Increased uric acid levels in bipolar disorder subjects during different phases of illness

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ABSTRACT

Background: Recent evidence indicates the possible involvement of adenosine and the purinergic system in the pathophysiology of bipolar disorder (BD). The aim of this study is to compare serum uric acid (UA) levels in a large group of BD patients (in mania, depression and euthymia) vs. a control group of patients with different psychiatric disorders.
Methods: 150 BD (SCID-I; DSM-IV) patients were compared to 150 age- and gender-matched subjects with MDD, OCD, or Schizophrenia. Mean serum UA values were compared with the ANOVA, with Bonferroni's post-hoc tests.
Results: Mean serum UA levels (5.06 ± 1.45 vs. 4.17 ± 1.05 mg/dL) and rates of hyperuricaemia (30.7% vs. 6.7%) were significantly higher in the bipolar than in the control group. No differences were detected between bipolars in different phases of illness, with all three groups (manic, depressive and euthymic bipolars) showing significantly higher UA levels as compared to controls. No correlations were found between UA levels and YMRS or HAM-D scores. Mean UA levels were also higher in bipolars never exposed to mood stabilizers vs. controls (5.08 ± 1.43 vs. 4.17 ± 1.05 mg/dL), with no differences compared to other bipolars.
Limitations: Our study suffers from the lack of a healthy comparison group; moreover, longitudinal data are missing.
Conclusions: Our study provides further evidence of a purinergic dysfunction associated with BD, in all phases of the illness. It is possible that increased UA levels are a trait marker of higher vulnerability to bipolar disorder, and are even more increased during mania (mostly in the first manic episode of drug-naïve patients).

1. Introduction

Bipolar Disorders (BD) types I and II affect about 2% of the world's population, with subthreshold forms of the disorder affecting another 2% (Merikangas et al., 2007, 2011). Despite a substantial expansion of research into bipolar disorder and potential treatments during the past 2 decades, true advances have been few (Geddes and Miklowitz, 2013). Little is known, in fact, concerning the etiology and underlying pathophysiology of bipolar disorder, in particular about the various manifestations of the disorder (depression and mania).

Some recent evidence indicates the possible involvement of adenosine and the purinergic system in the pathophysiology of bipolar disorder. Adenosine, a purine nucleoside, appears to modulate both dopamine and glutamine and has gained attention in the underlying pathophysiology of the human central nervous system (Boison, 2008). Adenosine has an anticonvulsant and antikindling activity and modulates second messenger systems, neurotransmitters, energy metabolism and different behaviors, such as sleep, motor activity, cognition, memory, aggressive behavior and social interaction (Machado-Vieira et al., 2002). Adenosine agonists have shown sedative, anticonvulsant, anti-aggressive, and antipsychotic properties, whereas its antagonists such as caffeine increase irritability, anxiety, and insomnia (Lara et al., 2006; Machado-Vieira, 2012). It has been hypothesized that a reduced adenosinergic activity, mostly at A1 receptors (with an increase in uric acid levels), is associated with the complex network of changes on neurotransmitters pathways related to manic behavior (Machado-Vieira et al., 2002).

Evidences suggesting a purinergic system dysfunction in the pathophysiology of bipolar disorder are briefly summarized in the following paragraphs. Randomized, placebo-controlled studies

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found that the purinergic modulator allopurinol, a xanthine oxidase inhibitor used for the treatment of gout and hyperuricemia, is effective in treating acute mania when used adjunctively with lithium (Machado-Vieira et al., 2008), lithium and haloperidol (Akhondzadeh et al., 2006), and sodium valproate (Jahangard et al., 2014). A recent large, well-powered, placebo-controlled study, however, did not find allopurinol addition to mood stabilizers (other than lithium) and/or antipsychotic (*taken for a period of between three days and two weeks*) more effective than placebo in manic patients (Weiser et al., 2014). A possible explanation of this discrepancy is that allopurinol might have a different effect in combination with different mood stabilizers. *Another possible explanation for the negative results of this trial is the possibility that the use of effective antipsychotic and mood stabilizing treatment* (*although the Authors do not report the average number of adjunctive treatments*) *may have caused a ceiling effect, masking the potential benefits of allopurinol*. Notwithstanding this negative trial, the hypothesis that allopurinol, by increasing adenosine levels in the brain, might exert an antimanic effect at least in some patients with bipolar mania remains interesting and results from controlled studies at least in part support purinergic system dysfunctions in the pathophysiology of mania (Hirota and Kishi, 2013). *Lithium also has a potential effect in lowering uric acid levels*: *historically, in the 19th century, it was used to dissolve uric acid crystals in urine obtained from patients with gout before the first use made by Cade to treat mania in chronically hospitalized patients* (*Oruch* et al., *2014*). *Given the specific effect of lithium on uric acid levels, it is also possible that it potentiates allopurinol* (*and* vice versa), *while the effect of other mood stabilizers on uric acid levels remains controversial*.

Uric acid levels were found, moreover, significantly increased in patients with bipolar disorder. Uric acid is an important nitrogenous end product of purinergic metabolism (ATP and adenosine). A first study found that plasma uric acid levels are higher during the manic phase of bipolar disorder but not during the depressive or euthymic phase (De Berardis et al., 2008); moreover, uric acid levels correlated with YMRS scores, suggesting a role in the pathophysiology of mania. A second study confirmed the increase in uric acid levels in drug-naive BD subjects during their first manic episode, although a correlation with YMRS scores was not found (Salvadore et al., 2010). A possible explanation of this finding is the small sample size (20 patients vs. 24 controls), which might have reduced statistical power. These findings suggest, however, that increased uric acid may be a specific state marker of mania rather than a trait (Machado-Vieira, 2012).

Preliminary evidence suggests, moreover, an increased occurrence of gout in patients with bipolar disorder (Chung et al., 2010). Increased levels of uric acid are the key biomarker in the diagnosis of gout. A nationwide population-based survey investigated the risk of developing gout among patients with/without bipolar disorder during a six-year follow-up period: the hazard of developing gout was 1.19 greater for bipolar patients than for the comparison cohort (16.4% vs. 13.6%)(Chung et al., 2010). The conclusion of the Authors was that patients with bipolar disorder probably have purinergic dysfunction and evolve into gout thereafter.

Finally, even in the absence of a psychiatric diagnosis, individuals with higher uric acid levels are more likely to show higher drive and disinhibition, suggesting that externalized traits of temperament are associated with higher serum uric acid levels (Lorenzi et al., 2010). A second study suggested that higher uric acid is associated with impulsivity in both humans (two longitudinal nonclinical community samples – total $n=6883$) and mice (Sutin et al., 2014).

Some evidence exists, in conclusion, suggesting the possible involvement of purinergic dysfunctions in the pathophysiology of bipolar disorder and mania in particular. However, controversies also exist: two negative studies failed to show a benefit of adding allopurinol in mania (Fan et al., 2012; Weiser et al., 2014); Salvadore et al., 2010 failed to confirm a correlation between serum uric acid levels and YMRS scores in manic subjects.

The aim of the present study is to compare serum uric acid levels in a large group of bipolar disorder patients during different phases of illness (mania, euthymia and bipolar depression) vs. a control group made of patients with different psychiatric disorders. Based on previous literature, we made the following predictions: 1) serum uric acid levels will be significantly increased in bipolar patients as compared to controls; 2) serum uric acid levels will be significantly higher only in bipolar patients during mania and not during depression or euthymia; 3) serum uric acid levels will be higher in bipolar patients never exposed to mood stabilizers as compared to controls.

2. Methods

2.1. Subjects

Participants for this case-control cross-sectional study were 150 patients with Bipolar Disorder and 150 controls made of age and gender-matched subjects with other Axis I Disorders.

Bipolar patients were male or female subjects who met DSM-IV-TR criteria for a diagnosis of Bipolar Disorder I or II. Controls met DSM-IV-TR criteria for Major Depressive Disorder – MDD, Obsessive–Compulsive Disorder – OCD, and Schizophrenia. All subjects included were inpatients and outpatients consecutively referred to the Department of Neuroscience, Psychiatric Unit of the University of Turin (Italy); they were at least 18 years of age and were willing to voluntarily participate in the study. They were selected from September 2011 to October 2013. The aims of the study as well as study procedures were thoroughly explained to potential participants who gave written consent before participation. The study design was reviewed and approved by the local ethics committee.

To be enrolled into this study, patients had to have a primary diagnosis of Bipolar Disorder I or II (DSM-IV-TR, SCID-I). To be enrolled in the control group, patients had to have an Axis I diagnosis other than bipolar disorder (DSM-IV-TR, SCID-I) and they had to have never been exposed to mood stabilizers in their life. We included in the present study controls with Major Depressive Disorder only if in euthymic state for at least two months because it was found that patients during major depressive episodes have lower serum uric acid levels (Wen et al., 2012). Subjects with severe or unstable medical illnesses were excluded from the study; patients with gout, chronic inflammatory disease, diabetes, renal failure or serum creatinine value >1.5 mg/dL, or other diseases associated with hyperuricemia were also excluded. Exclusion criteria were treatment with medications such as acetylsalicylic acid, allopurinol, thiazide diuretics, steroids, ibuprofen, vitamin E, and other drugs that could affect serum uric acid levels significantly.

2.2. Assessments and procedures

Data were obtained from each subject by a semi-structured interview with a format that covered the following areas: a) sociodemographic data (age, gender, marital status, years of education and occupational status); b) diagnosis: diagnoses (current and lifetime) were performed by clinicians with at least four years of postgraduate clinical experience by means of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I); c) clinical data (type of BD, age at onset of first affective episode, total

number of affective episodes, duration of illness). Severity of mania was assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and severity of depression using the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960).

Lifetime and current medical conditions and use of medications at the time of interview were assessed; moreover, lifetime exposure to mood stabilizers was recorded by means of direct interview, family members' interview (when available) and medical records review. Particular attention was devoted to lifetime exposure to lithium, valproate and carbamazepine because of the known potential effects of mood stabilizers on serum uric acid levels; in particular, lithium was found to lower uric acid plasma levels and to have uricosuric effects in mania (Anumonye et al., 1968); carbamazepine similarly decreased uric acid levels; in contrast, valproate appeared to have the opposite effect (Ring et al., 1991).

A blood draw for routine blood exam was performed at hospital admission for inpatients, as part of the clinical management routine. For outpatients, patients were scheduled for a blood test within a week from the study visit. At the time when blood was drawn, patients were fasting for the previous 10 h; patients who were not fasting were rescheduled. Blood exams included complete blood count, uric acid, creatinine, urea, sodium and potassium, thyroid hormone, AST, ALT, GGT, lithium, carbamazepine and valproate serum levels (for those on classic mood stabilizers). Blood samples were drawn in our clinic and examined in the "Baldi e Riberi" laboratory of analysis, San Giovanni Battista Hospital, Turin, Italy. Hyperuricaemia was defined by uric acid levels higher than 5.7 mg/dL, according to our laboratory reference range.

With regards to the potential effects of mood stabilizers on uric acid levels, in order to help to tease apart the effects of chronicity of illness or treatment on uric acid levels we selected respectively, *in primis*, from the manic group 13 drug-naïve patients during their first ever manic episode; secondly, a group of bipolar patients that had never received mood stabilizers.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 20.0.0 (SPSS Inc., Chicago, IL, USA). For the comparisons of variables between cases and controls (matched subjects) we used the paired *t*-test and the McNemar's test: continuous variables were compared using the paired *t*-test, categorical variables using the McNemar's test. When considering non matched groups, we used the Student's *t*-test and the Pearson's Chi-square test, respectively, for continuous and dichotomous variables. Group comparisons used ANOVAs for continuous measures. After the use of ANOVA, we performed a Bonferroni's post-hoc analysis in order to determine in which groups the significant differences were found. Results were considered significant at $p < .05$, two-tailed. Lastly, bivariate Pearson correlations were used to assess the relationship between serum uric acid levels and severity of manic symptoms as assessed using the YMRS (two analyses, all bipolars and only subjects with hypomania or mania, separately).

3. Results

Three hundred patients were enrolled: 150 bipolar patients and 150 age and gender-matched controls. Table 1 shows socio-demographic and clinical characteristics of bipolar patients included. We could enroll 75 patients during a major depressive episode, 46 patients during a hypomanic or manic episode, and 29 patients in stable euthymia (at least 2 months with HAM-D < 6 and YMRS < 8). Among bipolars, we could identify 84 patients who had never been exposed to mood stabilizers (which could affect serum uric acid levels), and 13 subjects with their first ever manic/hypomanic episode and who had not been previously exposed to mood stabilizers.

Table 1
Socio-demographic and clinical characteristics of bipolar patients included.

	Patients ($N=150$)
Actual age (years) (Mean ± SD)	47.74 ± 15.48
Gender (males), *N* (%)	63 (42.0)
Educational level (years) (Mean ± SD)	12.65 ± 4.42
Marital status, *N* (%)	
Married	70 (46.7)
Divorced	15 (10.0)
Never married	59 (39.3)
Widowed	6 (4.0)
Currently working, *N* (%)	79 (52.7)
Bipolar disorder, *N* (%)	
type I	85 (56.7)
type II	65 (43.3)
Age at onset (years) (Mean ± SD)	27.93 ± 10.76
Total number of episodes (Mean ± SD)	6.9 ± 4.12
Duration of illness (years) (Mean ± SD)	19.95 ± 13.05
Actual episode, *N* (%)	
MDE	75 (50.0)
Manic/hypomanic episode	46 (30.7)
Euthymic (for at least two months; HAM-D < 6, YMRS < 8)	29 (19.3)
YMRS, all patients ($N=46$) with manic/hypomanic episode (Mean ± SD)	19.37 ± 6.57
First ever Manic/hypomanic Episode, drug-naïve, *N* (%)	13 (8.7)
YMRS (Mean ± SD)	22.23 ± 8.31
HAM-D, all patients ($N=74$) with MDE (Mean ± SD)	16.11 ± 5.20
Patients ($N=30$) in euthymic phase	
HAM-D, (Mean ± SD)	3.17 ± 2.36
YMRS, (Mean ± SD)	1.55 ± 1.80
Bipolar cycle, *N* (%)	
MDI	60 (40.0)
DMI	17 (11.3)
Irregular	72 (48)
Rapid cycling	1 (.7)
BMI (Mean ± SD)	25.36 ± 4.58

BMI: Body Mass Index; YMRS: Young Mania Rating Scale; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; MDE: Major Depressive Episode.

The control group consisted of 46 (30.7%) patients with Obsessive–Compulsive Disorder (OCD), 95 (63.3%) with Major Depressive Disorder (MDD) (in euthymic state for at least two months) and 9 (6%) with Schizophrenia.

Mean serum uric acid levels and rates of hyperuricaemia were both higher in the bipolar group than in the control group (Table 2). Serum uric acid levels and rates of hyperuricaemia of bipolar patients never exposed to mood stabilizers (lithium, valproic acid, carbamazepine)($N=84$) were also higher than controls (Table 3). With regard to bipolars previously exposed to mood stabilizers ($N=66$), no differences were detected (mean uric acid levels: 5.08 ± 1.43 in never exposed vs. 5.03 ± 1.49 mg/dL in previously exposed; $t=-.210$, $p=.834$). *Patients taking lithium* ($N=59$) *also did not differ from those not taking it* ($N=91$) (*mean uric acid levels: 5.09 ± 1.51* vs. *5.04 ± 1.43* mg/dL; $t=-.226$, $p=.821$).

There were no statistically significant differences of serum uric acid levels between bipolar patients during different phases of illness, whereas uric acid levels in each phase were significantly higher than those of the control group (Fig. 1). When we selected drug-naïve bipolar patients during their first-ever (hypo)manic episode (First Episode, Drug-Naïve FEDN) we found their mean serum uric acid levels higher than those of all bipolar patients (except FEDN) and all manic patients (except FEDN)(Fig. 2). When we excluded FEDN

Table 2
Mean serum uric acid levels and rates of hyperuricaemia (bipolar patients vs. controls; paired *t*-test and McNemar test).

	Bipolar patients ($N=150$)	Controls ($N=150$)	t/χ^2	p
Uric acid (mg/dL) (Mean ± SD)	5.06 ± 1.45	4.17 ± 1.05	6.711	< .001
Normal range: 2.4–5.7 mg/dL				
Hyperuricaemia (Uric acid > 5.7 mg/dL), *N* (%)	46 (30.7)	10 (6.7)	28.454	< .001

Table 3
Mean serum uric acid levels and rates of hyperuricaemia (bipolar patients never exposed to mood stabilizers vs. controls).

	Bipolar patients ($N=84$)	Controls ($N=150$)	t/χ^2	p
Actual age (years) (Mean ± SD)	46.31 ± 15.49	47.99 ± 15.95	.780	.436
Gender (males), *N* (%)	41 (48.8)	63 (42.0)	1.011	.315
Uric acid (mg/dL), (Mean ± SD)	5.08 ± 1.43	4.17 ± 1.05	−5.578	< .001
Normal range: 2.4–5.7 mg/dL				
Hyperuricaemia (Uric acid > 5.7 mg/dL), *N* (%)	25 (29.8)	10 (6.7)	22.579	< .001

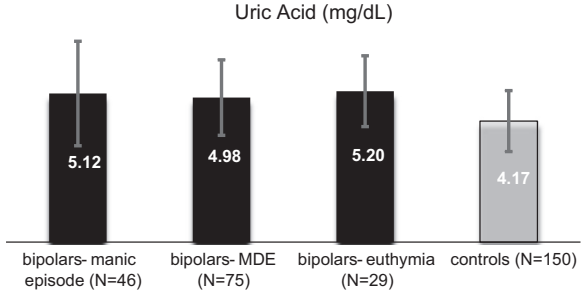

Fig. 1. Mean serum uric acid levels (± SD) of bipolar patients in different phases of illness vs. controls. ANOVA: $F=12{,}513$; $p<.001$. Post-hoc comparisons: all values of bipolar patients (in each phase of illness) were significantly higher than Controls. No differences were found between serum uric acid levels between different phases of illness.

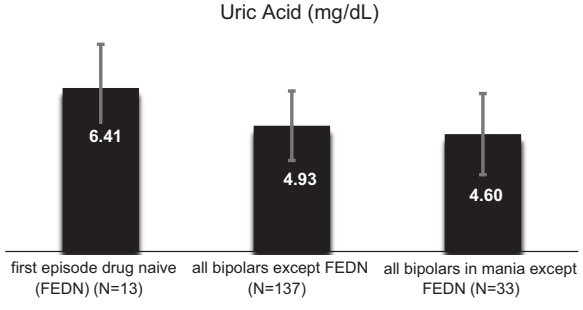

Fig. 2. Mean serum uric acid levels (± SD) of bipolar patients during their first-ever (hypo) manic episode (drug-naïve) (FEDN = First Episode Drug-Naïve) vs. all bipolar patients (except FEDN), vs. bipolar patients during manic episode (except FEDN). FEDN vs. all manias except FEDN: $t=-3.392$; $p<.001$. FEDN vs. all bipolars except FEDN: $t=-3.636$; $p<.001$.

patients from the bipolar group, serum uric acid levels of all bipolars and manic bipolars were still significantly higher than controls (respectively 4.93 ± 1.36 vs. 4.17 ± 1.05; $t=-5.326$, $p<.001$ and 4.60 ± 1.59 vs. 4.17 ± 1.05; $t=-5.910$, $p<.001$). There were no statistically significant differences between Bipolar I and II; bipolar II patients showed higher serum uric acid levels than MDD and OCD patients, whereas bipolar I subjects only differed from MDD patients (Fig. 3); schizophrenia subjects ($N=9$ – data not shown in Fig. 3) showed the lower mean uric acid levels (4.07 ± .67).

Uric acid levels were not correlated with manic episode severity as assessed using the YMRS in neither all bipolars together (Pearson correlation $r=.043$; $p=.604$) nor patients in hypomania/mania only

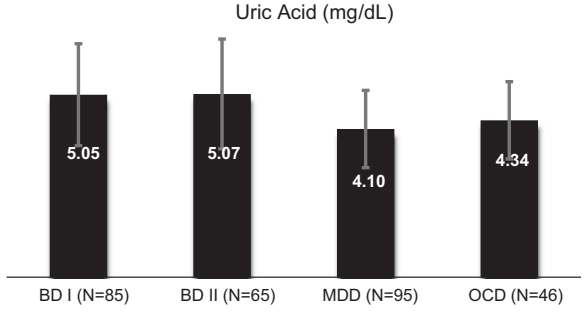

Fig. 3. Mean serum uric acid levels (± SD) of patients with BDI and BDII, MDD, and OCD. ANOVA: $F=9{,}485$; $p<.001$. Post-hoc comparisons: BDI = BDII; BDI > MDD; BDII > MDD; BDII > OCD.

(Pearson correlation $r=.158$; $p=.295$). *In bipolar depressed patients uric acid levels were not correlated with HAM-D total scores* (*Pearson correlation r=.037; p=.756*).

4. Discussion

Results of our study support a role of purinergic system dysfunctions in the pathophysiology of bipolar disorder and are in line with results of different studies which investigated not only serum uric acid levels in bipolars (De Berardis et al., 2008; Salvadore et al., 2010; Kesebir et al., 2014), but also the efficacy and tolerability of the purinergic modulator allopurinol as an add-on treatment in bipolar mania (Akhondzadeh et al., 2006; Machado-Vieira et al., 2008; Jahangard et al., 2014). We measured serum uric acid levels because peripheral and central uric acid levels have a strong positive association (Bowman et al., 2010); we then assume that differences in serum uric acid levels found in our study reflect differences in central uric acid levels.

According to our predictions, we found that serum uric acid levels are significantly increased in bipolar patients as compared a control group made of patients with different psychiatric disorders, such as Major Depressive Disorder, Obsessive–Compulsive Disorder, and Schizophrenia (only 9 subjects). As gender-based differences in oxidative stress parameters have been found (women seem more susceptible to oxidative stress than male and have higher serum uric acid levels) (Wiener et al., 2014), control subjects were matched to patients by gender. Moreover, as age might increase the rate of hyperuricaemia we also matched our controls by age of bipolars. Increased levels of uric acid mean

accelerated purinergic transformation and decreased adenosinergic transmission (Burnstock, 2008). As adenosinergic receptors (mostly A1 receptors) limit cellular excitability by inhibiting neurotransmitter release in the central nervous system, the increase in serum uric acid levels found in bipolars as compared to other psychiatric disorders might account for the vulnerability of bipolars to the development of recurrences (trait vulnerability marker: the nervous system of bipolars is more vulnerable to develop affective episodes in response to stress because of a purinergic dysfunction – mania as a kindling-like behavioral manifestation of purinergic dysfunction) or might only imply that once a manic episode starts, the purinergic dysfunction results from mania and contributes to the maintenance of manic symptoms (state marker of mania).

Uric acid levels were also significantly different between bipolar I and II patients and those with unipolar MDD, extending in a larger sample what recently found by Kesebir et al. (2014) in a group of 41 bipolars and 30 MDD subjects: they found that uric acid levels of BD patients were higher than both patients with recurrent MDD and healthy controls. Additionally, they also found that uric acid levels of MDD patients were lower than healthy subjects. Another study found uric acid levels significantly reduced in MDD patients compared to controls (Wen et al., 2012), suggesting that purinergic dysfunctions might affect the whole spectrum of affective disorders.

Whether purinergic dysfunctions as shown by an increase in serum uric acid levels are a state marker of mania or a trait marker of bipolar disorder still remains unanswered: contrary to our prediction, based on results of the study by De Berardis et al. (2008), we failed to detect differences between bipolar patients in (hypo)mania, major depressive episode and stable euthymia (at least two months). We also failed to detect a correlation between uric acid levels and severity of mania as from YMRS scores, both in manic patients only and in the whole group of bipolars (Salvadore et al., 2010 also failed to find this correlation). However, we enrolled a group of relatively severe bipolar patients, as evidenced by the long duration of illness (mean 19.95 ± 13.05 years from onset of first affective episode and enrollment in the study) and the high number of lifetime affective episodes (mean 6.9 ± 4.12). A possible explanation of the failure to detect an effect of the current (hypo)manic state on uric acid levels is then that patients in depression (bipolar depression) and euthymia might still present higher serum uric acid levels because of recent (maybe too recent) episodes of (hypo)mania.

An alternative explanation is that uric acid levels are a trait marker of bipolar disorder rather than a state marker of mania. This hypothesis is supported by results of two studies performed by the same research group (Kesebir et al., 2013; Kesebir et al., 2014). In the first study they also failed to find a significant difference in uric acid levels between manic, depressive and euthymic bipolars, while all three groups differed from healthy subjects (increased levels as compared to healthy subjects) (Kesebir et al., 2013); in a recent study they included only bipolars in remission, and still found a significant increase in serum uric acid levels as compared to controls (Kesebir et al., 2014). Rather than a state marker, uric acid levels may be then viewed as a trait marker of a continual predisposition for bipolar disorder.

A third possible explanation for our failure to detect differences among bipolars is that patients (manic patients as well as all bipolars) have been exposed to mood stabilizers such as lithium, valproate or carbamazepine, among others, that alter uric acid levels. We then performed a separate analysis on a small group of manic patients who were drug-naïve at measurements, had never been exposed to mood stabilizers, and had their first-ever affective episode (FEDN = First Episode, Drug-Naïve); this group consisted of only 13 patients. Uric acid levels were significantly higher (6.41 mg/dL) in this group as compared to both all bipolars (except FEDN), and all manic patients (except FEDN). This result, to our opinion, supports the hypothesis that uric acid levels are particularly higher in first manic episodes not yet treated with mood stabilizers and is in agreement with results of Salvadore et al. (2010).

The investigation of serum uric acid levels as a screening test in mania, as proposed by Machado-Vieira. (2012), may help to identify earlier those bipolar patients who will respond better to treatments, including the addition to mood stabilizers of allopurinol. It may be speculated, from results of our study, that the addition of allopurinol would be particularly effective in first episode manic patients. Routine monitoring of serum uric acid levels might be then useful in individualizing treatments and monitoring clinical outcome.

Our study has some limitations; first, our study lacks a control group made of healthy subjects. Second, the choice of a control group of patients with mainly OCD or MDD in remission was made for practical reasons, and limits our ability to examine the specificity of the purinergic dysfunction with regard to other psychiatric conditions. A third limitation is that we could not completely control for the exposure to mood stabilizers or antipsychotics in the bipolar group; however, we identified a large subgroup of subjects ($N = 84$) who had never been exposed before to lithium, carbamazepine (both drugs seem to decrease uric levels – Anumonye et al., 1968), or valproate (which does not reduce uric levels but might increase them – Ring et al., 1991) and this subgroup also showed increased uric acid levels as compared to controls. It is important to note that the effect of mood stabilizers (and mostly of antipsychotics used for the treatment of bipolar disorder) on uric acid levels in relationship to clinical improvement has not been systematically evaluated. With this regard, longitudinal studies with multiple measurements of serum uric acid levels at different stages of illness in the same patient are strongly needed in order to clarify both the state or trait value of the increase in uric acid levels and the effect of treatments. *Other limitations of our study consist in the fact that we did not adjust our results for BMI, or the presence of metabolic syndrome or its components*; *association between bipolar disorder and hyperuricemia does not mean causation*, *and hyperuricemia could be linked to metabolic syndrome* (*which is highly prevalent among bipolar subjects*) (Salvi et al., 2008) *or its component*.

In conclusion, our study provides further evidence of a purinergic dysfunction associated with bipolar disorder; the notion that the purinergic system might be involved in bipolar disorder dates back to Kraepelin, who was the first to report an association between mania, uric acid excretion, hyperuricaemia and gout (Kraepelin, 1921). Since then, several studies provided support to the hypothesis of purinergic dysfunctions, both by measuring serum uric acid levels (De Berardis et al., 2008; Salvadore et al., 2010; Kesebir et al., 2014) and by effectively treating manic patients with allopurinol as add-on (Akhondzadeh et al., 2006; Machado-Vieira et al., 2008; Jahangard et al., 2014). The role of uric acid, adenosine and the whole purinergic system in the pathophysiology not only of bipolar disorder but also of affective temperaments (as suggested by Kesebir et al. 2014) and major depression needs to be further elucidated. It is possible that increased uric acid levels are both a trait marker of higher vulnerability to impulsivity, hyperthymic and irritable temperaments (as suggested by Lorenzi et al., 2010; and Sutin et al., 2014) and frank bipolar disorder, and are even more increased during mania (mostly in the first manic episode of drug-naïve patients).

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Conflict of interest

All the authors declare that they have no conflicts of interest.

Contributors

Umberto Albert: study design set-up, patients diagnosis and recruitment, data collection, data analyses and manuscript writing.

David De Cori: study design set-up, patients recruitment, data collection, data analyses and manuscript writing.

Andrea Aguglia: patients recruitment, data collection.

Francesca Barbaro: patients recruitment, data collection.

Giuseppe Maina: patients diagnosis and manuscript critical revision.

Filippo Bogetto: manuscript critical revision.

All authors contributed to and have read and approved the final manuscript.

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