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An observational study on variations of serum uric acid level in patients of depression and healthy controls and its correlation with hidden bipolarity

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ABSTRACT

Background: Bipolar disorder (BD) is one of the most studied psychiatric disorders, this being one of the leading causes of disability in young individuals. In search for its predictive biomarker, serum uric acid (UA) level was seen to have a pathophysiologic role in the genesis of BD through oxidative stress and other mechanism. **Aims and Objectives:** The aim of the study was to estimate serum UA levels in patients with 1st episode depression, to compare serum UA levels between patients and matched healthy controls and to compare serum UA levels between patients with and without hidden bipolarity and therefore, and to evaluate whether it can be used as a predictor of bipolarity. **Materials and Methods:** A study was conducted in a tertiary care center in Eastern India for a duration of 3 months with a sample size of 92, comprising 46 cases with major depressive disorder (MDD) and 46 control groups of healthy subjects. Their serum UA levels were estimated. The study population was subjected to a mood disorder questionnaire (MDQ) and Montgomery–Asberg Depression Rating Scale (MADRS) scoring. All these data were tabulated in a master sheet and analyzed using Statistical Packages for the Social Sciences 25 software. **Results:** The mean age of the study population was 32 years with 46 males and 46 females. The mean UA levels for MDD group was 5.27 ± 1.14 mg/dL and for control group was 4.6 ± 1.2 mg/dL, which was seen to be statistically significant (P = 0.001). No statistically significant association was seen between the group with a high likelihood of bipolarity versus a low chance of bipolarity with respect to UA levels. A positive correlation was seen between MDQ scores and UA levels of depressed individuals (using Spearmen's rho: rs = 0.345, P = 0.019), but not with their MADRS scores. **Conclusion:** Serum UA levels are significantly higher in depressed patients as compared to healthy subjects. A non-statistical association was seen between UA levels and their bipolar tendencies, owing to a small sample size of comparable groups. However, a higher MDQ score was associated with high UA levels. A larger study population is needed to conclusively establish the predictive role of UA with respect to BD.

Key words: Bipolar disorder; Montogomerry–Asberg Depression Rating Scale; Major depressive disorder; Mood disorder questionnaire; Uric acid

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INTRODUCTION

Bipolar disorder (BD) has long been one of the most studied psychiatric disorders. With a prevalence of 2.4% and is associated with reduced functioning, cognitive impairment, and decreased quality of life lasting lifelong, it is one of the leading causes of disability in young people and increases mortality, especially death by suicide.[1] The

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exact pathophysiological pathogenesis of BD still eludes us, and genetic factors are believed to be the main cause of the disease, while acquired environmental factors promote it.[2] In search of a biomarker and novel treatments, some studies have shown that the purinergic system with uric acid (UA) is closely related to the occurrence and development of BD.[3] As one of the non-enzymatic antioxidant systems, UA may participate in the pathogenesis of BD through oxidative stress or other mechanisms and is predicted to be a potential biomarker with a very good-to-excellent prognostic accuracy for conversion to BD in depressed subjects.[4] Hence, our study aims to explore the crucial association between UA levels and prediction of bipolarity.

Aims and objectives

a. To estimate serum UA levels in patients with 1st episode depression
b. To compare serum UA levels between patients and matched healthy controls
c. To compare serum UA levels between patients with and without hidden bipolarity and therefore, to evaluate whether it can be used as a predictor of bipolarity.

MATERIALS AND METHODS

The current study was conducted in a tertiary center in Eastern India. The study obtained ethical clearance from the Institutional Ethics Committee (Ref No-MC/KOL/IEC/NON-SPON/472/10–2019). The study duration was 3 months (January 2021–March 2021). The sample size was calculated taking the confidence level as 95%, margin of error as 5%, and prevalence of hidden bipolarity as 15%[5] using the formula $\{Z^2P(1-P)/d^2\}$.[6] From the psychiatry outdoor patient department and indoor patient department, purposive sampling was done and 46 consecutive patients fulfilling the inclusion criteria, that is, (a) diagnosed with a depressive episode by ICD-10 criteria, (b) age 18–65 years, (c) able to converse in Hindi, Bengali, or English, (d) willing to participate in the study and give informed consent and exclusion criteria: (a) Having a known disorder altering UA level, (b) receiving a known medication altering UA level, (c) started receiving treatment for a depressive episode, (d) refusing consent was selected. Correspondingly 46 age and gender-matched non-related healthy individuals were included to serve as controls. This resulted in a sample size of 92. The study subjects were administered a mood disorder questionnaire (MDQ) and Montgomery–Asberg Depression Rating Scale (MADRS) and subjected to serum UA level estimation by the uricase peroxidase method.

All the data were compiled into a master chart. For statistical analysis, descriptive statistics were used in terms of percentage and mean with standard deviation. Analytical statistics were done by Software Statistical Packages for the Social Sciences 25.

RESULTS

Our study population was 92 which had a mean age of 32 years, ranging from 14 to 70 years, and comprised 46 males and 46 females. The age range in the group of patients with depressive disorder was 14–56 years (mean 32 years). The normal healthy control group had a mean age of 32 years (range: 18–70 years). The study population comprising healthy controls, Major Depressive Disorders with low bipolarity and Major Depressive Disorders with high bipolarity are distributed as shown in Figure 1. The mean value of UA levels for the control group was calculated to be 4.6 mg/dL with a standard deviation of 1.2 mg/dL. The mean value of UA levels for the patients with depression was calculated to be 5.27 mg/dL with a standard deviation of 1.14 mg/dL (Figure 2). Patients with a higher chance of bipolarity had a mean value of 5.72 mg/dL with a standard deviation of 0.33 mg/dL and patients with a low chance of bipolarity had mean UA levels of 5.23 mg/dL with a standard deviation of 1.18 mg/dL.

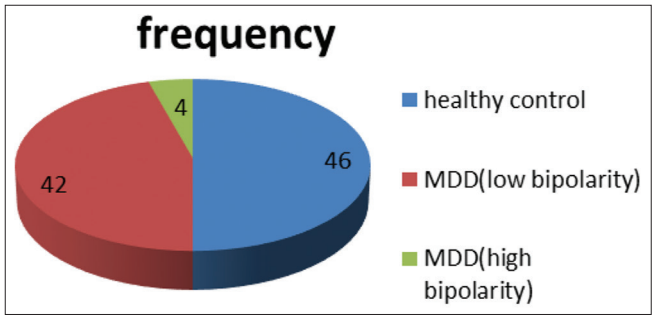

Figure 1: Pie diagram showing the distribution of study subjects into healthy controls, major depressive disorder with low bipolarity, and major depressive disorder with high bipolarity

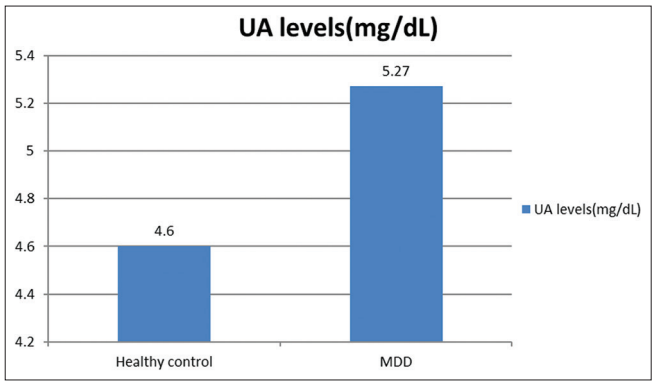

Figure 2: Bar diagram showing mean uric acid levels (mg/dL) in healthy subjects versus major depressive disorder

Although a significant difference in mean UA levels was found between patients and controls (P=0.001), the difference in mean UA levels between patients with high bipolarity and low bipolarity was not significant (P=0.417) (Table 1).

Spearman's Rho test revealed a statistically significant positive correlation between MDQ scores and UA levels of depressed patients (rs=0.345, P=0.019) (Figure 3). No such statistical significance was found between MADRS scores and UA levels of depressed patients.

DISCUSSION

UA is the final result of purine decomposition in the body and it has a large correlation with oxidative stress.[7] Studies show that the purine system may be involved in the regulation of the patient's exercise, sleep, cognition, mood, and behavior, alongside the effect of purine on neurotransmitter activity probably leading to the emergence of various mental symptoms.[8] The study of the relationship between purine and BD can go back to the nineteenth century when researchers found that some gout patients had a common emotional disorder, and the symptoms were reduced by the treatment with lithium.[9] Recently, a long-term epidemiological study by Chung found that the risk of UA levels in BD patients was significantly higher than in healthy people, thereby indicating that BD and hyperuricemia could have a similar neurobiochemical basis.[10] In normal physiological conditions, UA as a non-enzymatic antioxidant prevents superoxide dismutase degeneration and enhances the antioxidant effect. However, paradoxically the high level of UA will be transformed into a powerful oxidant,[11] causing the cell membrane to have a chain oxidation reaction, damaging the stability, liquidity, and permeability of the cell membrane, and leading to the development of BD.[12] Abnormal purine metabolism in BD leads to mood disorders by also affecting the activity of neurotransmitters such as dopamine, glutamate, gamma-aminobutyric acid, and 5-HT.[13,14]

Table 1: Distribution of study subjects as per their demographic variables, mean uric acid levels of different study populations, and corresponding P-values

Gender	Number	
Male	46	
Female	46	
Study population	**Mean age**	
MDD	32 years	
Healthy controls	32 years	
Study population	**Mean uric acid levels (mg/dL)**	**P-value**
MDD	5.27±1.14	0.001
Healthy controls	4.6±1.2	(significant)
High chance of bipolarity	5.27±0.3	0.417 (not
Low chance of bipolarity	5.23±1.18	significant)

MDD: Major depressive disorder

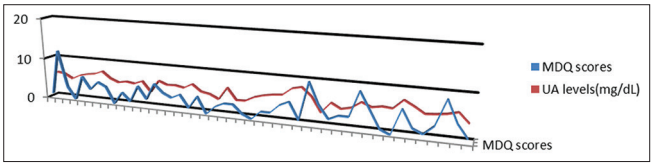

Figure 3: Line diagram showing a trend of mood disorder questionnaire scores and uric acid levels in depressed individuals

In 2016, a meta-analysis revealed[15] that serum UA levels were significantly increased in BD patients compared with healthy controls. In 2023, another meta-analysis indicated a strong association between serum UA levels and BD in Chinese patients.[16]

Some evidence from genetic studies emphasizes the key role of the purinergic system during manic episodes, stating that elevated UA may be a specific phenomenon resulting from metabolic abnormalities during manic episodes.[17] Bartoli's et al. study[18] found that although gender, metabolic syndrome, and triglycerides have a special effect on UA, after controlling the factor of gender, most of the effects of BD on UA are direct and only influenced by some metabolic parameters.

Individuals with higher UA levels tend to show higher drive and hyperactive or irritable temperament.[19] A randomized controlled trial of allopurinol adjuvant therapy in patients with bipolar manic episodes concluded that allopurinol can play a contributory role in the treatment of bipolar manic episodes by increasing adenosine levels through xanthine oxidase inhibition.[20] Bartoli et al. study[21,22] through a meta-analysis on drugs for mania indicated that allopurinol significantly reduces manic symptoms and gives clinical remission, thus confirming the link between BD and UA.

Dos Santos Oliveira et al.[4] found in a 10-year follow-up study of major depressive disorder (MDD) patients that serum UA levels showed an excellent accuracy for predicting conversion to BD in inpatients with MDD.

Our study found significantly higher serum UA levels in patients with MDD compared to normal healthy subjects in concordance with the results of Shaker et al.[23] In contrast, Meng et al., in their study, found a lower mean UA level in patients with MDD.[24] However, the mean serum UA level of MDD patients with higher MDQ scores was not significantly higher than that of the MDD patients with lower MDQ scores. This perhaps can be because of the lower number of patients who finally crossed the MDQ

threshold (≥7) for being considered positive in bipolarity screening. It is to be noted that Teixeira et al. found no significant difference in UA levels between patients of MDD and BD in their study.[25] Interestingly, a statistically significant positive correlation was found between the serum UA levels and MDQ scores of MDD patients but not with their MADRS scores. We recommend more studies exploring UA levels in MDD and BD with higher sample sizes along with the usage of other predictive scales.

Limitations of the study

The study is limited by a smaller sample size and shorter study duration. The number of patients crossing the MDQ threshold for consideration for positivity in bipolarity screening is too low to draw any statistically significant association with serum UA levels. Hence, a larger study conducted over a longer study duration is needed to draw statistically significant conclusions from the measured parameters.

CONCLUSION

BD is one of the most studied psychiatric disorders with serum UA level having some role in its occurrence and development. Serum UA level was seen to be significantly higher among patients with MDD as compared to comparable healthy individuals. Owing to the small sample size, no statistical significance was found between the MDD group with a high chance of bipolarity versus those with a low chance of bipolarity with respect to their mean serum UA levels. Interestingly, a positive correlation was seen between MDQ scores and serum UA levels in MDD group but not with MADRS scores. Hence, a larger study is needed to conclusively prove/negate the predictive role of serum UA levels for BDs.

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SM- Definition of intellectual content, literature survey, prepared the first draft of the manuscript, coordination and manuscript revision, preparation of figures, submission of the article; **RA-** Collection of cases, coordination, and manuscript revision; **MM-** Manuscript preparation, coordination, and manuscript revision; **AC-** Collection of cases and manuscript preparation

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