Uric acid levels in psychiatric population

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Abstract-
Background: **Uric Acid (UA) is an end product of purine metabolism which is transported via blood and is primarily excreted through kidneys. Elevated serum UA levels are found to be closely associated with agitation, not only present in healthy subjects but is also found in individuals suffering from organic or functional psychiatric illnesses in the form of aggression.** ***Aim and Objective:*** **Assessment and comparison of serum UA levels between patients with agitated mania and agitated non-affective psychotic disorders and correlation of serum UA levels with severity of mania and non-affective psychosis.**
Material and Methods: **A cross-sectional study was conducted that compared serum UA levels in 100 in-patients (50 in each group) aged 18 years and above, of either sex, with International Classification of Mental and Behavioral Disorders-10th Edition Diagnostic Criteria for Research (ICD-10 DCR) diagnosis of mania and non-affective psychotic disorders, admitted in a state of acute agitation. Agitated Behavior Scale (ABS), Young Mania Rating Scale (YMRS), and Brief Psychiatric Rating Scale (BPRS) were applied for the assessment of the severity of agitation, mania, and psychosis respectively. Strength of association was obtained using fisher's exact test and unpaired-t-test. Severity scores obtained were correlated with serum UA levels using Pearson's correlation coefficient.**
Results: **UA levels were found to be significantly higher in individuals suffering from mania than those with non- affective psychosis ($p = 0.04$). Similarly, a significant positive correlation was found between UA levels and YMRS scores ($r = 0.34$) ($p = 0.01$).**
Conclusion: **UA level is found to be significantly higher in individuals with mania and correlates significantly positively with symptom severity.**

Keywords: Uric acid, agitation, bipolar disorder, mania, non-affective psychosis

INTRODUCTION:

Uric Acid (UA) is an end product of purine metabolism which is transported via blood and is primarily excreted through kidneys. Elevated serum UA levels are found to be closely associated with agitation, which can manifest in the form of aggression (verbal or physical), impulsivity, disinhibition, and thrill-seeking behavior. This association of UA with agitation is not only present in healthy subjects but is also found in individuals suffering from organic or functional psychiatric illnesses [1].
Lorenzi *et al*. [2] conducted a study on non-clinical community samples and found UA levels significantly correlate with disinhibition. Sutin *et al*. [3] in their longitudinal study found that hyperuricemia was associated with increased impulsivity in humans and increased novelty- seeking behavior in genetically modified mice with disrupted urate oxidase gene. Mrug and Mrug [4] were the first to conduct a study on adolescents with bipolar disorder and found that increased uricosuria predicted future aggression episodes. A study by Nurmedov *et al.* [5] on individuals with substance use disorder found serum UA levels and impulsivity scores to be significantly higher in these individuals when compared to the healthy controls, however, when a correlation was attempted to find an association between UA and impulsivity, a significant negative correlation was found. Chatterjee *et al*. [6] conducted a study that compared serum UA levels in individuals with first-episode mania with healthy controls and correlated serum levels with impulsivity scores. Increased serum UA levels were found in manic individuals which correlated well with impulsivity. A variety of hypotheses have been put forth regarding the basis of the underlying patho- physiology of psychiatric illnesses. Purinergic system dysfunction and impairment in antioxidant defense mechanisms are a few of them [7-8]. An underlying purinergic dysfunction as patho- physiology was put forward by Kraepelin in 1921 when he found an increased risk of the development of gout in individuals with bipolar disorder [9]. Later studies contributed to this finding by providing preliminary evidence for the same in the form of purinergic modulators such as allopurinol, having a therapeutic benefit in bipolar disorder patients when used adjunctively with lithium [10]. Likewise, the use of purinergic modulators as an adjunct to haloperidol has been highlighted to have a therapeutic benefit in the treatment of chronic schizophrenia. However, mixed evidence exists regarding UA levels in schizophrenia, with some studies suggesting it is raised in schizophrenic patients whereas some suggesting otherwise[7, 11]. A mediation analysis to study the association between UA and mental illnesses (such as bipolar disorder, schizophrenia, and depression) revealed a significant positive correlation with bipolar disorder only [12].
There is a dearth of literature on the relationship between agitation, UA, and the aforementioned psychiatric illnesses. The current study has been taken up to assess serum UA levels in patients with agitated mania and to compare them with serum levels in agitated patients with non-affective psychotic disorders. Also, since contradictory evidence exists regarding the relationship between UA and Young Mania Rating Scale (YMRS) scores as a marker of symptom severity, this study aims to find the relation between the two.

Material and Methods

This study was a cross-sectional study. The sampling procedure used was purposive sampling method. The study included a total

of 100 agitated patients (50 in each group) diagnosed with mania or non-affective psychosis, as per the International Classification of Mental and Behavioral Disorders- 10th Edition Diagnostic Criteria for Research (ICD- 10 DCR) criteria [13]. The study sample comprised of in-patients who were admitted to a tertiary care hospital in North madurai at any point in time over the course of one year. The inclusion criterion was an ICD-10 DCR diagnosis of mania and non- affective psychosis (which includes acute and transient psychotic disorders, schizophrenia, persistent delusional disorders, induced delusional disorders, and unspecified non-organic psychosis) with or without previous episodes of mania and psychosis and those who scored greater than 21 on Agitated Behavior Scale (ABS) [14]. The diagnosis was made based on the clinical history and mental status examination by a senior consultant.

Exclusion criteria were agitation in bipolar patients presenting with a mixed episode, agitation due to any other psychiatric disorder like substance use disorder (other than tobacco use disorder) apart from those mentioned in the inclusion criteria, organic psychiatric illnesses, and patients with polyarthritis or diagnosed hyperuricemia. No screening tools were used to rule out other psychiatric disorders. Before commencement, ethical clearance was obtained from Institutional Ethics Committee. The relatives of patients who fulfilled the selection criteria were explained about the nature of the study and subsequently, voluntary written informed consent was obtained.
Admitted patients were first assessed for severity of agitation using ABS. Those who scored greater than 21 were included in the study and were further evaluated for symptoms of mania and psychosis. YMRS was applied to the mania group for assessment of the severity of manic symptoms, and Brief Psychiatric Rating Scale (BPRS) was applied to the non-affective psychosis group for the assessment of the severity of psychotic symptoms [15-16]. Subsequently, fasting blood samples were collected on the second day of admission and sent to the biochemistry laboratory for serum UA estimation, which was done via an enzymatic colorimetric test.

Statistical analysis
Data obtained was tabulated in Microsoft excel and subjected to appropriate statistical analyses. Descriptive statistics in the form of the socio- demographic profile were presented as percentages, mean and standard deviation. The strength of the association (p value) was calculated using Fisher's exact test for qualitative data and using the unpaired t-test and Analysis of Variance (ANOVA) for quantitative data. Pearson's correlation coefficient (r) was used to find the correlation between serum UA and other variables such as agitation, mania symptom severity, and psychotic symptom severity. All tests were two-tailed, with a p value <0.05 considered to be significant.

Results
A total of 100 subjects were included in this study out of which 50 individuals belonged to the mania group and 50 individuals belonged to the non- affective psychosis group. The mean age in the former was found to be 32.42 ± 12.47 years, and in the latter was found to be 33.3 ± 9.17 years. Under the mania group, males formed the majority of the population, whereas, under the non-affective psychosis group, females had a slightly higher representation. As per other socio-demographic data, there was no significant difference between the two groups (Table 1).
When mean serum UA levels were compared, significantly higher levels were found in the mania group (5.64 ± 1.60 mg/dL) than the non- affective psychosis group (4.99 ± 1.49 mg/dL) ($p= 0.04$) (Table 2).
Our results showed that the study sample as a whole, irrespective of the diagnosis, showed a moderate positive correlation between UA levels and agitation. This result was found to be statistically significant ($r = 0.31$, $p = <0.001$). However, when correlation was attempted individually in the two groups, a weak positive correlation was found between UA levels and agitation in mania ($r = 0.22$, $p = 0.13$) as well as non-affective psychosis, however, the statistical significance existed only for the latter ($r = 0.29$, $p = 0.04$). Under the mania group, serum UA levels were seen to have a weak positive correlation with manic symptom severity, which was statistically significant ($r = 0.34$, $p = 0.01$). However, when correlated with psychotic symptom severity, a very weak positive correlation was found which was not statistically significant ($r = 0.18$, $p = 0.20$) (Table 3).

Table 1: Socio-demographic profile of the study sample

Variables	Subcategories	Mania (n = 50)	Non-affective Psychosis (n = 50)	p
Age (Mean ± S.D)		32.42 ± 12.47 years	33.3 ± 9.17 years	0.69
Sex	Male	34 (68%)	24 (48%)	0.07
	Female	16 (32%)	26 (52%)	
BMI (Mean ± S.D)		22.93 ± 3.76 kg/m^2	24.04 ± 3.57 kg/m^2	0.13
Religion	Hindus	41 (82%)	41 (82%)	1.20
	Muslims	9 (18%)	9 (18%)	
Domicile	Rural	22 (44%)	18 (36%)	0.54
	Urban	28 (56%)	32 (64%)	

Table 2: Comparison of mean serum uric acid levels among maniaandnon-affective psychotic disorders

Sample (n = 100)	Serum UA levels Mean ± S.D (mg/dl)	p
Mania	5.64 ± 1.60	**0.04***
Non-affective psychosis	4.99 ± 1.49	

**Significant, P<0.05*

Table 3: Correlation between uric acid levels and Agitated Behavior Scale (ABS), Young Mania Rating Scale (YMRS) and Brief Psychiatric Rating Scale (BPRS) scores

Variables	Diagnosis	Pearson's correlation (r)	p
UA and ABS	Mania	0.22	0.13
	Non-affective psychosis	0.29	**0.04***
	Total sample	0.31	**<0.001***
UA and YMRS	Mania	0.34	**0.01***
UA and BPRS	Non-affective psychosis	0.18	0.20

**Significant, P<0.05*

Discussion

Our study revealed that among the two groups, serum UA levels were significantly higher in the mania group than the non-affective psychosis group. Our finding is supported by the suggested hypothesis underlying these conditions and available literature. Over the years, from the studies conducted, a causal association has been proposed which is increased metabolism of purines and an altered adenosinergic activity ultimately resulting in bipolar disorder [17-18]. For psychotic disorders such as schizophrenia, a dysfunctional purinergic system creates a hypo-functioning glutamine and a hyper-functioning dopamine neurotransmission resulting in neuroinflammation which increases susceptibility to schizophrenia [19-20]. Studies supporting this hypothesis and thus highlighting our results have been conducted. A 1.14-fold higher risk of gout was found for bipolar patients as compared to healthy controls in a study [21]. Similar results were reported by another study that found a significant association of UA levels with bipolar (r = 0.76, p = 0.02) but not with schizophrenia spectrum disorders (r = 0.35, p = 0.22) and other mental illnesses [12].

Agitation in the overall sample (irrespective of the diagnosis) had a statistically significant positive correlation with UA levels, which meant that individuals with more severe forms of agitation had higher serum UA levels. A link between UA and agitation was first put forward by Lesch and Nyhan [22] who published a case report about a rare familial disorder of UA metabolism (later termed as Lesch-Nyhan syndrome) in which the affected children were noted to have hyper- uricemia and aggressive behavior in the form of self-mutilation. A link between the UA and agitation was thus found and over the course of years, with further studies

on both animal models and humans, the association was established [2-4]. A study conducted on African-American adolescents diagnosed with bipolar disorder found higher rates of aggression correlated with uricosuria ($r = 0.28$, $p = 0.01$) [4]. Similarly, a study in adult patients with bipolar disorder found UA to correlate with impulsivity ($r = 0.60$, $p<0.01$) [6]. However, another study that attempted to find a correlation between the two in substance use disorder patients revealed contradictory evidence [5]. Agitation in an individual, in general, can have multiple etiologies. Dysfunctions of neuro- transmitter systems such as dopamine, serotonin, GABA, and noradrenaline have been stated to be a few of the likely causes. Impulsivity, a form of agitation, as per the existing literature has been linked to impaired glutamate transmission and increased dopamine transmission. As mentioned earlier, in the adenosine hypothesis of schizo- phrenia, similar alterations in neurotransmitter systems were noted there as well [23]. The finding of our study agrees with the available literature. The individual analysis resulted in a positive correlation between UA levels and both agitated mania and agitated non-affective psychotic disorder with only the latter being statistically significant.

When serum UA levels were correlated to YMRS in the mania group, a positive correlation was found which was statistically significant, which meant that individuals with more severe mania had higher UA levels. Multiple studies have attempted to find a correlation between serum uric acid levels and YMRS scores. Salvadore *et al.* [24] found a negative correlation between the two which wasn't statistically significant ($r = -0.20$, $p = 0.39$). Gultekin *et al*. [25] found no correlation with the severity of symptoms; however, correlation with clinical improvement was noted, that is fall in UA levels correlated with fall in YMRS scores after a week of treatment. Another study by Chatterjee *et al*. [6] on bipolar subjects found no significant association ($r = 0.05$, $p = 0.80$). Our study hence adds to the literature by suggesting UA to be a probable marker of symptom severity being higher in those with severe mania than those with lesser severe forms of mania.

When correlated with BPRS scores, our study revealed a very weak positive correlation between serum UA levels and psychotic symptom severity in the non-affective psychosis group which was not found to have any statistical significance. Previous studies that have compared serum uric acid levels among different psychiatric illnesses have used Positive and Negative Syndrome Scale (PANSS) scores for the assessment of psychotic symptoms in schizophrenia. No known literature is available that has attempted to correlate UA with BPRS scores to assess psychotic symptom severity. A study by Hirota and Kishi [26] found allopurinol to be superior over placebo, by causing a significant reduction in total scores, positive symptom scores and general scores on PANSS. Our study included individuals with both acute as well as chronic psychosis and we used BPRS to assess symptom severity. A very weak positive correlation was found which was not statistically significant.

Limitations

The inclusion of healthy controls as a third arm in our study would have helped us understand the association of UA and agitation better. A bigger sample size would have helped obtain results that would have been more generalizable. Our study included individuals with a long-standing course of illness who were likely to be on multiple psychotropics, the effect of which on UA was not considered. For example, individuals on lithium (uricosuric agent) at the time of admission would have had lesser than expected serum levels. Also, the influence of drugs for illnesses such as hypertension, diabetes and other medical co- morbidities that are likely to influence serum UA levels was not taken into account.

Our study showed significantly higher serum UA levels in individuals with mania and a positive correlation between agitation and serum UA levels in the study sample as a whole, irrespective of the diagnosis. A statistically significant correlation between serum UA levels and agitation was found in the non-affective psychosis group. UA levels correlated significantly positively with the severity of manic symptoms as measured by YMRS in the mania group. Our study hence reconfirms the possible link between uric acid and agitation. It adds to the evidence of its close association with psychiatric illnesses, more so with bipolar disorder than non-affective psychosis.

Conclusion

Our study could find the association between uric acid, agitation and manic excitement. With further studies on uric acid in mania and more evidence, uric acid could become a biomarker to assess the severity of manic symptoms.

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