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Metabolic Dysregulation in Psychotic Mania: Exploring the Role of Uric Acid as a Potential Biomarker

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Abstract

Background: Psychotic mania is a severe manifestation of bipolar disorder characterized by elevated mood, hyperactivity, and psychotic features. It often disrupts metabolic processes, putting patients at risk for metabolic syndrome and cardiovascular diseases.

Method: This study employed a prospective study design involving 30 patients with psychotic mania, 30 first-degree relatives, and 30 age- and sex-matched healthy controls. Serum uric acid levels and various metabolic parameters were analyzed concurrently to elucidate their potential interrelationship.

Results: Results: Serum uric acid levels showed no significant changes between baseline (mean ± SD: 5.84 ± 1.74 mg/dL) and follow-up (mean ± SD: 5.15 ± 1.63 mg/dL). However, notable increases were observed in triglycerides (from 125.73 ± 69.67 to 169.07 ± 72.46 mg/dL, $p = 0.010$), systolic blood pressure (from 116.80 ± 7.59 to 119.80 ± 6.99 mm Hg, $p < 0.001$), and body mass index (BMI) (from 20.90 ± 3.91 to 21.12 ± 3.91 kg/m², $p < 0.001$). Negative correlations emerged between changes in uric acid and select metabolic indicators, including triglycerides and low-density lipoprotein (LDL).

Conclusion: This study demonstrates the necessity for integrated care approaches that address both psychiatric symptoms and metabolic health in patients with psychotic mania, emphasizing the potential of uric acid as a marker of underlying metabolic dysfunction.

Background

Psychotic mania is a severe psychiatric condition, often characterized by intense mood elevation, hyperactivity, impulsiveness, and grandiosity, as well as psychotic features such as delusions and hallucinations (1). It represents one of the most acute manifestations of bipolar disorder, with the first episodes typically occurring in late adolescence or early adulthood (2). The prognosis for patients experiencing psychotic mania can be variable; while many achieve symptomatic relief through appropriate treatment, long-term outcomes remain concerning (3). Research indicates that individuals who have experienced manic episodes are at a heightened risk for recurrence, functional impairment, and comorbid medical conditions (1). Furthermore, recurrent manic episodes may contribute to cognitive deficits and decreased overall quality of life (4).

The impact of psychotic mania extends beyond psychological distress; it has profound effects on bodily functions and metabolic processes (5). Patients often exhibit alterations in appetite, weight, sleep, and energy levels alongside behavioral changes associated with mood states (6). These factors may predispose individuals to metabolic syndrome, a cluster of conditions that includes abdominal obesity, hypertension, dyslipidemia, and insulin resistance (7). Approximately 37% of individuals with bipolar disorder have been shown to have metabolic syndrome (8, 9), underscoring the complex interplay between mental health and physical well-being (10).

Significant metabolic changes are often observed during manic episodes, including dysregulation of glucose and lipid metabolism (11, 12). These alterations may manifest in laboratory investigations, prominently reflected in serum uric acid (UA) levels (13). Normal serum uric acid levels in adults typically fall within the range of 3.5 to 7.2 mg/dL; however, during manic episodes, elevated uric acid levels have been reported, pointing to potential purinergic dysregulation (14). Elevated UA levels may indicate an increase in purinergic turnover and decreased adenosinergic transmission, and their elevation is mainly associated with severe manic symptoms (15).

The implications of metabolic changes and increased uric acid levels can be significant for patients with psychotic mania. Elevated uric acid is associated with cardiovascular risks, insulin resistance, and worsening metabolic profiles, which can compound the clinical course of mood disorders (16, 17). The relationship between hyperuricemia and hypertension has been recognized, with research suggesting that uric acid may influence endothelial function and contribute to hypertension development (18). Additionally, obesity and dyslipidemia are frequently observed in this population and can further exacerbate the risk of metabolic syndrome and cardiovascular diseases (19).

Given this context, there is a pressing need to explore serum uric acid levels as both state and trait markers of psychotic mania. Understanding whether uric acid fluctuations correlate with acute manic symptoms or represent a consistent marker of bipolar disorder can inform diagnosis and treatment strategies. Additionally, the potential influence of metabolic profiles on uric acid levels

warrants investigation, as it may reveal underlying biological mechanisms that contribute to the progression of bipolar disorder and associated risk factors.

Aim and Objectives

This study aims to investigate the role of serum uric acid and metabolic profiles as potential biomarkers of illness state and trait in individuals with psychotic mania. Specifically, it examines their associations with clinical outcomes and psychopathological changes during illness.

The specific objectives of the study are:

1. To compare serum uric acid levels among patients with psychotic mania at baseline, their first-degree relatives, and healthy controls.
2. To compare metabolic profiles (including glucose, lipid parameters, and BMI) among the same three groups.
3. To evaluate changes in serum uric acid levels and metabolic parameters between the acute phase and clinical remission in patients with psychotic mania.
4. To assess correlations between changes in serum uric acid/metabolic parameters and changes in psychopathology during the transition from acute illness to remission.

Methodology

Study Design and Setting

This study was a prospective observational study to examine the changes in uric acid and metabolic parameters from baseline to clinical remission in patients with psychotic mania and explore their correlations with psychopathology. By evaluating and comparing metabolic parameters within these cohorts, the study seeks to elucidate the potential role of serum uric acid levels as state and trait markers in bipolar disorder, particularly in its acute manic phase.

The study is conducted at the Central Institute of Psychiatry (CIP) in Ranchi, India, at a premier postgraduate teaching hospital that offers extensive psychiatric evaluation and treatment services. The Institute serves as a tertiary care referral centre, catering to diverse populations from Jharkhand, Bihar, West Bengal, Odisha, Chhattisgarh, and neighbouring regions, including parts of northern India and select foreign countries. This setting provides an optimal environment for recruiting a representative sample relevant to the study's objectives.

Inclusion and Exclusion Criteria

Table 1 shows the Inclusion and exclusion criteria for each group.

The first group comprised thirty individuals aged 18 to 50, diagnosed with "Mania with Psychotic Symptoms" according to ICD-10 criteria. The second group included thirty unaffected first-degree relatives of the patients, allowing for the exploration of potential familial influences on uric acid levels and metabolic profiles. Lastly, the third group consisted of thirty matched healthy controls, selected to have comparable demographic characteristics (age and sex) to the patient group, ensuring a controlled comparison. This comprehensive sampling strategy aimed to provide valuable insights into the relationships between uric acid levels, metabolic parameters, and the associated conditions.

Data Collection Procedures

Data collection for the study commenced with the careful enrolment of eligible participants, who were introduced to a structured assessment to gather essential personal and clinical information, including socio-demographic and clinical details such as age, sex, education, occupation, and socioeconomic status, duration of the illness, past psychiatric events, family history of mood disorders, and previous treatments. The Young Mania Rating Scale (YMRS) was used to assess the severity of manic symptoms, while the Brief Psychiatric Rating Scale (BPRS) evaluated a broader range of psychiatric conditions. The Clinical Global Impression-Severity Scale (CGI-S) objectively measures illness severity relative to peers with similar diagnoses.

Following this, a comprehensive health assessment was conducted, which included administering the General Health Questionnaire (GHQ-12) to evaluate psychiatric distress among first-degree relatives and healthy controls. Clinical examinations recorded vital metabolic indicators such as blood pressure, waist circumference, and body mass index (BMI). Blood samples were subsequently collected via venipuncture after an overnight fast, allowing for the analysis of serum uric acid levels, fasting blood glucose, and a lipid panel. To ensure confidentiality, unique identification codes were assigned to each participant.

Sample Size Calculation and Sample Technique

A purposive sampling technique is employed to recruit participants for this study. This non-probability sampling method allows for intentionally selecting individuals who meet specific criteria pertinent to the research aims (20). Participants are categorised into three distinct groups: patients with psychotic mania, their first-degree relatives, and age- and sex-matched healthy controls. This approach facilitates the collection of relevant data from individuals who can provide valuable insights into investigating serum uric acid levels and metabolic profiles.

The sample size for this study was determined through power analysis, guided by existing literature that highlights significant differences in uric acid levels and metabolic parameters between individuals with bipolar disorder and healthy controls. An estimated effect size of 0.5 indicated that a minimum of 30 participants per group would achieve sufficient power (80%) to detect statistical differences at a significance level 0.05. Therefore, 90 participants were recruited to ensure adequate representation across three specific groups.

Study Instrument

A self-report instrument was utilized as a measurement tool to investigate the extent of the research phenomena. It comprises two sections: (1) Demographic data, (2) Young Mania Rating Scale, (3) Brief Psychiatric Rating Scale (BPRS), (4) Clinical Global Impression- Severity Scale, and (5) General Health Questionnaire.

Socio-demographic and Clinical Data Sheet

It includes information like age, gender, occupation, marital status, family type, and habitat. The clinical data sheet provides information such as duration of illness, past medical history, and treatment history.

Young Mania Rating Scale

The Young Mania Rating Scale (YMRS) is a crucial tool developed by Young and Biggs in 1978 to assess the severity of manic symptoms in individuals with bipolar disorder. Comprising 11 items, the scale employs a dual scoring system, with some items rated from 0 to 4 and others from 0 to 8, allowing for a comprehensive evaluation of manic behaviors and emotions. The total score ranges from 0 to 59, where higher scores indicate greater severity of mania. Known for its strong psychometric properties, the YMRS has demonstrated high reliability and validity, with excellent inter-rater consistency and strong correlations with other measures of mania (21, 22).

Brief Psychiatric Rating Scale (BPRS)

The Brief Psychiatric Rating Scale (BPRS), developed by Overall and Gorham in 1962, is a crucial tool for assessing psychiatric symptoms in patients with severe mental illnesses, such as schizophrenia and mood disorders (23). Comprising 18 items, it evaluates a broad spectrum of symptoms, including positive, negative, affective, and cognitive disturbances. Clinicians rate each symptom on a scale from 1 to 7, resulting in a total score ranging from 18 to 126. A higher score indicates greater psychiatric severity, reflecting a more profound level of distress or dysfunction in the patient. The BPRS exhibits strong validity and reliability, making it a trusted instrument in clinical and research settings (23).

Clinical Global Impression- Severity Scale

The Clinical Global Impression Severity of Illness (CGI-S) is a crucial tool for assessing the severity of mental health conditions, utilizing a 7-point ordinal scale. Scores range from 1, indicating "Normal, not at all ill," to 7, reflective of an "Extremely ill" patient. Each increment captures varying levels of impairment, guiding clinicians in understanding a patient's overall functioning and symptomatology. High CGI-S scores highlight critical levels of psychiatric illness, signaling the need for comprehensive evaluation and potential treatment adjustments (24). The CGI-S boasts strong construct and concurrent validity, correlating well with

established psychiatric assessments. Its high inter-rater reliability ensures consistent scoring across clinicians, while test-retest stability enhances its robustness (25). Despite being a single-item measure, the CGI-S maintains internal consistency alongside multi-item assessments. Ultimately, this instrument is vital in formulating effective treatment plans and improving patient outcomes (26). The tool is available at no charge on the web.

General Health Questionnaire

The General Health Questionnaire (GHQ-12) is a widely used self-report tool designed to assess psychological well-being and detect psychiatric disorders across various populations (27). It comprises 12 items that evaluate mental health through dimensions such as anxiety, depression, social dysfunction, and loss of confidence. Respondents rate their experiences over the past week using a 4-point Likert scale, where options include "better than usual" (0 points), "same as usual" (0 points), "worse than usual" (1 point), and "much worse than usual" (1 point). This scoring format allows for a total score ranging from 0 to 12, with higher scores indicating more severe psychological distress. The tool's reliability and validity have been established in multiple cultural contexts, making it adaptable for diverse demographic groups. Meta-analyses have shown high internal consistency, with Cronbach's alpha coefficients typically ranging from 0.70 to 0.93 (27). The tool is available for free on the web.

Clinical Examination and Laboratory Parameters

The clinical examination thoroughly assessed key metabolic indicators, including waist circumference, blood pressure, and body mass index (BMI). These components are critical for evaluating the metabolic profile of patients, especially given the known associations between psychotic mania and metabolic disturbances. Waist circumference was recorded to evaluate central obesity, a key factor in metabolic syndrome, while blood pressure measurements were taken to screen for hypertension, a common comorbidity in this population. BMI was calculated using standardized protocols to provide insights into overall body weight relative to height.

For the laboratory component of the study, various metabolic markers were analyzed, focusing primarily on serum uric acid levels, fasting blood sugar, and lipid profile metrics, including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and very-low-density lipoprotein (VLDL). Serum uric acid levels were measured using a standard biochemistry kit, employing the uricase method for direct measurement, thereby ensuring accuracy and reliability. Additionally, the OLYMPUS U 680 biochemistry analyzer was utilized for the assessment of fasting lipid profile parameters and serum uric acid levels, facilitating the precise evaluation of metabolic abnormalities that may present in patients with psychotic mania. These laboratory analyses were crucial for establishing the relationships between metabolic changes and psychiatric symptoms in the studied cohort.

Data Analysis

Data analysis from 90 participants in this study was conducted using SPSS version 25. Descriptive statistics summarized the demographic and clinical characteristics, providing insights into means and frequencies. To compare changes in metabolic parameters, paired sample t-tests were employed to assess differences between baseline and exit assessments within the patient group. Independent samples t-tests facilitated comparisons across the three groups: patients with psychotic mania, first-degree relatives, and healthy controls. Pearson's correlation coefficients were calculated to explore relationships between changes in serum uric acid levels, various metabolic indicators, and psychopathological dimensions. A significance level of $p < 0.05$ was established, with additional thresholds for stricter assessments. Effect sizes were calculated to highlight the magnitude of the results. Data cleaning ensured validity by addressing outliers and assumptions for normality. Ultimately, these analytical procedures aimed to elucidate the intricate interplay between metabolic health and psychotic mania, guiding clinical management and understanding.

Ethical statement

Ethical approval was granted by the research and ethics committee at the Central Institute of Psychiatry (CIP), Kanke, Ranchi, Jharkhand-834006, India, with Registration ECR/891Anst/MW2016. Before participation, each subject was thoroughly informed about the study's purpose, procedures, potential risks, and benefits, and written consent was obtained. Participants were assured that their identities would remain confidential, with all data anonymised and accessible only to authorised research personnel. They were informed of their right to withdraw from the study without repercussions, thereby reinforcing their autonomy.

Study Results

Table 1 and 2provides a detailed overview of the sociodemographic characteristics of three distinct groups: cases (individuals diagnosed with psychotic mania), first-degree relatives (FDRs) of the cases, and healthy controls, comprising a total of 90 participants. The mean age of the case and control groups is 25 years (± 7 years), while the FDR group has a higher mean age of 42 years (± 8 years), indicating significant age differences. The gender distribution shows a predominant male representation across all groups (90%). Employment status is relatively consistent, with approximately 70% of individuals employed in each group, indicating a similar socio-economic status. Notably, marital status reveals significant differences; 93.3% of the case group is married, compared to only 6.7% who are unmarried. Meanwhile, family type indicates a higher prevalence of joint families among the case and FDR groups, suggesting cultural influences on familial structures.

Table 3 outlines the clinical variables of the case group, revealing that most patients experienced illness durations between 1 and 3 months, with a mean duration of 63.50 (SD= 58.88) days. Notably, 76.7% (n=23) had no family history of mental illness, while all participants reported no prior treatment history—a significant proportion (33.3%, n=10) required approximately four weeks to achieve remission. The data indicates a pattern of an insidious onset, a continuous course, and deteriorating progress in the patients' illnesses.

Table 4 compares the uric acid and metabolic profiles of the case group between baseline and exit using a student's t-test. Serum uric acid levels showed no significant change, while there were significant increases in triglycerides ($t = 2.95$, $p = 0.010$*), systolic blood pressure ($t = 3.22$, $p < 0.001$), and diastolic blood pressure ($t = 3.12$, $p < 0.001$). Waist circumference showed no significant change ($t = 0.36$, $p = 0.730$), and weight differences were insignificant ($t = 1.89$, $p = 0.070$). Body mass index (BMI) results indicated a significant change ($t = 2.91$, $p = 0.010$), while high-density lipoprotein (HDL) levels significantly decreased ($t = 5.75$, $p < 0.001$). These results highlight the deterioration in several metabolic parameters over the study period, indicating potential health concerns in the case group.

Table 5 illustrates the correlations between changes in psychopathology, uric acid, and metabolic parameters from baseline to exit. Significant negative correlations were found between changes in uric acid and appearance (p=0.025) and content (p=0.049), as well as between content and triglycerides (p=0.036) and VLDL (p=0.034). Additionally, changes in speech correlated negatively with diastolic BP (p=0.027) and waist circumference (p=0.024), while disruptive behavior was negatively related to LDL (p=0.031) and CGIS SI to diastolic BP (p=0.001).

Table 6 presents the correlations among changes in uric acid and various metabolic parameters. Notably, a significant negative correlation was observed between changes in triglycerides (TG) and systolic blood pressure (SBP) ($p = 0.047$) and between SBP and very low-density lipoprotein (VLDL) ($p = 0.039$). Additionally, a significant correlation was found between changes in diastolic blood pressure (DBP) and low-density lipoprotein (LDL) levels ($p = 0.020$). This indicates essential interrelations between uric acid levels and metabolic health parameters.

Discussion

The findings of this study provide critical insights into the complex interplay between serum uric acid levels, metabolic changes, and the clinical manifestations of psychotic mania. First and foremost, the investigation revealed that while serum uric acid levels did not exhibit significant fluctuations between the baseline and exit assessments, notable changes in various metabolic parameters, including triglycerides, blood pressure, and body mass index (BMI), were observed. This aligns with previous research highlighting that manic episodes can profoundly affect metabolic processes, even in the absence of dramatic alterations in uric acid levels (28). For instance, the increase in triglyceride levels is particularly concerning, as elevated triglycerides are associated with an augmented risk of cardiovascular diseases, which are already prevalent in individuals with mood disorders (29). Furthermore, the rise in systolic and diastolic blood pressure during manic episodes serves as a potential indicator of increased cardiovascular risks in this population (30). These findings emphasize the need for a comprehensive approach to managing patients with psychotic mania, where not only mental health symptoms are addressed, but also their metabolic health is closely monitored.

Additionally, the relationship between serum uric acid levels and particular metabolic parameters emerged during our analysis, revealing a nuanced interaction that warrants further exploration. Although the overall serum uric acid levels among groups did not significantly differ, the study demonstrated significant correlations between uric acid and various metabolic indices. Negative correlations were identified between changes in uric acid levels and specific metabolic parameters, particularly triglycerides and low-density lipoprotein (LDL) levels. This suggests that as uric acid levels shifted, there were concurrent changes in metabolic health

metrics, highlighting the role of uric acid as a potential marker for underlying metabolic disturbances (31, 32). Moreover, while uric acid levels themselves did not act as a reliable predictor of psychopathological severity throughout the phases of manic episodes, they may still reflect systemic metabolic health, influencing the physiological state of the patients (33). By elucidating the relationship between uric acid and metabolic parameters, our study underscores the potential for utilizing uric acid as a biomarker, which may serve as an early warning signal for developing metabolic syndrome and support proactive health management.

The study illuminated significant correlations between changes in uric acid levels and various psychopathological dimensions. Specifically, certain behaviors associated with manic episodes, such as disruptive behavior and elevated mood, were related to variations in metabolic parameters (34). These associations suggest that fluctuations in psychopathology might reflect underlying metabolic changes, further complicating the clinical landscape of psychotic mania. Understanding these correlations could enhance the capacity of clinicians to anticipate health complications and tailor interventions, accordingly integrating physical health metrics into psychiatric assessments. The implications of this study extend beyond immediate clinical practices. The findings propose that uric acid may not merely be a transient marker during manic episodes but could play a more significant role as a potential biomarker of underlying metabolic dysfunction and psychopathological severity. Recognizing uric acid levels with metabolic health measures could provide clinicians with a more nuanced understanding of their patient's conditions, guiding treatment decisions that address psychiatric symptoms and metabolic health concerns (35, 36).

Furthermore, the significant insights gained regarding the familial relationships of first-degree relatives may reveal heritable patterns linked to both psychopathology and metabolic disturbances. The observation that first-degree relatives exhibited lower levels of psychiatric distress supports the notion that genetic and environmental factors influence the manifestation of both mood disorders and associated metabolic syndromes (37). This raises an important avenue for future research into the familial transmission of mood disorders, which could ultimately pave the way for preventative strategies and interventions in at-risk populations. Given the interplay between psychiatric and metabolic health highlighted by this study, there is a pressing need to consider metabolic monitoring as an integral component of the therapeutic approach for patients with psychotic mania (38). Screening for metabolic syndrome in this population could help identify those at greater risk for cardiovascular complications, allowing for earlier interventions that may bolster overall health outcomes (39).

Study Implication

The findings of this study emphasize the critical need for integrated care approaches in managing patients with psychotic mania by recognizing the intricate relationship between psychiatric symptoms and metabolic health. Clinicians should prioritize routine metabolic monitoring, including assessments of serum uric acid levels, triglycerides, blood pressure, and body mass index (BMI). These parameters can serve as important indicators of metabolic syndrome and potential cardiovascular risks, which are prevalent in this population. By incorporating these evaluations into standard psychiatric care, healthcare providers can develop personalized treatment strategies that focus on mood stabilization and address physical health concerns, potentially improving long-term outcomes and preventing future health complications for patients.

In addition, the study highlights the significant correlations between metabolic disturbances and changes in psychopathology, suggesting that fluctuations in uric acid levels and other metabolic markers may reflect underlying physiological changes associated with manic episodes. This understanding equips clinicians with valuable insights for more effective intervention planning. For instance, recognizing that behaviors such as irritability or elevated mood might be linked with shifts in metabolic health could guide monitoring strategies and treatment decisions. Active engagement with patients regarding their metabolic status could foster a collaborative treatment environment, empowering individuals to take part in managing their physical health alongside their psychiatric treatment.

Moreover, the familial relationships observed in the study suggest a need for preventive strategies targeting at-risk populations, particularly first-degree relatives of individuals with psychotic mania. Clinicians should consider conducting screenings for patients and their family members for metabolic and psychiatric health. This proactive approach could identify individuals at risk for developing similar conditions, facilitating early interventions that may mitigate the onset of both mood disorders and metabolic syndromes. Ultimately, recognizing the interconnectedness of psychiatric and metabolic health through ongoing assessment and intervention can enhance the overall quality of care, promote holistic wellness, and improve the quality of life for those affected by psychotic mania.

Study Limitations and Recommendations

This study is limited by its cross-sectional design, which restricts the ability to establish causal relationships between uric acid levels, metabolic disturbances, and psychopathology in psychotic mania. Additionally, the relatively small sample size and focus on a specific demographic may limit the generalizability of the findings to broader populations. Another limitation is the reliance on self-reported data and scales, which may introduce reporting bias. Future research should aim to conduct longitudinal studies to assess changes in uric acid and metabolic profiles over time, providing insights into their potential roles as predictive markers for psychiatric episodes. Including a more extensive and diverse sample population could enhance the applicability of the results. Furthermore, exploring the mechanisms underlying the relationship between metabolic and psychiatric health could lead to more targeted interventions in managing psychotic mania. Finally, further investigations into the familial implications and genetic predispositions associated with metabolic syndrome in psychotic disorders would be beneficial.

Conclusion

In conclusion, this study underscores the intricate relationship between serum uric acid levels, metabolic disturbances, and the clinical presentation of psychotic mania. While uric acid levels did not exhibit significant changes during the study, notable fluctuations in metabolic parameters were observed, highlighting the need for comprehensive metabolic monitoring in this population. The correlations found between psychopathological behaviors and metabolic health suggest that psychosomatic integration is essential for effective treatment strategies. Understanding these interconnections can enhance clinical practices, ultimately improving patient outcomes. Future research should aim to elucidate these relationships further and explore the underlying biological mechanisms at play. By prioritizing both psychiatric and metabolic health, clinicians can foster a holistic approach to managing psychotic mania.

Declarations

Ethical approval:

This study followed the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Institutional Ethics Committee of the Central Institute of Psychiatry (CIP), Kanke, India. The study was approved under the reference number (ECR/891/inst/JH/2016). Informed consent was obtained from all participants before their inclusion in the study, ensuring their voluntary participation, confidentiality, and the right to withdraw at any stage without repercussions.

Consent for Publication: Not applicable. However, consent for publication was obtained through ethics approval and consent to participate.

Competing Interest: None.

Data Availability Statement: The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Code availability: not applicable

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Author Contributions:

SQ, IA, RI, SH, and MQ designed the study and participated in data collection. MQ provided data analysis and statistical expertise. SH, IA, RI, and SQ prepared the initial manuscript draft and circulated it repeatedly among all authors for critical review. SH and SQ contributed to conceptual work, framework, draft writing, editing, and critical evaluation. All authors read and approved the final manuscript.

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Tables

Table-1: Socio-demographic Characteristics of Cases (N=30), their First Degree Relatives (FDR) and Normal Controls (N=30)							
Variable	**Category**	**Case n (%)**	**FDR n (%)**	**Control n (%)**	**χ^2 / Fisher's Exact**	**df**	***p*-value**
Sex	Male	27 (90.0)	27 (90.0)	27 (90.0)	0.000	2	1.000
	Female	3 (10.0)	3 (10.0)	3 (10.0)			
Religion	Hindu	26 (86.7)	26 (86.7)	26 (86.7)	0.000	2	1.000
	Other	4 (13.3)	4 (13.3)	4 (13.3)			
Occupation	Employed	21 (70.0)	22 (73.3)	20 (66.7)	0.317	2	1.000
	Unemployed	9 (30.0)	8 (26.7)	10 (33.3)			
Marital Status	Unmarried	15 (50.0)	2 (6.7)	17 (56.7)	18.8	2	0.000***
	Married	15 (50.0)	28 (93.3)	13 (43.3)			
Family Type	Nuclear	12 (40.0)	4 (13.3)	20 (66.7)	17.78	2	0.000***
	Joint	18 (60.0)	26 (86.7)	10 (33.3)			
Habitat	Rural	29 (96.7)	27 (90.0)	7 (23.3)	46.98	2	0.000***
	Urban	1 (3.3)	3 (10.0)	23 (76.7)			

Table 2. Comparison of Socio-Demographic Variables Between Case, First-Degree Relatives (FDR), and Control Groups							
Variable	**Case (Mean ± SD)**	**FDR (Mean ± SD)**	**Control (Mean ± SD)**	**F**	**df**	***p*-value**	**Post hoc Comparison**
Age (Years)	25 ± 7	42 ± 8	25 ± 7	51.2	2	0.000***	Case < FDR
Years of Education	8.17 ± 4.40	5.67 ± 4.64	11.53 ± 3.98	13.7	2	0.000***	Case < Control, Case > FDR
Family Income (Rs.)	10,350.00 ± 3535.90	11,616.67 ± 4298.52	15,466.67 ± 4904.14	11.6	2	0.000***	Case < FDR < Control
Note: ANOVA was used for comparison. ** $p < 0.001$.							

Table 3: Clinical Variables of The Case Group

Variable			
Duration of Illness in days	Mean 63.50		
	SD 58.88		
		N	%
Treatment History	Nil	30	100.0%
	Taken	0	0.0%
Past History	Nil	30	100.0%
	Other	0	0.0%
Family History	Nil	23	76.7%
	Present	7	23.3%
Time to Achieve Remission (Weeks)	2.00	1	3.3%
	3.00	5	16.7%
	4.00	10	33.3%
	5.00	6	20.0%
	6.00	3	10.0%
	7.00	5	16.7%

Table 4. Baseline Comparison of Uric Acid and Metabolic Profiles Between Study Groups

Variable	Case (Mean ± SD)	FDR (Mean ± SD)	Control (Mean ± SD)	F	*p*-value	Post Hoc Comparison
UA-b (mg/dL)	5.84 ± 1.74	5.38 ± 1.38	5.93 ± 1.43	1.130	0.320	–
FBS-b (mg/dL)	77.43 ± 15.01	84.20 ± 24.47	89.30 ± 9.39	3.490	0.030*	Case < Control
TC-b (mg/dL)	126.57 ± 30.70	145.40 ± 36.41	153.47 ± 33.44	5.060	0.010**	Case < Control
TG-b (mg/dL)	125.73 ± 69.67	119.47 ± 51.33	118.90 ± 75.00	0.090	0.910	–
HDL-b (mg/dL)	39.13 ± 7.31	44.80 ± 9.04	39.47 ± 9.26	4.120	0.020*	Case < FDR
LDL-b (mg/dL)	66.63 ± 26.11	73.47 ± 23.88	90.40 ± 27.39	6.730	0.000***	Case < Control < FDR
VLDL-b	25.03 ± 13.74	27.93 ± 24.33	24.30 ± 14.57	0.330	0.710	–
SBP-b (mmHg)	116.80 ± 7.59	128.27 ± 9.46	118.73 ± 6.34	18.110	0.000***	Case < FDR
DBP-b (mmHg)	76.93 ± 5.55	80.80 ± 10.17	79.00 ± 4.95	2.120	0.120	–
WC-b (cm)	78.17 ± 8.92	80.57 ± 8.25	80.87 ± 7.45	0.970	0.380	–
W-b (kg)	51.50 ± 10.60	62.53 ± 10.44	62.07 ± 9.49	11.250	0.000***	Case < Control < FDR
H-b (cm)	156.73 ± 7.06	164.20 ± 7.01	165.43 ± 8.18	12.020	0.060*	–
BMI-b	20.90 ± 3.91	23.15 ± 3.20	22.66 ± 2.68	3.860	0.020*	Case < Control < FDR

Note: UA = Uric Acid; FBS = Fasting Blood Sugar; TC = Total Cholesterol; TG = Triglycerides; HDL = High-Density Lipoprotein; LDL = Low-Density Lipoprotein; VLDL = Very Low-Density Lipoprotein; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; WC = Waist Circumference; W = Weight; H = Height; BMI = Body Mass Index.
*Significant at $p < 0.05$, **$p < 0.01$, ***$p < 0.001$. ANOVA used for comparisons.

Table 5: Correlation between Change (Δ) in Psychopathology, Uric Acid and Metabolic Parameters from Baseline and Exit.

	UA	FBS	TC	TG	HDL	LDL	VLDL	SBP	DBP	WC	W	BMI
YMRS Total	-0.128	-0.047	-0.027	-0.207	0.072	-0.041	-0.17	-0.011	-0.289	-0.23	0.113	0
Elev. Mood	-0.232	-0.041	0.056	0.034	0.12	0.017	0.103	-0.061	-0.307	-0.12	0.267	0.296
Incr. Motor	-0.087	-0.054	-0.068	-0.035	0.138	-0.125	0.004	-0.174	-0.194	-0.28	0	-0.08
Sex Interest	-0.296	0.131	0.021	0.086	0.039	-0.003	0.107	0.014	-0.172	-0.085	0.279	0.26
Sleep	0.264	-0.149	0.093	0.153	0.209	-0.055	0.177	-0.031	-0.03	-0.154	-0.102	-0.11
Irritability	-0.03	-0.114	0.104	0.265	-0.01	-0.088	0.281	-0.106	-0.275	-0.06	-0.07	-0.133
Speech	-0.05	0.112	-0.17	-0.251	-0.145	-0.042	-0.208	-0.116	-.404*	-.411*	0.193	0.154
Language and thought	-0.272	0.003	0.05	-0.28	0.057	0.059	-0.25	0.117	-0.028	-0.027	0.184	0.101
Content	-.362	0.277	-0.219	-.386*	-0.004	0.055	-.389*	0.113	-0.174	0.049	0.29	0.188
Disruptive Behavior	-0.193	-0.124	-0.332	0.003	-0.133	-.396*	-0.006	-0.089	0.111	0.000	-0.035	-0.125
Appearance	-.408	-0.056	-0.044	-0.186	0	0.083	-0.164	0.018	-0.012	-0.32	0.2	0.029
Insight	-0.083	-0.071	0.07	-0.336	-0.192	0.216	-0.288	0.088	-0.217	-0.219	-0.007	0.033
BPRS Total	-0.237	-0.111	0.076	-0.032	-0.25	0.099	0.026	-0.051	-0.173	-0.137	0.038	0.149
CGIsSI Total	-0.205	-0.022	0.025	-0.18	-0.168	0.206	-0.147	-0.152	-.556**	0	-0.187	-0.175

YMRS= The Young Mania Rating scale

BPRS= Brief Psychiatric Rating Scale

CGIsSI= The Clinical Global Impression – Severity scale

Table 6: Correlation of Change (Δ) among Uric Acid and Various Metabolic Parameters

	UA Δ	FBS- Δ	SBP- Δ	DBP- Δ	WC- Δ	W- Δ	BMI- Δ
TC- Δ	0.12	-0.20	-0.25	-0.25	0.08	-0.17	-0.17
TG- Δ	0.05	-0.16	-.36*	-0.09	-0.03	-0.21	-0.08
HDL- Δ	0.07	0.09	0.27	0.29	-0.17	0.13	0.17
LDL- Δ	-0.07	-0.01	-0.22	-.42*	0.14	-0.02	-0.09
VLDL- Δ	0.003	-0.16	-.37*	-0.11	-0.07	-0.22	-0.08

*p< 0.05; **p< 0.01