Journal of Affective Disorders 173 (2015) 170–175

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

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

Umberto Albert [a,*], David De Cori [a], Andrea Aguglia [a], Francesca Barbaro [a], Filippo Bogetto [a], Giuseppe Maina [b]

[a] Rita Levi Montalcini Department of Neuroscience, Anxiety and Mood Disorders Unit, University of Turin, Italy
[b] Department of Mental Health, "San Luigi-Gonzaga" Hospital, University of Turin, Orbassano (TO), Italy

ARTICLE INFO

Article history:
Received 22 July 2014
Received in revised form
1 November 2014
Accepted 3 November 2014
Available online 15 November 2014

Keywords:
Uric acid
Bipolar disorder
Mania

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

* Corresponding author. Tel.: +39 011.6335425; fax: +39 011 673473.
E-mail address: umberto.albert@unito.it (U. Albert).

http://dx.doi.org/10.1016/j.jad.2014.11.005
0165-0327/

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