, MDD and healthy controls.

	BD, n=41	MDD, n=30	HC, n=43	Analysis (F/χ^2 , p)
Age (Mean \pm SS)	30.6 \pm 4.2	32.3 \pm 5.7	29.1 \pm 2.9	30.617 0.275
Gender (F/M)	22/19	17/13	26/17	8.294 0.312
UA levels (Mean \pm SS)	5.4 \pm 1.3	3.2 \pm 0.4	4.8 \pm 0.8	4.183 0.039

PostHoc analysis (Bonferroni) for UA: BD > HC > MDD ($p=0.047$, 0.008, 0.016).

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