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Original Research Article

Serum uric acid as biomarker for mania: An exploratory prospective study

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ABSTRACT

Bipolar Disorder is a major mental illness characterized by episodic occurrence of mood symptoms which can be of mania, depression or a mixed episode. The role of Uric Acid in the etiopathogenesis of episodic mental illnesses might be considered recognized long back in 19th century. Lithium was used as treatment for gouty arthritis and that in some cases helped to control mental illnesses. Multiple role of uric acid in the Central Nervous System have been recognized now. In the present study 30 patients in manic episodes were included and their serum Uric Acid level was compared to age and sex matched healthy controls twice at the interval of three weeks. It was found that Uric Acid level of cases was significantly higher than in controls before the initiation of treatment. Uric Acid level of manic group showed a significant decline after three weeks of treatment initiation. There was no significant change in Uric Acid level of control group after three weeks.

Conclusion: Serum Uric Acid levels are elevated during manic phase of Bipolar Disorder and decreases after initiation of treatment. There may be more research to find whether uric acid can be considered a biomarker for Bipolar illnesses and also an indicator for treatment response.

1. Introduction

Bipolar Disorder is a severe mental illness causing marked disability due to its early age of onset, severity and recurrence. It impacts the main economically productive years of life. Moreover in young it may impact someone's achievement negatively. Increased life expectancy has further increased the burden of the disease. The Global Burden of Disease study 2013 has found that 48.8 million people around the world suffer from it. It is responsible for 9.9 million DALYs in 2013 and 1.3% of total YLDs.[1] Bipolar disorder resulted in 8·50 million (95% UI 5·20–13·0) global DALYs in 2019, equivalent to 0·3% (0·2–0·5) of DALYs. Bipolar disorder contributed to 6·8% (4·9–9·1) of DALYs for the aggregate of mental disorders.[2]

Bipolar disorder is known for its episodic nature. In Bipolar Disorder the mood swings from the euthymic state to a state of depressed mood, manic state or a mixed state. Manic episodes are characterized by elevated mood of varying intensity or irritability with increase in physical and mental activities. Depending upon the severity the patient in manic episode can be in state of hypomania, mania without psychotic symptoms and mania with psychotic symptoms.

Uric Acid in humans is formed by the catabolism of purine nucleosides. It is a water soluble compound and excreted largely by the renal system. For a very long time uric acid was mainly known for its role in the gouty arthritis and kidney stones but now many of its role have been identified even in the Central Nervous System (CNS).[3] It is produced in CNS by adenosine and its precursors can enter the brain. It has been proposed that uric acid formed by increased adenosine degradation and associated

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decreased adenosinergic transmission in CNS plays a role in the development of symptoms of mania. Uric acid controls sleep, motor activity, appetite, cognition, memory and social interaction. Adenosine agonists have shown sedative anticonvulsant, anti aggressive and antipsychotic effects, where as its antagonists such as caffeine increases irritability, anxiety and insomnia[4]. Uric acid has antioxidant properties which prevents oxidative damage to neurons.[3] It also stimulates expression of glutamate transporter in astroglia which protects neurons from glutamate induced toxicity. It also confers neuronal protection via stimulation of astroglia.[5] However at higher levels which varies from individual to individual it forms monosodium urate crystals which induces inflammatory response and causes damage to neurons in the CNS.[5]

These findings have increased the interest in the role of adenosinergic neurotransmission, uric acid levels and possible role of drugs acting on purinergic systems in Bipolar Disorders.[4] Serum uric acid estimation is a simple laboratory investigation and has the potential of being used as a biomarker for Bipolar Disorder.

2. Materials and Methods

The present study is a prospective study done at LGB Regional Institution of Mental Health, Tezpur Assam, where the serum uric acid level of manic patients was compared with healthy controls before and three weeks after the initiation of treatment.

During the study period of one year, 30 adult patients in mania admitted in LGBRIMH, not taking any medication for last one month were included in the study. Patients who had any other psychiatric co-morbidity were excluded in the study. Age and sex matched healthy first degree relatives of patients served as control group and were selected purposively. Conditions effecting purine metabolism and serum uric acid levels were ruled out in both case and control groups with help of clinical history, physical examination and laboratory investigations. Conditions which lead to elevated uric acid levels are purine rich diet, diabetes mellitus, obesity, hypertension, cardiovascular disease, renal diseases, liver diseases, endocrine disorders, alcohol abuse, caffeine intake, strenuous exercise, cancer or chronic inflammatory diseases and drug that effect purine metabolism and uric acid excretion.

Scientific and ethical clearance was obtained for the study. Informed consent was obtained from the legally available representatives of patients and from the controls. Case group comprises of patients in current episode mania diagnosed according to ICD-10, and other psychiatric co-morbidities were ruled out using MINI 6.0.0. Young Mania Rating Scale (YMRS) was used to assess the manic symptoms at intiation of treatment and at end of 3 weeks.

A detailed medical, surgical and drug history of the cases was obtained, a thorough physical examination was done and relevant investigations which included the total blood count, random blood sugar estimation, kidney, liver and thyroid function tests were done, lipid profile and serum sodium and potassium levels of the patients was obtained, markers of inflammation such as ESR and CRP were also done to make sure that they fit well in the study criteria. Blood samples for uric acid estimation were obtained after eight hours of fasting. Three weeks after the initiation of treatment second blood sample for serum uric acid level estimation was obtained. Patient who received Electro Convulsive Therapy were excluded from the study.

Control group comprised of age and sex matched first degree relatives of the cases were also administered MINI 6.0.0 to screen for any psychiatric condition and clinical interview, physical examination and laboratory investigations were done to rule out presence of any condition which would affect the serum uric acid levels. Blood sample for uric acid was collected after 8 hours of fasting twice at a time interval of 3 weeks.

The blood samples were processed and uric acid level measurement was done by uricase method. Data was analyzed using SPSS version 21. Paired t test was applied to compare the change in serum uric acid level over the period of three weeks for both groups. Wilcoxan signed rank test was used to compare the means of serum uric acid levels in the groups.

3. Results

A total of 60 participants were included in the study comprising of 30 cases who were in manic episode at the time of admission and 30 controls who were healthy first degree relative of the cases. Both groups had 21 males and 9 females each (Table 1). The mean age of cases was 33.17 years and that of control group was 32.27 and the difference between them was not significant (p=0.743). The mean YMRS score was 38.87+/-5.99 and 19.9 +/-6.99 at initiation of treatment and end of 3 weeks. It reflected significant reduction of YMRS scores over 3 weeks' time with treatment.

Mean uric acid level of cases at the time of admission was 5.49 +/-1.22 mg/dl and after three weeks of admission it was 5.073+/-0.99 mg/dl and the decline in uric acid level was significant (p = 0.013).

In the control group the mean of uric acid level at first point of contact was 4.813+/-1.56 mg/dl and that after three weeks period was 4.86+/- 1.59 mg/dl, the change however was not found to be significant (p= 0.573).

Mean uric acid level of case group (5.49+/-1.22) at the time of admission was significantly higher than the uric acid level of control group at first point of contact (4.81+/-1.56) with p value of 0.02. After 3 weeks the mean of serum uric acid in case group (5.07+/-0.99) did not differ significantly from the mean serum uric acid level of control group(4.86+/-1.59) after 3weeks (p=0.129).

Table 1: Number and age- distribution of the participants

		Control	Case	Total
Sex	Male	21	21	42
	Female	9	9	18
Total		30	30	60

Table 2: Comparison of serum uric acid level between cases and controls:

	Group	N	Mean	Std. Deviation	Std. Error Mean	Mean Rank	Sum of Ranks	p value
Uric acid level at time of admission	Control	30	4.813	1.5627	.2853	25.25	757.50	
	Case	30	5.490	1.2237	.2234	35.75	1072.50	0.02
Uric acid level after three weeks	Control	30	4.860	1.5939	.2910	27.08	812.50	
	Case	30	5.073	.9917	.1811	33.92	1017.50	0.129

4. Discussion

A significant (p=0.013) decline in uric acid levels of case group was seen after three weeks of their admission and initiation of treatment (5.49+/- 1.2 vs 5.07+/-0.99). Gultekin et al. 2014 also found a significant change in uric acid level in patient in mania after a period of three weeks of initiation of treatment (6.06+/- 1.48 vs 5.17+/-1.15, p= 0.015).[6] This was related with the clinical response to medications of all classes.

There was no significant change in the mean uric acid level of controls over the period of three weeks (4.813+/- 1.36 to 4.860 +/-1.59, p= 0.573). The result in the present study has shown that fluctuation in uric acid level in healthy individual is insignificant after a period of 3 weeks and this is in expected line.[7]

The mean value of serum uric acid of cases was significantly higher than that of controls at the time of admission (5.49 +/- 1.2 vs 4.813+/- 1.56, p=0.02). But after 3 weeks there was no significant difference in serum uric acid levels of case and control groups (5.073+/- 0.99 vs 4.86+/- 1.59 p=0.129). Albert et al in 2015 also studied uric acid level in manic patients in comparison to controls.[8] They also found significantly higher uric acid level in comparison to controls (5.06+/-1.4 vs 4.17+/- 1.05, p <0.01), but their control group comprised of patients suffering from schizophrenia, obsessive compulsive disorder and major depressive disorder which can confound the results.[8] Salvadore et al., in 2010 found uric acid level to be significantly higher in manic patient in comparison to healthy controls (4.85 +/-1.6 vs 2.96+/- 0.63 with p<0.001).[9] Thus increased value of Serum Uric acid may be a potential candidate for state marker for bipolar illness particularly in manic state.

After three weeks of initiation of treatment no significant difference was found in the uric acid levels of case and control group, which implies that with treatment the uric acid level decreases. Kesebir et al, in 2013 have found that the uric acid level of euthymic bipolar patients was also elevated in comparison to healthy controls.[10]

Bartoli et al, in their metanalysis in 2016 also found elevated uric acid level in bipolar patient in comparison to healthy controls.[11] In the present study bipolar patient with metabolic syndrome were not included but prevalence of metabolic syndrome in patients with bipolar disorder is higher than its prevalence in community.[12] Elevated uric acid level is also seen in metabolic syndrome which can confound the results. Purinergic signalling and its interaction with other neurotransmitter and second messenger systems play a role in development of mood symptoms of Bipolar Disorder by its effect on synapse formation, neuronal plasticity and glial immune functions.[13–16] Uric Acid, the end product of purine degradation is not only an anti-oxidant but also a pro inflammatory agent that may contribute to the pathogenesis of Bipolar Disorder.[17] Allopurinol increases Adenosine and lowers uric acid formation is found to be efficacious in mania too.[18] So we may conclude that Srum uric acid may be a potential state biomarker for bipolar illness, more particularly in manic state and a decline in Serum uric acid is associated with improved clinical status of the subjects. Thus it may also a candidate to demonstrate clinical efficacy of treatment.

These findings are from a relatively small sample size and thus should be interpreted with caution. A comparative interventional study with different antimanic agents may give us more information on the utility of serum Uric acid as a biomarker.

5. Conflict of Interest

The author declares no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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None.

References

1. Ferrari AJ, Stockings E, Khoo JP, Erskine HE, Degenhardt L, Vos T, et al. The prevalence and burden of bipolar disorder: findings from the Global Burden of Disease Study. *Bipolar Disord*. 2013;18(5):440–50.
2. Bipolar Disorder-Level 3 Cause. The Lancet. Available from: http://www.healthdata.org/results/gbd_summaries/2019/bipolar-disorder-level-3-cause.accessedon17.11.2021.
3. Tovchiga OV, Shtrygol SY. Uric acid and central nervous system functioning (a literature review). *Biol Bull Rev*. 2014;4(3):210–21.
4. Machado-Vieira R. Purinergic system in the treatment of bipolar disorder: uric acid levels as a screening test in mania. *J Clin Psychopharmacol*. 2012;32(5):735–6. doi:10.1097/JCP.0b013e318268391d.
5. Drulovic J, Dujmovic I, Stojsavljevic N, Mesaros S, Andjelkovic S, Miljkovic D, et al. Uric acid levels in sera from patients with multiple sclerosis. *J Neurol*. 2001;248(2):121–6.
6. Gultekin BK, Kesebir S, Kabak SG, Ergun FF, Yaylaci ET. Are uric acid levels different from healthy subjects in bipolar affective disorder and schizophrenia?: relationship between clinical improvement and episode severity in male patients. *Noro Psikiyatri Arsivi*. 2014;51(3):229–32. doi:10.4274/npa.y6827.
7. So A, Smedt D, Revaz T, Tschopp S, J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther*. 2007;9(2):1–6. doi:10.1186/ar2143.
8. Albert U, Cori DD, Aguglia A, Barbaro F, Bogetto F, Maina G, et al. Increased uric acid levels in bipolar disorder subjects during different phases of illness. *J Affect Disord*. 2015;173:170–5. doi:10.1016/j.jad.2014.11.005.
9. Salvadore G, Viale CI, Luckenbaugh DA, Zanatto VC, Portela LV, Souza DO, et al. Increased uric acid levels in drug-naïve subjects with bipolar disorder during a first manic episode. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(6):819–21. doi:10.1016/j.pnpbp.2010.02.027.
10. Kesebir S, Süner O, Yaylaci ET, Bayrak A, Turan C. Increased uric acid levels in bipolar disorder: is it trait or state. *J Biol Regul Homeost Agents*. 2013;27(4):981–8.
11. Bartoli F, Crocamo C, Mazza MG, Clerici M, Carra G. Uric acid levels in subjects with bipolar disorder: a comparative meta-analysis. *J Psychiatr Res*. 2016;81:133–9. doi:10.1016/j.jpsychires.2016.07.007.
12. Chen J, Chen H, Feng J, Zhang L, Li J, Li R, et al. Association between hyperuricemia and metabolic syndrome in patients suffering from bipolar disorder. *BMC Psychiatry*. 2018;18(1):1–7.
13. Adinolfi E, Giuliani AL, Marchi ED, Pegoraro E, Orioli A, Virgilio FD, et al. The P2X7 receptor: a main player in inflammation. *Biochem Pharmacol*. 2018;151:234–44. doi:10.1016/j.bcp.2017.12.021.
14. Machado-Vieira R, Lara DR, Souza DO, Kapczinski F. Purinergic dysfunction in mania: an integrative model. *Med Hypotheses*. 2002;58(4):297–304. doi:10.1054/mehy.2001.1543.
15. Ortiz R, Ulrich H, Zarate CA, Machado-Vieira R. Purinergic system dysfunction in mood disorders: a key target for developing improved therapeutics. *Prog Neuropsychopharmacol Biol Psychiatry*. 2015;57:117–31. doi:10.1016/j.pnpbp.2014.10.016.
16. Cheffer A, Castillo AR, Corrêa-Velloso J, Gonçalves MC, Naaldijk Y, Nascimento IC, et al. Purinergic system in psychiatric diseases. *Mol Psychiatry*. 2018;23(1):94–106. doi:10.1038/mp.2017.188.
17. Shi Y. Caught red-handed: uric acid is an agent of inflammation. *J Clin Investig*. 2010;120(6):1809–11. doi:10.1172/JCI43132.
18. Bartoli F, Crocamo C, Clerici M, Carra G. Allopurinol as add-on treatment for mania symptoms in bipolar disorder: systematic review and meta-analysis of randomised controlled trials. *Br J Psychiatry*. 2017;210(1):10–5. doi:10.1192/bjp.bp.115.180281.

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