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Increased uric acid levels in drug-naïve subjects with bipolar disorder during a first manic episode

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Abstract

Recent evidence suggests that purinergic system dysfunction may play a role in the pathophysiology and therapeutics of bipolar disorder (BPD). Uric acid is a key nitrogenous end product of purine metabolism. In addition to being a potential marker of treatment response, high levels of uric acid may represent a state marker during mania. In this study, we assessed the presence of purinergic dysfunction in 20 treatment-naïve first episode patients with BPD who were experiencing a manic episode. Patients were matched with 24 healthy controls. We found that acutely manic patients had significantly higher levels of plasma uric acid (4.85 ± 1.60 mg/dL) compared to healthy controls (2.96 ± 0.63 mg/dL, $p < 0.001$; $F = 28.1$). No association between uric acid levels with severity of manic symptoms was observed. These results support the role of purinergic system dysfunction in BPD early in the course of illness, and suggest that this phenomenon is not the result of chronicity or medication exposure. Overall, our findings suggest a novel mechanism in the pathophysiology of BPD.

Keywords

Bipolar disorder; Depression; Gout; Mania; Purines; Uric acid

1. Introduction

Improved understanding of the pathophysiological basis of bipolar disorder (BPD) is critical for the development of improved therapeutics needed to treat this devastating illness.

Recent evidences from genetic and clinical studies suggest that purinergic system dysfunction may play an important role in the pathophysiology and therapeutics of BPD (McQuillin et al., 2009; Zarate and Manji, 2008; Machado-Vieira et al., 2008). A recent randomized, placebo-controlled trial showed that the purinergic modulator allopurinol, a xanthine oxidase inhibitor, was effective in treating acute mania when used adjunctively with lithium (Machado-Vieira et al., 2008). The same study also found that change in Young Mania Rating Scale (YMRS) (Young et al., 1978) scores from baseline to endpoint was

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positively correlated with change in plasma uric acid levels. Furthermore, remitters were significantly more likely to have lower uric acid plasma levels than non-remitters. This suggests that uric acid levels might serve not only as a surrogate marker of clinical efficacy, but also as a state marker during manic episodes.

Previous studies reported that plasma uric acid levels were higher only during the manic phase of BPD but not during the depressive or euthymic phases (De Berardis et al., 2008). However, several factors could affect interpretation of those findings, including the use of concomitant medications, cycling, and chronicity of the illness. Examining plasma uric acid levels early in the course of illness in patients experiencing their first episode of mania, and prior to first medication exposure, might help disentangle the effects of some of these potential confounders.

In the present investigation, plasma uric acid levels were evaluated in first episode, drug-naïve, manic patients. We hypothesized that patients with BPD would have higher uric acid levels than age- and gender-matched healthy controls.

2. Methods

2.1. Subjects

Twenty drug-naïve inpatients meeting criteria for a first manic episode of BPD were enrolled in this study (4 men, 16 women; mean age=24.9±2.8 years). Diagnoses were established by a psychiatrist using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002a,b). Subjects with other Axis I disorders and/or severe or unstable medical illnesses were excluded from the study. Patients with gout, chronic inflammatory disease, or other diseases associated with hyperuricemia were also excluded. All subjects were medically healthy, as determined by physical and neurological examination and laboratory tests. Severity of mania was assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978). The control group included 24 healthy individuals evaluated with the SCID, non-patient version (First et al., 2002b) (7 men, 17 women; mean age=26.5± 4.7 years). The study was approved by the Ethics Committee of the Espirita Hospital (Porte Alegre, Brazil). Written informed consent was obtained from all the participants in this study. Blood samples were obtained using vacutainer tubes and kept on ice. Samples were centrifuged at 3000×g for 15 min and stored at −80 °C until assay.

2.2. Statistical analysis

Statistical analysis was performed using SPSS 17.0.1 (SPSS Inc., Chicago, IL, USA).

Group comparisons of demographic variables used ANOVAs for continuous measures and Fisher's Exact Test for categorical variables. Analysis of variance was used to compare uric acid levels between patients and healthy controls. Gender and age were added as covariates to determine whether those factors would alter the results. Levene's test was used to examine homogeneity of variance and Shapiro-Wilk's test was used to examine normality. Variables with any assumption violations were log transformed. However, log transforming variables did not alter significance for any results, so raw variables are reported.

The relationship between uric acid and severity of manic episode was tested with Pearson correlations. Results were considered significant at $p<0.05$, two-tailed. Bonferroni corrections were applied separately for the group comparisons and correlations and for whole group and individual group correlations.

3. Results

Patients and controls did not differ in age (24.9 ± 2.81 vs 26.46 ± 4.71 , $F=1.69$; $p=0.20$) or gender composition (Fisher's Exact test, $p=0.73$). The distribution of plasma uric acid levels for patients and controls is shown in Fig. 1.

Drug-naïve patients during their first episode showed higher plasma uric acid levels (4.85 ± 1.61 mg/dL) than healthy controls (2.96 ± 0.63 mg/dL) ($F=28.12$, $df=42$, $p<0.001$). Results remained significant after controlling for age and gender, two factors that might influence uric acid plasma levels ($F=24.20$, $p<0.001$).

Uric acid levels were not correlated with manic episode severity as assessed using the YMRS (37 ± 5.3 , $r=-.20$, $p=0.39$).

4. Discussion

To our knowledge this study is the first to report higher plasma levels of uric acid in drug-naïve patients during a first episode of mania. The results of the present study support a direct role for purinergic system dysfunction in the pathophysiology of mania in BPD.

Purines play an essential role in energy metabolism and regulate neurotransmission. Uric acid is the end product of purine catabolism and is produced by the enzyme xanthine oxidoreductase from xanthine or hypoxanthine; increased uric acid plasma levels may indicate increased purinergic turnover and reduced adenosinergic transmission (Machado-Vieira et al., 2001). Notably, adenosinergic transmission dysfunction may determine the emergence of manic symptoms, given that one of the key functions of central nervous system (CNS) adenosinergic receptors is to inhibit the release of other neurotransmitters and limit cellular excitability (Burnstock, 2008; Machado-Vieira et al., 2002).

Indeed, the idea that the purinergic system might be involved in BPD dates back to Kraepelin, who was the first to describe an association between manic symptoms, uric acid excretion, hyperuricemia, and gout (Kraepelin, 1921). Recent accumulating evidence regarding the clinical efficacy of purinergic modulators for the treatment of acute mania (Machado-Vieira et al., 2008; Akhondzadeh et al., 2006; Machado-Vieira et al., 2001) has led to considerable interest in studying markers of purinergic system activity—for instance, uric acid levels—as illness markers and mediators of treatment response (de Berardis et al., 2008; Machado-Vieira et al., 2008). With regards to the potential association between peripheral and central uric acid levels, one recent study noted a significant positive correlation between plasma and CSF uric acid levels in patients with Alzheimer's disease ($r=0.669$, $p=0.001$) (Bowman et al., 2010).

The purinergic system modulates sleep, motor activity, cognition, attention, behavior, and mood (Machado-Vieira et al., 2001). Even in the absence of a psychiatric diagnosis, individuals with higher uric acid levels are more likely to show higher drive, disinhibition, hyperthymia, or irritable temperament (Lorenzi et al., 2009). Similarly, diseases characterized by purinergic turnover dysfunction and uric acid overproduction (e.g., Lesch-Nyhan syndrome) are associated with impulsive/aggressive behavior, disinhibition, and increased sexual drive (Jinnah, 2009). With regards to the potential effects of mood stabilizers on uric acid levels, lithium was found to lower uric acid plasma levels and to have uricosuric effects in mania (Anumonye et al., 1968). Carbamazepine and phenytoin similarly decreased uric acid levels; in contrast, valproate appeared to have the opposite effect (Ring et al., 1991). However, it is important to note that the effect of these drugs on uric acid levels in relationship to clinical improvement in patients with BPD has not been systematically evaluated.

Notably, in this investigation manic patients were studied during their first manic episode and had never received psychopharmacological treatments; both of these characteristics can help tease apart the effects of chronicity of illness or treatment on uric acid levels. Also, the exclusion of patients with other Axis I disorders (including drug/alcohol abuse or dependence) allowed us to better identify potential state biomarkers in mania. Despite these strengths, the sample size used here is relatively small. Furthermore, we did not perform a longitudinal measurement of these markers, so it remains unknown whether this evidence of purinergic system dysfunction in drug-naïve patients persists after clinical remission. However, a previous study from our laboratory highlighted the potential role of uric acid levels as a surrogate outcome in subjects with BPD treated with lithium plus allopurinol during a manic episode (Machado-Vieira et al., 2008).

5. Conclusion

Evidence of increased urinary excretion of uric acid during remission from hypomania (Anumonye et al., 1968), along with the absence of plasma uric acid abnormalities during euthymia (De Berardis et al., 2008; Machado-Vieira et al., 2008), suggest that increased uric acid may be a state rather than a trait marker of mania in BPD. Taken together, the results support the role of purinergic system dysfunction in BPD early in the course of illness, and suggest that this phenomenon is not the result of chronicity or medication exposure. Overall, our findings suggest a novel mechanism in the pathophysiology of BPD.

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Abbreviations

BPD	bipolar disorder
CNS	central nervous system
YMRS	Young Mania Rating Scale

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Fig. 1. Uric acid levels during a first manic episode in drug-naïve subjects compared to healthy controls.