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Serum uric acid levels and different phases of illness in bipolar I patients treated with lithium

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ABSTRACT

Recent findings support the role of purinergic system dysfunction in the pathophysiology of bipolar disorder (BD). The present study aimed to evaluate the pattern of serum uric acid levels in a sample of 98 BD I patients followed-up prospectively in a naturalistic study and treated with lithium monotherapy or in association with other mood stabilizers (valproate or carbamazepine), in relation to different phases of illness and to pharmacological treatment. The results showed that uric acid levels were significantly higher in patients suffering from a manic/mixed episode, than in those euthymic or during a depressive phase. Further, these levels were related to the Clinical Global Impression-Bipolar Version (CGI-BP) scale score for the severity of manic symptoms. A positive correlation was found also with male sex and with serum lithium levels. These findings suggest that a dysregulation of the purinergic system may occur during manic/mixed episodes, and they support a possible role of serum uric acid levels as a state-dependent marker of BD manic phases.

1. Introduction

Uric acid (UA) is the end product of purine metabolism, produced by the xanthine oxidoreductase enzyme from xanthine or hypoxanthine. Purines play an essential role in the energy intracellular metabolism, mediated by adenosine triphosphate (ATP), as well as in the extracellular space, by performing neurotransmitter and neuromodulatory functions mediated by adenosine and ATP (Burnstock, 2006, 2007).

The purinergic system was reported to be involved in the regulation of sleep, motor activity, cognition, memory, appetite, aggressive behavior and social interaction (Machado-Vieira et al., 2002). Since the 1960s, a relationship between serum UA levels and some behavioral and psychological features was reported. In particular, high energy/drive, positive affect achievement, good performance, higher social status and leadership were correlated with higher UA levels (Katz and Weiner, 1972). Even in the absence of a psychiatric diagnosis, individuals with high UA levels were more likely to show elevated drive, disinhibition, hyperthymic or irritable temperament, impulsivity and excitement seeking (Lorenzi et al., 2010; Sutin et al., 2014). Moreover, elevated UA levels were associated with a number of psychiatric disorders characterized by high impulsivity, such as attention-deficit/hyperactivity disorder, bipolar disorder (BD), pathological gambling and substance abuse (Manowitz et al., 1993; Moeller et al., 2001; Rösler et al., 2009; Salvadore et al., 2010). Similarly, diseases characterized by purinergic turnover dysfunctions, with reduced purine pool and UA overproduction (e.g., Lesch–Nyhan syndrome), are associated with impulsive/aggressive behavior, disinhibition, and increased sexual drive (Schretlen et al., 2005; Jinnah, 2009).

Since the 19th-century, some authors suggested that mental disorders could be the result of an imbalance of UA, and introduced the concept of "UA diathesis". Early accounts for a purinergic system dysfunction in BD can be attributed to Kraepelin (1921) who described an association between manic symptoms, UA excretion, hyperuricemia and gout. Some decades later, Cade (1949) suggested a role of urates in manic behavior, and used lithium to keep UA more soluble, before discovering its antimanic properties. Subsequently, Anumonye et al. (1968) described an increased urinary UA excretion during initial remission phase from mania with lithium.

Recent evidence from genetic and clinical studies supports the involvement of purinergic system in the pathophysiology of BD and recurrent major depression, with therapeutic implications (Barden et al., 2006; Lucae et al., 2006; Zarate and Manji, 2008; McQuillin et al., 2009; Kesebir et al., 2013). Increased serum UA levels in manic episodes might be the result of the increased purinergic turnover,

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which would lead to a reduced adenosinergic transmission (Machado-Vieira et al., 2002). Since one of the key functions of these receptors in the central nervous system is to inhibit the release of other neurotransmitters and limit cellular excitability, a dysfunction at this level might play a key role in the emergence of manic and psychotic symptoms (Burnstock, 2008).

In support of this theory, the xanthine oxidase inhibitor allopurinol, which reduces UA production, has been shown to produce antimanic (Machado-Vieira et al., 2001; Akhondzadeh et al., 2006; Machado-Vieira et al., 2008, 2011), antiaggressive (Lara et al., 2000, 2003) and antipsychotic effects (Lara et al., 2001; Akhondzadeh et al., 2005; Brunstein et al., 2005). The improvement of manic symptoms provoked by the add-on treatment with allopurinol was associated with a consistent decrease in serum UA levels (Machado-Vieira et al., 2001, 2008). These evidences further support the possible role of purinergic system in the onset of manic symptoms. The purinergic modulator allopurinol has been widely used also for the treatment of mitochondrial disorders associated with increased oxidative stress levels (Pacher et al., 2006). Mitochondrial dysfunctions and concomitant changes in oxidative stress parameters have been described in BD, while suggesting indirectly a potential role of allopurinol for the treatment of this illness (Kato and Kato, 2000; Soeiro-de-Souza et al., 2013).

The increasing evidence of a possible therapeutic efficacy of purinergic modulators in acute mania led to the current interest of researchers for the purinergic system's activity (e.g., serum uric acid levels) in BD, as a possible marker of illness phase and treatment response (Machado-Vieira, 2012). In this regard, high serum UA levels have been observed only during the manic phase of BD (De Berardis et al., 2008), while depressed patients showed significantly lower levels than patients presenting with delirium, dementia and other cognitive disorders, substances related disorders, schizophrenia, BD or healthy controls (Wen et al., 2012). Furthermore, serum UA levels of depressed patients were reported to normalize after a five-week treatment with antidepressants (Wen et al., 2012). Finally, some evidence showed increased serum UA levels in drug-naïve BD subjects during a first manic episode, compared with healthy control subjects (Salvadore et al., 2010).

With regards to the potential effect of some mood stabilizers in modifying UA levels, lithium was found to reduce them and to display uricosuric action during a manic episode (Anumonye et al., 1968; El-Mallakh and Jefferson, 1999). Similarly, carbamazepine and phenytoin decreased UA levels; by contrast, valproate appeared to have the opposite effect (Ring et al., 1991). However, the effect of these drugs on UA levels in BD patients has not been systematically investigated.

In consideration of literature data, therefore, we aimed to evaluate if manic/mixed episodes could be associated with higher UA levels than those observed during euthymic or depressive phases in a sample of BD patients treated with lithium alone or combined with anticonvulsants (valproate or carbamazepine). As secondary purpose, we decided to investigate the relationship between pharmacological treatment and UA levels; particularly, we focused on the pattern of relation between UA and serum lithium levels.

2. Method

2.1. Subjects

Ninety-eight (35 men, 63 women; mean age = 42.2 ± 14.1 years) BD I outpatients according to DSM-IV-TR criteria (APA, 2000), treated with lithium monotherapy or in combination with anticonvulsants (valproate orcarbamazepine), were included in this study. Patients were recruited at the day hospital of the psychiatric unit of the Department of Clinical and Experimental Medicine, in collaboration with the section of Pharmacology of the Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, over a two-year period (May 2010–May 2012), as part of a naturalistic prospective study carried out to evaluate the use of lithium in BD (Del Grande et al., 2012; Muti et al., 2013).

Inclusion criteria were age of at least 18 years, a DSM-IV-TR (APA, 2000) diagnosis of BD, and current treatment with lithium monotherapy or in combination with anticonvulsants. All patients with substance/alcohol abuse until three months prior to the study entry and/or with severe somatic disorders were excluded from the study. All they participated voluntary in the study, approved by the Ethics Committee, after written informed consent for the assessment procedures was obtained.

Out of the total of 98 patients recruited at baseline, nine (9.2%) were euthymic, 25 (25.5%) were depressed, 10 (10.2%) were in a manic phase and 54 (55.1%) presented with a mixed episode. Forty-four (44.9%) patients were treated with lithium alone, 39 (39.8%) with lithium and valproate, and 15 (15.3%) with lithium and carbamazepine.

2.2. Assessments

The SCID-I (Structured Clinical Interview for DSM-IV-TR Axis I Disorders) (First et al., 2002) was used to establish the diagnosis of BD type I and the polarity of current episode (depressive, manic or mixed). The Clinical Global Impression-Bipolar Version (CGI-BP) scale (Spearing et al., 1997) was administered to assess the severity of the episode. Besides the baseline evaluations, all patients underwent at least two other standardized clinical assessments by the administration of the CGI-BP at each subsequent check of serum lithium levels.

Serum UA levels were evaluated as well at each blood sampling of patients. Blood samples were collected after participants had been fasting for at least 12 h. Aliquots of serum were obtained in vacutainer tubes containing EDTA and kept on ice. Samples were centrifuged at 3000*g* for 15 min and stored at −80 °C until assay. UA (mg/dL) was measured using enzymatic–colorimetric methods (Bayer, GmbH, Leverkusen, Germany).

The study data refer to an average follow-up period of 6 ± 1.5 months. The frequency of clinical and biological assessments was established by independent psychiatrists, who were in charge of the therapeutic management of patients, on the basis of the variations of symptomatology, with a mean sampling interval of 46.5 ± 5.7 days. During the observational period 205 clinical and biological evaluations of the 98 subjects were carried out, from a minimum of two to a maximum of six for each patient. Fifty-four (26.4%) evaluations were made on depressive, 22 (10.7%) on euthymic, 15 (7.3%) on manic and 114 (55.6%) on mixed phases. The number of events observed during the follow-up was ten for depressive, 4 for manic and 11 for mixed episode.

The mean lithium levels were 0.46 ± 0.19 mEq/L, while those of UA were 5.16 ± 1.38 mg/dL. The mean baseline serum UA levels (mg/dL) were 5.43 ± 1.24 for euthymic subjects, 4.92 ± 1.59 mg/dL for depressed, 5.01 ± 1.70 for manic and 5.46 ± 1.19 for patients with a mixed episode. The mean baseline serum lithium levels (mEq/L) were 0.38 ± 0.16, 0,43 ± 0.19, 0.40 ± 0.13 and 0.47 ± 0.19 in patients with euthymic, depressed, manic and mixed episode respectively.

During the observational period, the mean lithium level (mEq/L) divided by polarity of episode was 0.44 ± 0.20 for depressive, 0.38 ± 0.19 for euthymic, 0.51 ± 0.15 for manic and 0.48 ± 0.20 for mixed phases.

2.3. Statistical analyses

Statistical analyses were performed using the Statistical Package for Social Science, version 17.0.1 (SPSS Inc., Chicago, IL, USA, 2010).

The comparison of the categorical variables was carried out by the Student's *t*-test or by ANOVA analysis, if the groups were two or more than two, while for the comparison between dimensional variables the chi-square analysis was used. The relationship between UA and severity of manic episode, age and serum lithium levels was tested by Pearson's analysis.

In order to better understand the strength of associations and to reduce potential confounding factors, a multiple linear regression analysis was carried out including all variables that resulted correlated with UA levels (sex, age, manic/mixed episode, CGI-BP score for severity of manic symptoms, combination treatment with lithium and valproate, and serum lithium levels), by using serum UA levels as the dependent variable.

A probability (p) less than 0.05 was considered statistically significant.

3. Results

The results showed the presence of significantly higher serum UA levels in men than in women (men 6.02 ± 1.21 mg/dl vs women 4.71 ± 1.25 mg/dl; t-test = 7.152; $p = 0.001$).

After comparing UA levels of subjects with different phases of BD, it emerged that subjects suffering from a manic/mixed episode