"ASSESSMENT OF URIC ACID LEVELS IN AGITATED MANIA AND OTHER AGITATED NON-AFFECTIVE PSYCHOTIC DISORDERS- A ONE YEAR HOSPITAL BASED COMPARATIVE STUDY"

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ACRONYMS

ABS	Agitated Behavior Scale
ATP	Adenosine triphosphate
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
BRMRS	Bech-Rafaelson Manic Rating Scale
CNS	Central Nervous System
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
FDA	Food and Drug Administration
HAM-D	Hamilton Depression Rating Scale
ICD-10-DCR	International Statistical Classification of Diseases and Related Health Problems- 10th revision- Diagnostic Criteria for Research
NMHS	National Mental Health Survey
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PANSS	Positive and Negative Syndrome Scale
YMRS	Young Mania Rating Scale

ABSTRACT

Introduction: Studies have shown role of purines and purinergic system in psychiatric disorders. Also, agitation as a separate entity has been found to be associated with hyperuricemia and uricosuria.

Objective: To assess uric acid levels in patients with agitated mania and to compare them with levels in patients having agitated non-affective psychotic disorders

Methods: A cross-sectional study comparing serum uric acid levels in 100 inpatients, aged 18 years and older, of either sex, with ICD-10 DCR diagnosis of mania and non-affective psychotic disorders admitted in acute agitation. YMRS, BPRS and ABS rating scales were applied for assessment of severity of mania, psychosis and agitation. Scores obtained were correlated with uric acid levels using pearson's correlation coefficient. P value was obtained using fisher's exact test and paired-t test.

Results: Uric acid levels were found to be significantly higher in individuals suffering from mania than those with non-affective psychosis ($p=0.0381$). Similarly, a significant positive correlation was found between uric acid and YMRS scores ($r=0.3433$). A significant correlation of uric acid levels was found with agitation in psychotic individuals ($r=0.2949$).

Conclusion: Uric acid level is found to be significantly higher in individuals suffering from mania and correlates well with symptom severity. However, even though uric acid levels were insignificant in psychotic disorders they correlated to agitation in this subgroup.

Keywords: Uric acid, agitation, mania, non-affective psychosis, purinergic dysfunction.

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INTRODUCTION

Uric acid is an end product of purine metabolism which is transported via blood and is primarily excreted through kidneys. Elevated serum uric acid level is found to be closely associated with agitation, which could be in the form of aggression (verbal or physical), impulsivity, disinhibition and thrill seeking behaviour. This association of uric acid with agitation is not only present in healthy subjects, but is also found in individuals suffering from organic or functional illnesses. Lesch et al. (1964) published a case report about a rare familial disorder of uric acid metabolism (later termed as Lesch-Nyhan syndrome) occurring in children less than ten years of age. The affected children were noted to have hyperuricemia and aggressive behavior in the form of self-mutilation.[1] A link between the two was thus found and over the course of years, with further studies on both animal models and humans, the association was established.[2, 3, 4]

A variety of hypothesis have been put forth that form the basis of underlying pathophysiology which ultimately results in a psychiatric illness. Purinergic system dysfunction and impairment in antioxidant defense mechanism are a few of them.[5, 6]

Emil Kraeplin was the first person to identify a link between purinergic dysfunction and bipolar disorder in his study in 1921. He found that the individuals suffering from mania had hyperuricemia, uricosuria and an increased risk of development of gout.[7] 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.[8]

Similarly, an underlying pathophysiology of purinergic dysfunction and impaired antioxidant defense mechanism has been found in schizophrenia as well.

Likewise, 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 evidences exist regarding uric acid levels in schizophrenia, with some studies suggesting it to be raised in schizophrenic patients whereas some suggesting otherwise.[5, 9]

This study is intended to assess uric acid levels in patients who present in agitated mania, and to compare it with those who present with other non-affective psychotic disorders in an agitated state. This will help us correlate uric acid levels to agitation in mania and to agitation in psychosis and find out if there is a stronger correlation that exists among any one out of the two. Since there is a dearth of literature on this issue, it might help us understand the relationship of agitation, uric acid and the aforementioned psychiatric illnesses better. This study also might aid in future research to help establish a relationship of uric acid as a potential biomarker in mania, to develop better and more targeted therapeutic interventions.

OBJECTIVES

To assess uric acid levels in patients with agitated mania and to compare them with levels in patients having agitated non-affective psychotic disorders.

REVIEW OF LITERATURE

Uric Acid

Metabolism of purines such as Xanthine and Hypoxanthine leads to uric acid production. In mammals other than humans, uric acid is further broken down to form allantoin with the help of enzyme uricase. Due to the deficiency of this enzyme in humans, higher uric acid levels are found in humans than the other mammals. In humans, source of uric acid could be either exogenous, that is based on the diet we take, or endogenous, that is depending on the rate of its production inside our body. Endogenous production of uric acid is done by liver, that helps catabolize the nucleotides.[10,11] Uric acid is a weak acid, 99% of which exists in ionized form at body's physiological pH. In the blood, it exists as monosodium urate, and in urine it exists as potassium, calcium and ammonium urate. In the genito-urinary tract where the pH is low it exists as uric acid. 70% of uric acid is excreted in the unchanged form via kidneys, and the remaining 30% is metabolized and excreted in stools.[12]

- **Properties of uric acid**

Uric acid has been identified to play a role as an oxidant as well as an antioxidant in plasma. This paradox has been the reason for extensive research on uric acid.[13] When elevated, in acute stages, uric acid has been reported to reduce the oxidative stress. Various studies have highlighted its protective role in illnesses such as acute stroke, multiple sclerosis, Parkinson's disease etc.[14, 15, 16] However, it has also been found that when chronically elevated, it is pro-inflammatory in nature, a finding which was corroborated by studies that showed an increased risk of stroke in such patients.[17, 18]

- **Role of uric acid as an antioxidant:**

Aerobic organisms that need oxygen for survival need various mechanisms to protect cells from oxidative damage. Human brain which constitutes primarily of lipids, mainly unsaturated fatty acids is susceptible to damage by these free radicals. Uric acid and ascorbic acid are the two main plasma antioxidants that are responsible for protecting against this oxidative damage, thus promoting longevity and survival. Uric acid exerts its antioxidant action by acting primarily on singlet oxygen, oxo-heme oxidants and hydroxyl radicals (as explained in Figure A).

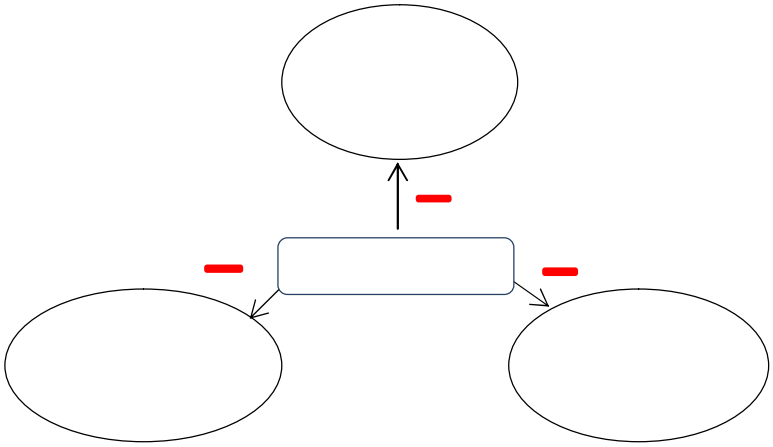


Figure A: Free radicals on which uric acid acts upon

Studies done in the past have shown evidence of raised urate levels in plasma during times of increased oxidative stress, such as physical exercise. This was explained by the mechanism of decreased renal clearance of uric acid. Hence, it was later on hypothesized that other conditions associated with increased oxidative stress, such as alcohol use and obesity, could also have increased uric acid levels due to same causal association. Apart from its own free radical scavenging property, uric acid also prevents oxidation of ascorbic acid by forming stable co-ordination complexes with iron thus preventing its catalytic oxidation further preventing lipid

peroxidation.[19]Research has highlighted the protective role of urate and ascorbate by preventing or diminishing the rate of decline of cognitive impairment in Alzheimer's disease (as explained in Figure B).[20]

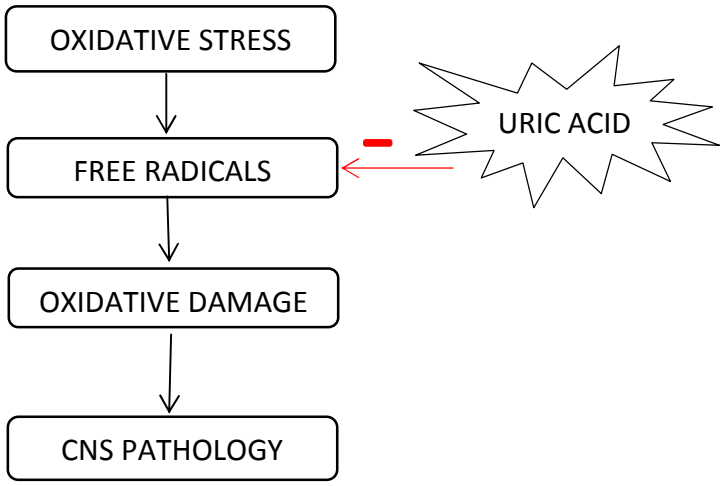


Figure B: Mechanism of antioxidant action of uric acid

- **Role of uric acid as an oxidant**

While hydrophilic environment is known to promote antioxidant action of uric acid, hydrophobic environment promotes its oxidant action. Uric acid via its action on peroxynitrite radical forms free radicals, which further interact with uric acid to generate more free radicals. Thus, its pro-inflammatory nature is seen primarily by causing lipid peroxidation of cell membrane lipids.[13]

Purines, Purinergic system and Purinergic dysfunction

Purines

There are two nitrogenous bases that are known to us- purines and pyrimidines. Purines such as adenine, guanine, xanthine and hypoxanthine are heterocyclic aromatic organic compounds which after combining with a pentose sugar i.e. ribose or deoxyribose form nucleosides.[21]

Purinergic system

Purines act on purinergic receptors. Purinergic receptors are widely distributed throughout the body including the nervous system.[22] They can be of two types- Adenosine receptors and ATP receptors. Adenosine receptor (P1) has four subtypes- A1, A2a, A2b, A3. Adenosine binds to A1 receptor with greatest affinity and acts by regulating the release of other neurotransmitters, reducing the neuronal activity at the synapse and decreasing the excitability of neurons. ATP receptor (P2) has 5 subtypes- P2Y, P2T, P2U, P2Z, and P2X. P2X receptor is present in the CNS.[23, 24]

Physiology of purines and the purinergic system

Adenosine and ATP are the neurotransmitters that play an important role in the central nervous system. ATP also known as the energy currency of the cell was widely known for its intracellular action. However, its extracellular action in the form of its property as a co-transmitter (both as a central and peripheral neurotransmitter) was lesser known and discovered much later. As a neurotransmitter, ATP is stored in the synaptic vesicles in the axon terminals and released in the synapse on stimulus. The released ATP is then acted upon by exonucleotidases that cause its degradation into its metabolites. These metabolites act on the purinergic receptors to cause the

necessary action. Adenosine in neuronal synapse can be either formed as a product of degradation of ATP or can be directly released from the synaptic vesicles that are stored in the neuron terminals.[22]

Adenosine has sedative, anticonvulsant and anti-kindling properties. The inhibitory property of adenosine is exerted mainly via its action on the A1 receptors that modulate neurotransmitter release. Therefore contrary to adenosine agonists, adenosine antagonists function as stimulants that result in an increase in symptoms of insomnia, irritability, anxiety etc. thereby promoting behavior which is 'mania-like'.[24, 25, 26, 27]

Adenosine influences memory, cognition, aggression and social interaction. It is also known to regulate second messenger system and other neurotransmitters.[24, 25] Thus, they play an essential role in neurotransmission.[28, 23, 22] Defects in these neurotransmitter systems form the basis of pathophysiology of various psychiatric illnesses.[29, 30, 6]

Purinergic system dysfunction

Purinergic dysfunction is stated to be one of the possible underlying pathophysiology responsible for causation of psychiatric illnesses. This hypothesis has been drawn based on the available literature as per the studies conducted in the past. Role of mitochondria is of utmost significance in the central nervous system since it governs the activities of the purinergic system in the form of synthesis and functional regulation of the receptors, transporters and the enzymes involved. Hence, apart from its function as a neurotransmitter, it also serves as a neuromodulator. Therefore, an adequate number of healthy functioning mitochondria are essential for proper functioning of the neurons. Mitochondrial dysfunction is hence suspected to

play a crucial role in the pathophysiology of various psychiatric illnesses such as bipolar disorder and schizophrenia.[29] Uric acid is found to be elevated in any condition that involves an excessive breakdown of purines or reduced adenosinergic neurotransmission (as explained in Figure C).[25, 31]

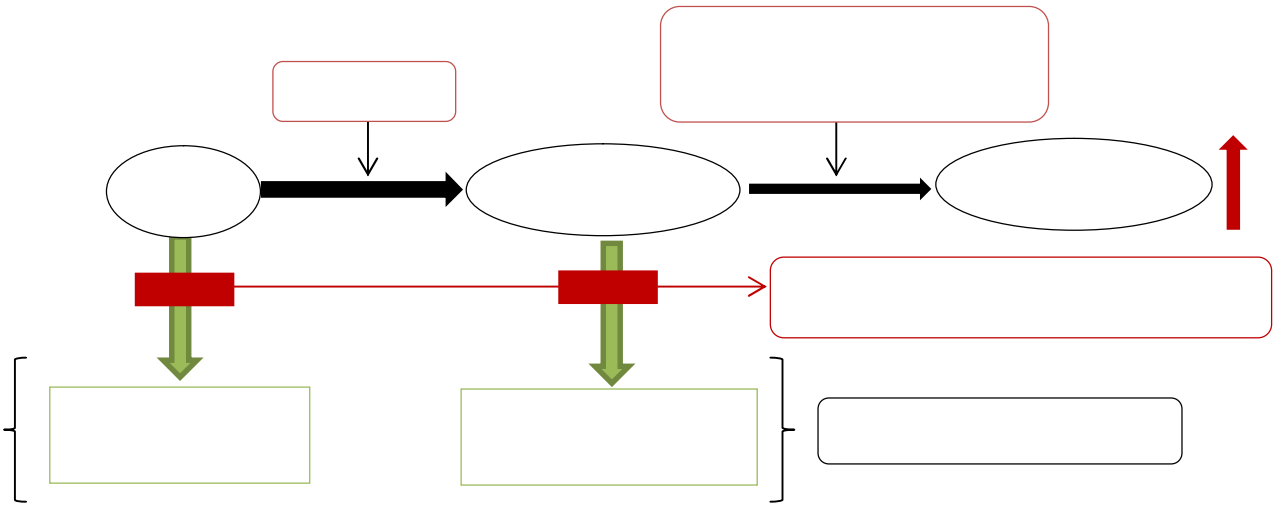


Figure C: Purinergic system dysfunction

Hyperuricemia

- **Definition**

Hyperuricemia is defined as serum uric acid levels being greater than or equal to 7mg/dl for males and greater than or equal to 6mg/dl for females.[32]

- **Factors influencing serum uric acid levels**

Uric acid levels are influenced by multiple factors such as gender, dietary patterns such as consumption of purine rich diet, fructose and caffeine intake, abdominal circumference, exercise etc.[33]

Male gender is associated with higher uric acid levels than females, the reason being an increased clearance due to the presence of estrogen in females.[34]It is also influenced by the simultaneous use of various drugs such as losartan, fenofibrate, NSAIDs etc. Additionally psychotropics used for the treatment of mental illnesses themselves are known to alter serum uric acid levels. One such study by Ring et al. (1991) showed that anticonvulsants such as valproate and phenobarbitone cause an increase in serum levels, whereas phenytoin and carbamazepine cause a decrease in serum levels.[35] Medical conditions associated with elevated uric acid levels are gout, hypertension, metabolic syndrome, cardiovascular disease, nephrolithiasis, chronic kidney diseases etc.[36, 37, 38, 39, 40, 41]

- **Estimation of uric acid levels**

Association between the peripheral uric acid levels and central levels has been found, therefore testing for serum uric acid levels have been suggested to be able to highlight the underlying pathophysiology.[26, 42]

Agitation

The term 'agitation' has a Latin origin and is derived from the word 'agere' which means 'to drive'.[43] It is described as a state of constant to and fro motion.[44] It is often termed as 'psychomotor agitation' when used in context to medical science. The word psychomotor is made of 'psyche' which means the mind and 'motor' which means to move.[43] This term 'psychomotor agitation' has been suggested by some as an outward manifestation of physical or behavioral disturbance which is a result of underlying mental disturbance.[45,46] Some suggest the same being present without there being necessarily an associated mental distress.[47] However, some specify the subjective sense of inner restlessness and objectively noted symptoms of hyperactivity, both to be there compulsorily to label someone with increased psychomotor agitation.[48,49]

- **Definition:**

There have been many definitions of agitation that have been put forward however, no particular definition has been universally agreed upon.[50] Agitation as per the literature available in textbooks is defined as a "state of anxiety associated with severe motor restlessness".[51] DSM-III-R defines it as "excessive motor activity associated with a feeling of inner tension, which is usually non-productive and repetitious."[52] DSM-IV describes agitation as a set of behavior that includes wringing of hands, biting of nails, fiddling with hair, inability to stand still etc.[53] Bianchi, (1906); Stoddart, (1921); Cohen-Mansfield and Billig, (1986); Mungas et al., (1989) stated that excessive and repetitive verbalization was commonly associated with agitated behavior.[54,55, 56, 57]

- **Terminologies related to agitation:**

There are a variety of terms that may seem to have overlapping features with agitation such as restlessness, jitteriness, akathisia, fidgetiness, hyperactivity etc. These set of behaviors may or may not be related to one another or to agitation per say. Also, each of these behaviors may have their own varying course and have different underlying etiologies.

Akathisia, which is of the above mentioned behavioral manifestation, can be misconstrued with agitation that has manifested as a part of or secondary to an illness. This is why it becomes important to differentiate between the two. Both akathisia and illness-related agitation have a subjective and objective component of psychological and motor restlessness, however, akathisia is known to occur as a result of high potency neuroleptic medication. Also, akathisia is specifically used for sensation of restlessness that is mostly restricted to lower limbs which worsens when the patient stands still. Illness-related agitation on the other hand refers to the sensation that is restricted mainly to the upper limbs.[58, 59]

Hyperactivity is another term that is associated closely with agitation. Hyperactivity is described as being purposeful and goal-directed, whereas agitation has been described as being purposeless and non-goal-directed.[60, 61]

Anxiety has been linked to agitation as well, whether the latter is an independent entity in itself or whether it is a manifestation of inner subjective anxious state of an individual. Since various affective states lead to symptoms suggestive of agitation, it was then put forth that anxiety is one such emotional state that can result in agitation. This was in line to what Jaspers said about agitation which he described as an "emotional state of inward excitement that can occur on its own without anxiety."[62]

- **Subtypes of agitation:**

Classification of agitation has been stated in the available literature as a challenging task because of the inclusion of various sets of unrelated behavior under one umbrella of agitation. However, various attempts have been made by different authors with regards to the same.

Zimmer et al. (1984) identified a set of problem behaviours based on object of behaviour i.e if the person was 'endangering self' or 'endangering others' and the level of disruption because of it i.e. whether it was 'disturbing to others' or was 'non-endangering or disturbing to others'.[63]

Later, Cohen-Mansfield and Billig (1986) put forward two dimensions of 'aggressive-abusive versus non-aggressive behaviour' and 'verbal-vocal versus physical behaviour' based on which four categories were drawn, as explained in the table A below.[64]

S no.	Category of agitation	Behavior
1.	Aggressive-physical component	Pushing, kicking, spitting, throwing, destroying property, fighting, grabbing others, hurting self
2.	Aggressive-verbal component	Shouting, cursing
3.	Nonaggressive-physical component	Pacing, wandering aimlessly
4.	Nonaggressive-verbal component	Constant help seeking, complaining, accusing

Table A: Subtypes of agitation as described by Cohen-Mansfield and Billig (1986)

- **Pathophysiology of agitation:**

There are multiple etiologies that can lead to aggression in an individual. Role of androgens is already well known with regards to the same. Also, dysfunctions of neurotransmitter systems such as dopamine, serotonin, GABA, and noradrenaline have been stated to be few of the likely causes.[65, 66]

- **Conditions associated with agitation:**

Agitation can be seen in normal individuals as well as in individuals with an organic or a functional illness. It can manifest as delirium secondary to an organic pathology such as electrolyte disturbances, infections, CNS insult by toxic substances or any other neurological abnormalities.[65]

Among psychiatric illnesses, agitation is commonly seen in individuals suffering from bipolar affective disorder wherein it manifests mainly in the form of impulsivity.[67] It is also seen in schizophrenia, dementia syndromes (Alzheimer's disease, fronto-temporal dementia, dementia with Lewy Bodies), panic disorder, generalized anxiety disorder, intellectual disability, personality disorder such as borderline and antisocial personality disorder, and individuals with substance intoxication and withdrawal.[68]

- **Implications of agitation:**

Thus, agitation can increase the likelihood of frequent admissions under psychiatry, demanding immediate management and warranting a long hospital stay. It is also frequently associated with legal problems, poor quality of life and immense care-giver burden.[50]

- **Rating scales for agitation:**

There have been a variety of scales that have been developed to assess the severity of agitation. They can be categorized as follows:

Self-rated scale

a) The Brief Agitation Measure- self-rated scale[69]

Observer-rated scales

b) Agitated Behavior Scale (ABS) [70]

c) Agitation Severity Scale (ASS) [71]

d) Behavioral Activity Rating Scale (BARS) [72]

e) Clinical Global Impression Scale for Aggression (CGI-A) [73]

f) Cohen-Mansfield Agitation Inventory (CMAI) [74]

g) Overt Aggression Scale (OAS) [75]

h) Overt Agitation Severity Scale (OASS) [76]

i) Positive and Negative Syndrome Scale Excited Component (PANSS-EC) [77]

j) Staff Observation Aggression Scale (SOAS) [78]

- **Association of purinergic dysfunction with agitation**

Elevated serum uric acid levels have been associated with behavioral changes that are characterized by irritability, aggression, disinhibition, thrill-seeking tendency and impulsivity. Various cross sectional studies done in the past have revealed the association of uric acid with agitation and the findings were consistent with agitation in any form i.e. agitation in normal people and those diagnosed with any psychiatric or non-psychiatric illnesses.

Individuals with illnesses characterized having purinergic dysfunction and simultaneous increased serum uric acid levels (e.g. Lesch-Nyhan syndrome) have been found to have similar symptoms suggestive of agitation.[1]

Lorenzi et al. (2009) conducted a study to find an association between serum uric acid levels and affective temperaments. They developed a Combined Emotional and Affective Temperament Scale (CEATS) that combined the constructs of the two

temperaments into one self-rated scale. A total of 129 subjects were enrolled into the study which included 44 males and 85 females and following findings were observed. Uric acid levels significantly correlated with disinhibition and drive in the sample as a whole. However, no statistically significant correlation was found among males. Among females, a significant correlation was found only with disinhibition.[3]

Sutin et al. (2014) conducted a study on humans and mice to find an association between impulsivity and uric acid. Study 1 was on humans. Study sample was drawn from two different longitudinal studies, and the participant's personality was assessed using Revised NEO Personality Inventory (NEO-PI-R) at Time 1 and Time 2 with a gap of 3-5 years in between. A 12 hour fasting sample of serum uric acid was collected on both these occasions. Results revealed that individuals who had impulsivity traits had higher uric acid levels. They had higher impulsiveness, more excitement seeking tendencies, lower self-discipline and deliberation scores. Results were not altered when previous psychiatry comorbidity was controlled for. Study 2 was on mice, samples included the genetically modified type, in which the urate oxidase gene was disrupted making them more prone to uric acid collection in their body (UOX mice) and the wild type (WT mice). Three sets of behavioral tests were conducted- open field test, elevated plus maze test, and novel object test to test for exploratory behavior, spontaneous locomotor activity and novelty seeking behavior. Results revealed that UOX mice with higher uric acid levels displayed more exploratory and novelty seeking behavior than the WT mice.[2]

A prospective study conducted on 84 adolescents by Mrug et al. (2016) evaluated the relationship between uric acid excretion and aggression, whether the former predicted the future episodes of the latter. The study was conducted in two waves, the first being a baseline assessment and the second one after a gap of one and

a half years. At each wave the patient was made to fill a self-rated Physical Aggression Scale based on their involvement in a fight or aggression in any form. Also, urine sample following a 12 hour overnight fast for uric acid estimation in the week following the baseline interview of wave 1. The results revealed that higher uric acid levels predicted higher levels of physical aggression in wave 2 after being adjusted for age and aggression at wave 1.[4]

A study conducted by Nurmedov et al. (2016) assessed serum uric acid levels and their relationships with impulsivity in eighty patients with substance use disorders. Also, a comparison was drawn with eighty other healthy volunteers. Serum uric acid levels were found to be significantly higher in substance use disorder patients and these patients also scored higher on attentional and motor scores on the Barrat Impulsivity Scale. However, a negative correlation was found between uric acid levels and impulsivity among substance use disorder patients. This study hence showed results opposite to the ones that were done earlier.[79]

Bartoli et al. (2018) conducted a cross-sectional study on subjects to measure the correlation between uric acid levels in patients with affective disorders such as bipolar disorder and depression and compared it with healthy controls. Different scales were applied to measure the psychological distress, suicidal ideations, impulsivity and agitation features. Uric acid levels were found to have no correlation with any of the aggressive features on Modified Overt Aggression Scale with the exception of verbal aggression with which it had a positive association which was statistically significant. Other significant finding noted in this study was an inverse relationship with psychological distress and suicidal ideations.[80]

Bipolar disorder

- **Overview of bipolar disorder:**

Bipolar affective disorder is a psychiatric illness that as per ICD-10 belongs to the category of mood disorders.[81] It deals with disorders of the emotional state of an individual which ultimately reflects in the person's behavior and on the way the person interacts with the outer world. Kraeplin used the term 'manic-depressive illness' for it earlier on, a term that is no longer used now.[51]

- **Epidemiology:**

Bipolar disorder is a fairly common occurring psychiatric disorder that usually begins in the adolescence and has an overall sex ratio of approximately 1:1, with males having more propensities to have manic episodes while women on the other hand are more likely to have mixed and depressive episodes.[51]

It has a life time prevalence ranging from 0-2.4% for bipolar type I and 0.3-4.8% for bipolar type II. The National Mental Health Survey conducted by the Ministry of Health and Family Welfare in India in 2015-16 reported the life-time prevalence of bipolar disorder to be 0.5%. As per the NMHS report males had higher current prevalence (0.3%) than females (0.2%). Also, those belonging to the 40-49 age group (0.4%) and from urban region (0.7%) were found to have higher current prevalence rates.[82]

- **Classification:**

Akiskal gave a classification of bipolar disorder in the form of a spectrum of different subtypes ranging from Bipolar I to VI.[83]

ICD-10 includes mania and depression under the same category of mood disorders. However, under mood disorders, it has segregated mania from bipolar

disorder as two separate entities. Manic episode is labeled for those with only a single episode mania and bipolar disorder, mania for those who have had a previous episode of mania, hypomania or depression. Mania and bipolar disorder are coded as ICD F 30 and ICD F 31 respectively. Other subcategories under the same umbrella are depressive, recurrent depressive, persistent, other and unspecified mood disorders.[81]

DSM-5 has a separate category for bipolar and related disorders and depressive disorders unlike ICD-10. Further subcategories under bipolar and related disorders include bipolar I, bipolar II, cyclothymic, substance or medication induced, secondary to another medical condition, other specified and unspecified bipolar disorder. Bipolar I disorder requires a minimum of one current or past episode of mania to have occurred along with depression whereas bipolar II disorder requires at least one current or past episode of hypomania along with an episode of depression.[84]

- **Clinical features:**

Manic episode in bipolar disorder is characterized by symptoms of elevated mood, inflated self-esteem, increased psychomotor activity, decreased need for sleep that have been present for at least a period of seven days and which has led to significant impairment of socio-occupational functioning. It might be accompanied with psychotic symptoms such as delusion or hallucination secondary to the mood. Hypomania, on the other hand as the name suggests, is a lesser severe form of mania having similar symptoms with some impairment of functioning. Also, unlike mania it is not accompanied by psychotic symptoms.[81]

- **Rating scale:**

In 1971, Biegel et al., developed a scale that was to be applied by the nursing staff depending on the ward behavior of the manic patients. It consisted a total of 26 items with each item having a frequency score and an intensity score, both ranging

from 0 to 5. The product of these two scores formed the individual score of each item.[85]

Petterson et al. in 1973 subsequently developed a scale with lesser number of items and a better inter rater reliability.[86] However, there was a need to develop a scale that was less extensive than the former and more sensitive than the latter.

In 1978, Young et al. developed Young Mania Rating Scale (YMRS).This rating scale was developed to assess the severity of symptoms, the response to treatment, and symptom relapse in individuals with mania. It was to be applied by a clinician based on his observation of the patient. It had a total of eleven items with seven items that were rated in between 0 to 4 and four items that were rated in between 0 to 8. The total score ranged from 0 to 60. This scale was not only found to sensitive but also reported to have good reliability and validity.[87]

Later on in 1997, Altman et al. developed a 5-item rating scale that was to be rated by the patient themselves based on symptoms over the course of previous week. It helped ruling out presence of mania and hypomania and helped assess severity of the same.[51, 88]

- **Bipolar disorder and its association with agitation**

Agitation may manifest itself in the form of a variety of symptoms in bipolar disorder patients. Impulsivity is reported to be one such symptom that is frequently associated and carries with it multiple risks in the form of threat to others in vicinity of the patient and threat to self in the form of suicide.[67]

A study conducted in 2011 by Gilbert et al. compared impulsivity as a behavioral symptom among 23 adolescents with bipolar disorder with 23 healthy controls based on self-rated scale-Barratt Impulsiveness Scale (BIS). This study revealed that BIS scores were significantly higher among bipolar disorder patients

than the healthy controls. The bipolar disorder patients who were in the euthymic phase at the time of study also showed higher total as well as higher attentional and motor subscale scores than the healthy adolescents. Among bipolar disorder patients, those with a history of chronic bipolar disorder and rapid-cycling had significantly higher total and motor subscale scores than those with the absence of these features.[67] fMRI studies have revealed structural and functional abnormalities in the ventral prefrontal cortex (vPFC) in bipolar disorder patients that are responsible to control impulsivity. Patients who were euthymic and those who were symptomatic both showed changes in the form of reduction of volume of vPFC and reduction of its involvement in tasks that require inhibition. However greater changes were noted in those who were rapid-cyclers than those who were not suggesting the former to be more likely to manifest impulsivity than the latter.[89, 90] Associated finding of motor disinhibition has been observed as well with vPFC changes.[91]

Non-affective psychotic disorder

- **Overview:**

Psychosis as defined by previous editions of DSM means 'gross impairment of reality testing' that leads to inability in carrying out daily routine activities. Unlike neurosis in which a person is aware of his or her illness, psychotic individuals have no insight into their illness.[84]

Psychotic disorders can be of two types, those associated with an affective component and those without one. The former are called 'affective psychotic disorders' that include disorders such as schizoaffective disorder. The latter are called as 'non-affective psychotic disorders' which include disorders such as acute

psychosis, delusional disorder, schizophrenia and its various types such as paranoid, undifferentiated, catatonic etc.[81]

- **Epidemiology:**

As per the NMHS report of 2015-16, the lifetime prevalence of schizophrenia and other psychotic disorders in India was found to be 1.4% and the current prevalence was found to be 0.5% with the rate of the illness being higher in males (0.5%) than females (0.4%). Also, higher prevalence was found in the 40-49 age group (0.6%) than the other, with more people residing in the urban area being inflicted with the disorder (0.7%) than the rural area.[82]

- **Classification:**

As per ICD-10, following are the entities that fall under 'schizophrenia, schizotypal and delusional disorders'. It includes schizophrenia, schizotypal disorder, persistent delusional disorder, acute and transient psychotic disorders, induced delusional disorder, schizoaffective disorder, other nonorganic psychotic disorders and unspecified non-organic psychosis. The commonest of this group is reported to be schizophrenia. The requirement of the duration of symptoms as per ICD-10 is stated to be less than one month, at least one month and at least three months for acute psychosis, schizophrenia and persistent delusional disorder respectively.[81]

- **Clinical features:**

Psychosis as mentioned above equates to impairment in reality testing with absence of insight. It is characterized by delusions, hallucinations or presence of both hallucinations and delusions. Also, formal thought disorder is found to be frequently associated with the above two symptoms in psychotic disorders. DSM-5 states that formal thought disorder along with symptoms of disorganized speech, catatonia

and/or negative symptoms alone or in combination can form a diagnosis of schizophrenia in the absence of delusions and hallucinations.[84]

- **Rating scale:**

There are many rating scales that are available for assessment of psychotic symptoms for their severity at the time of presentation and subsequent response on treatment. They are as follows:

a) Brief Psychiatric Rating Scale (BPRS)[92]

b) Scale for the Assessment of Positive Symptoms (SAPS)[93]

c) Scale for the Assessment of Negative Symptoms (SANS)[94]

d) Positive and Negative Syndrome Scale (PANSS)[95]

e) Scale of Prodromal Symptoms (SOPS)[96]

Association of purines and purinergic dysfunction with psychiatric illnesses

Purines are known to influence other neurotransmitter systems that play a key role in manifestation of other mental disorders. Several studies done in the past have attempted to find an association between uric acid levels and different psychiatric illnesses. They have also tried to compare the association among different illnesses to find any significant correlation. Severity of the illnesses as indicated as per the specific rating scales designed for each one of them was also correlated with uric acid levels to see whether the association exists when the patient is in acute exacerbation and subsequently during remission.

A) **Purines and bipolar disorder**

Emil Kraeplin was first to identify a link between purinergic system dysfunction and bipolar disorder in his study in 1921, and found that the individuals suffering from mania had hyperuricemia and increased uric acid excretion.[7] In 1949, Cade found that lithium helped keep uric acid in more soluble forms in the blood in bipolar patients and later went on to further suggest its role in mania.[97]

A study conducted by Anumonye et al. (1963) compared changes in plasma uric acid levels and 24 hour urinary uric acid excretion before remission and during remission in five patients diagnosed with manic-depressive illness (terminology used for bipolar disorder back then), two admitted with atypical mood swings and five healthy volunteers. The results revealed no significant changes in plasma levels with cycles of manic-depressive illness. However, uric acid levels in urine were found to be in lower concentration in periods of acute exacerbation and higher concentration during remission. No significant changes were seen among individuals with atypical mood swings and those who were healthy. [98]

Several studies put forward a hypothesis regarding dysfunction of the purinergic system having a causal association with bipolar disorder.[24, 99]

Studies highlighting beneficial use of allopurinol as an adjunct to oral psychotropics:

Akhondazeh et al. (2005) conducted a study that compared treatment efficacy of two groups of patients with mania-one that used allopurinol as an adjunct to haloperidol and lithium with another that used haloperidol and lithium with a placebo. Results revealed better treatment response in allopurinol group.[100]

The first study that provided evidence of a role of purinergic dysfunction in bipolar disorder was conducted by Machado-Vieira et al. in 2008. It was a randomized double blind placebo controlled study that evaluated therapeutic effects of allopurinol, dypyridamole and placebo group when combined with lithium in acute manic excitement and correlated it with YMRS scores at different time intervals. Allopurinol, which is an FDA approved drug for the treatment of gout is a xanthine oxidase inhibitor is known to decrease uric acid production whereas dypyridamole inhibits nucleoside uptake into the cells decreasing the intracellular concentration of the same.[101, 102] The results of the above mentioned study revealed allopurinol to play a significant therapeutic effect as an anti-manic agent when combined with lithium as significant decrease in uric acid levels were noted which also correlated with YMRS score reduction. This was found to be more significant in relation to the dypyridamole and the placebo group. Results with dypyridamole group were not found to be significant and possibility of reduced permeability via the blood brain barrier was drawn.[103]

Jahangard et al. in 2014 conducted a randomized controlled double-blind study on effects of allopurinol when given as an add-on agent to sodium valproate in patients suffering from bipolar disorder mania and compared it with control group that received placebo along with valproate. Clinical improvement as per CGI (Clinical Global Impression) scoring and fall in YMRS scores indicating extent of severity of manic symptoms was noted at the beginning and the end of the 4 week treatment period. The results revealed improvement in CGI scores in the allopurinol group that was 23 times more than the control group and which also corresponded with a significant fall in uric acid levels in the former.[104]

Weiser et al. (2014) conducted a large multicenter, randomized control study that comprised 180 individuals suffering from bipolar disorder. The participants in the study group were put on allopurinol along with mood stabilizers with or without anti-psychotics and were compared with a control group in which a placebo was given instead. A positive treatment outcome with allopurinol was not found as no significant difference was noted between the two groups. The final result of this study was thus not in line with the two studies mentioned above. The reason for this could be the adequate treatment response with mood stabilizers and antipsychotics that were used in both cases and controls.[105]

However, a double blind, placebo controlled, six week trial conducted by Fan et al. (2012) on 27 subjects with bipolar disorder reported no statistical significant outcome in the group that used allopurinol as an adjunct when compared to the placebo group.[106]

Previous studies have shown evidences suggesting significant elevation of serum uric acid levels in bipolar disorder.[99, 30] Some studies found a significant association only with the manic phase, suggesting that serum uric acid levels were a state marker in bipolar patients, elevated levels hence suggesting manic excitement. However, other studies found no significant difference among different phases of bipolar disorder, however stating that the levels were overall higher when compared to the healthy subjects.[107] The latter group of studies thus hypothesized that serum uric acid levels were a trait marker instead of being a state marker.

Studies showing assessment of uric acid levels in first episode mania

A study conducted by Salvadore et al. (2010) compared uric acid levels in 20 drug-naïve individuals with first episode mania with 24 healthy controls. The results revealed the former to have significantly higher uric acid levels than the latter.[42]

Similarly a study conducted by Chatterjee et al. (2018) compared 31 individuals suffering from first episode mania with 38 healthy controls. A statistical significant difference was noted in uric acid levels between the two groups, with higher levels being in manic individuals than healthy controls.[108]

Results obtained from both the studies were statistically significant and the significance remained even after being matched for age and gender. These results were hence suggestive of purinergic system early on in the course of bipolar illness.

Studies comparing serum uric acid levels in bipolar depression versus unipolar depression

Bartoli et al. (2017) conducted a cross-sectional study comparing subjects diagnosed with either bipolar mania or depression and those with major depressive disorder. The results revealed the serum levels to be significantly higher in the manic subtype than the depressive subtype but however no statistical significance was found between bipolar depression and major depressive disorder.[109]

Kesebir et al. (2014) conducted a study that compared serum uric acid levels in individuals who were 8 weeks in remission following bipolar type I illness and recurrent depressive disorder with 34 healthy controls that were matched for age and gender. Uric acid levels were found to be higher for individuals with bipolar illness and lower for individuals with depressive illness when compared with healthy

controls. The findings were significant and since they were noted in individuals who were in remission, they were suggestive of the possibility of uric acid levels being independent of the current affective state of the individual, therefore it being a trait marker than a state marker. It also shows that uric acid is associated not only with acute manic excitement phase of bipolar disorder but also with individuals with chronic bipolar disorder The study also revealed the association of various affective temperaments such as depressive, irritable, cyclothymic, hyperthymic, anxious traits with uric acid levels and compared the association of these traits among the two illnesses. It revealed moderate relation of uric acid levels with hyperthymic and irritable temperament traits which were more commonly associated with individuals with bipolar illness than recurrent depressive illness or healthy adults.[110]

Evidence from studies suggest that mania has a positive correlation with serum uric acid levels, similarly there are studies that show depression to have a negative correlation with serum uric acid levels.

Wen et al. (2011) conducted one such study that compared 124 individuals diagnosed with depression with 660 individuals diagnosed with other mental disorders. The results revealed significantly lower levels of uric acid in blood with those suffering from depression than other conditions such as schizophrenia, schizoaffective disorder, bipolar disorder, substance use disorders, delirium, dementia and healthy controls.[111]

Studies comparing serum uric acid levels in different phases of bipolar illness:

Similarly there have been studies conducted in the past that have compared uric acid levels among different phases of bipolar illness, one such study revealed the serum levels being significantly higher in the manic and mixed episodes than the euthymic and depressive episodes.[112] However, these findings were inconsistent with the results of other studies that revealed no significant difference in levels among different phases of bipolar disorder.[113]

Albert et al. (2015) conducted a study that compared uric acid levels in individuals with bipolar disorder in different phases of the illness (cases) such as mania, depression and euthymic phase with other psychiatric disorders (controls) such as major depressive disorder, obsessive compulsive disorder and schizophrenia. Serum uric acid levels were significantly higher in cases than the controls. Also, no significant differences in mean uric acid levels were found among the individuals suffering from bipolar disorder who were previously exposed and those were never exposed to mood stabilizers.[113]

There are various plasma antioxidants present in blood apart from uric acid such as albumin, bilirubin etc. Berardis et al. (2008) conducted a study to assess levels of these plasma anti-oxidants in different phases of bipolar disorder with respect to healthy adults. The results revealed uric acid to be significantly elevated in individuals in manic phase of bipolar disorder than the euthymic and depressive phase. However, bipolar disorder as a group together had higher serum levels than healthy controls. Uric acid levels were noted to have a positive correlation with YMRS, BRMRS and HAM-D scores with all bipolar subgroups. No significant association of albumin and bilirubin was found in patients with bipolar illness with

respect to healthy adults despite controlling for various possible confounding factors.[114]

Gultekin et al. (2014) conducted a study on 55 bipolar disorder patients in acute manic phase with 59 patients suffering from schizophrenia in acute psychotic exacerbation and compared uric acid levels in these subgroups with healthy controls at baseline and weekly for 4 weeks successively. Uric acid levels were compared to YMRS scores in manic patients and PANSS scores in psychotic patients to see if they corresponded to the scores as the patients received treatment on all instances. Significant elevation of uric acid levels were found in both the illness groups than the healthy controls in the initial stage. Fall in uric acid levels corresponded to fall in YMRS scores until first week of treatment reflecting clinical improvement, however lost significance thereafter. Even though significant reduction of PANSS scores were noted in the first week of treatment of patients with schizophrenia, fall in uric acid levels failed to correspond to fall in PANSS scores in patients at any given point of time during the treatment course.[115]

B) **Purines and schizophrenia**

Adenosine influences neurotransmitters such as dopamine and glutamate implicated in schizophrenia. One of the hypothesis the etiology of schizophrenia was hyper-functioning dopaminergic system and hypo-functioning glutaminergic system.[116, 117, 118, 119] Under normal circumstances, adenosine via its action on adenosinergic receptors interacts with dopamine and glutamate receptors and works as an endogenous modulator striving to maintain a balance. In case of adenosinergic dysfunction an imbalance is created which is considered to contribute to the development of schizophrenia (as explained in Figure D and E).[120, 121]

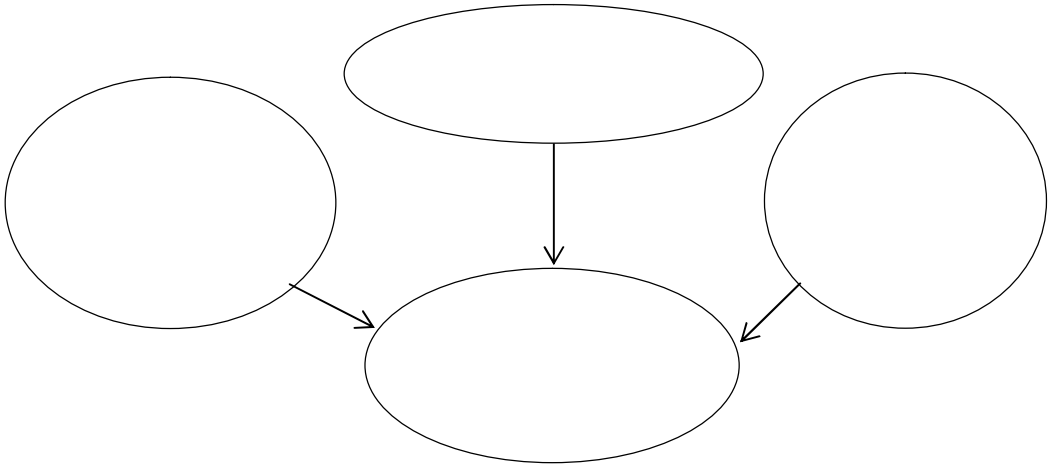


Figure D: Dopamine hypothesis of Schizophrenia

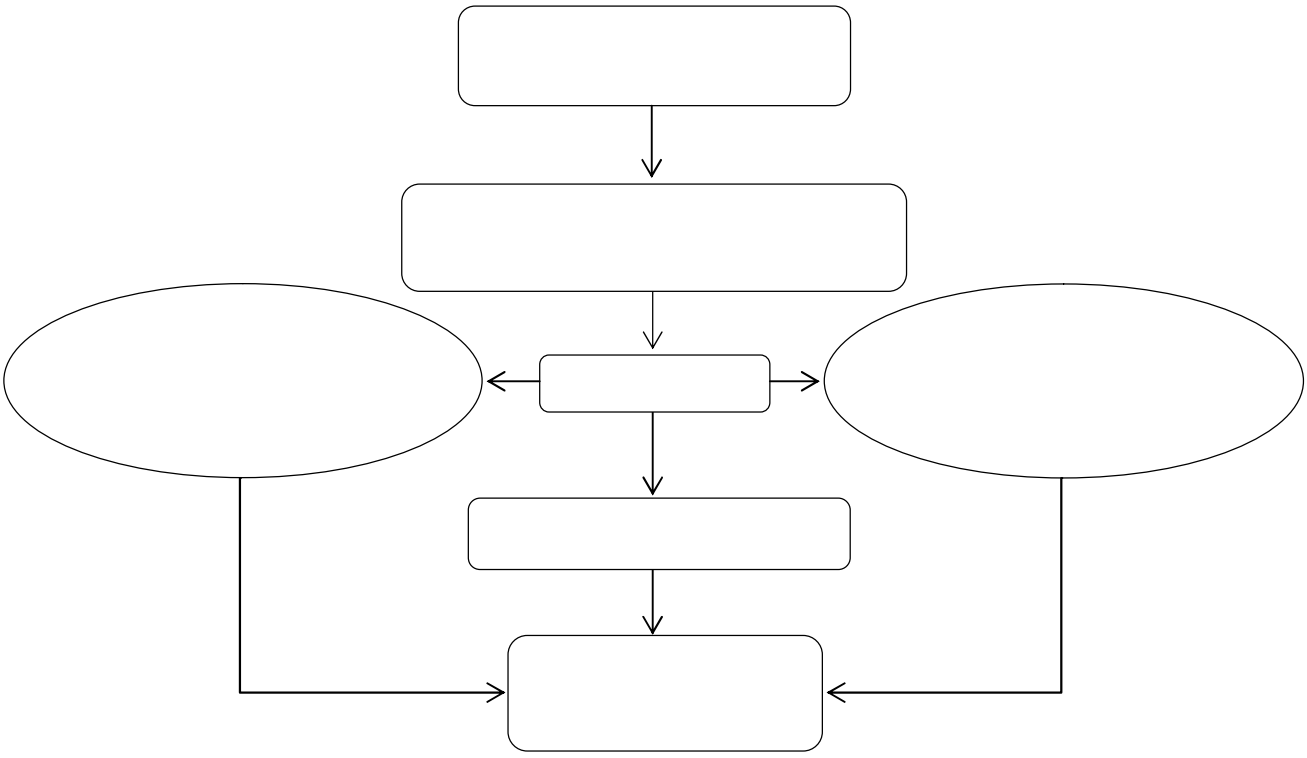


Figure E: Adenosine hypothesis of Schizophrenia

Hirota et al. (2013) performed a meta-analysis based on the data collected by randomized controlled trials that were done in individuals diagnosed with schizophrenia and bipolar disorder. The therapeutic effect of allopurinol and its tolerability in two patient subgroups were compared to placebo and the outcomes were assessed using PANSS and YMRS scores. An improvement of total, positive and general scores on PANSS was seen in schizophrenics who were a part of allopurinol group with respect to the placebo group. Also, significant reduction in YMRS scores was noted as well in manic individuals of bipolar subgroup. Thus, a beneficial role of allopurinol was highlighted by the findings of this study.[122]

The main objective of our study is to compare serum uric acid levels among agitated patients diagnosed with bipolar affective disorder, manic subtype (or first episode mania) and those diagnosed with non-affective psychosis such as schizophrenia. Also, since studies done in the past have shown contradictory evidences of correlation between manic symptom severity with serum uric acid levels, another objective of this study is to find whether YMRS scores of manic patients and BPRS scores of psychotic patients correlate with serum uric acid levels or not.

METHODOLOGY

The present study was conducted in the Department of Psychiatry of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from 1st January 2018 to 31st December 2018.

Study design

- The study is a cross-sectional comparative study.

Study period and duration

- The present one year study was done from 1st January 2018 to 31st December 2018.

Place

- The present study was conducted in the department of psychiatry, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi which is a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, KLE Academy of Higher Education and Research, Belagavi.

Source of data

- The present study comprised of individuals who were brought in an acute agitated state, who were diagnosed with either mania or any non-affective psychotic disorder and were admitted for the same.

Sample size

- A total of 100 individuals were included in the study- 50 patients of agitated mania and 50 patients of other agitated non-affective psychotic disorders.

Sampling procedure

- Purposive sampling method

Selection criteria

Inclusion criteria

- Agitated patients (with a score of >21 on agitated behavior scale) suffering from mania or any other non-affective psychotic disorder according to ICD – 10 DCR, of either sex, of age 18 years and above

Exclusion criteria

- Agitation due to any other psychiatric disorder apart from those mentioned in the inclusion criteria
- Organic psychiatric illnesses
- Patients with poly-arthritis or diagnosed hyperuricemia

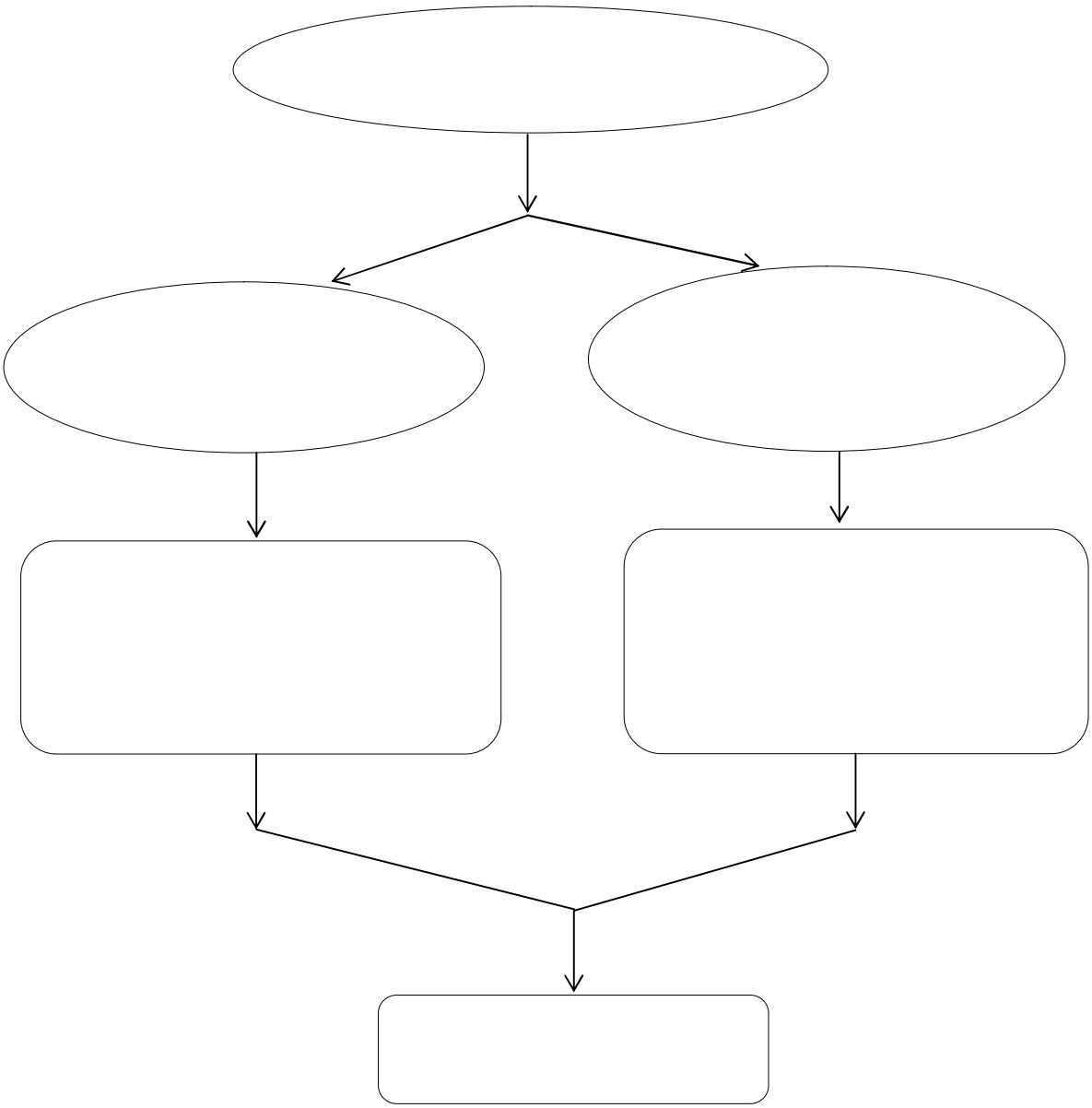
Ethical Clearance

Prior to commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed Consent

The relatives of patients who fulfilled the selection criteria were explained about the nature of the study and a written informed consent was obtained before enrolment.

Method of Collection of Data:



Patients provisionally diagnosed with mania or non-affective psychosis and admitted in the hospital were recruited in to the study after meeting the inclusion and exclusion criteria. Socio-demographic details were recorded on a specially designed proforma. Diagnosis of either disorder was made using ICD-10 DCR criteria. After confirming the diagnosis, Agitated Behaviour Scale was applied to measure the level of agitation. Patients who scored greater than 21 on the same were included into the study. Young Mania Rating Scale (YMRS) was applied to the manic subgroup to assess the severity of manic symptoms, whereas Brief Psychiatric Rating Scale (BPRS) was applied to the non-affective subgroup to assess severity of psychotic symptoms. Fasting blood samples of these patients was collected on the second day of admission and then sent to the biochemistry lab for serum uric acid level estimation.

Tools

Agitated Behaviour Scale (ABS)[70]

ABS is an observer-rated scale that was designed by Corrigan J (1989) for the measurement of acute agitation and for monitoring recovery in individuals with traumatic head injury. [123] It was based on a therapist's observation over a span of 30 minutes or nurses observation in an 8-hour shift. It was noted to have good inter-rater reliability, validity and internal consistency.[124]

It has a total of fourteen items that are scored based on observation on a 4-point rating scale depending on the frequency and intensity of the episodes. In case of absence of a particular behavior, a rating of "1" is given on that particular item. "2" or "slight" is rated when "the behavior is present but does not prevent the conduct of other, contextually appropriate behavior and the patients may redirect themselves spontaneously or the continuation of the agitated behavior does not preclude the

conduct of the appropriate behavior." "3" or "moderate" is rated when "the individual may need to be redirected from an agitated to an appropriate behavior, but is able to benefit from such cueing." "4" or "extreme" is rated when "the individual is not able to engage in appropriate behavior due to the interference of the agitated behavior, even when external cueing or redirection is provided."

Total score is calculated by summing up the ratings on each item and is then interpreted as follows:

- 21 or below = within normal limits
- 22-28 = mild
- 29-35 = moderate
- >35 = severe

Young Mania Rating Scale (YMRS)[87]

` The Young Mania Rating Scale is a widely used rating scale used for the severity assessment of mania based on the patient's report in the previous 48 hours and as per the clinician's observation. It has a total of eleven items, out of which four items such as irritability, speech, thought content and disruptive/aggressive behavior are scored in between 0 and 8 whereas the remaining seven items are scored in between 0 and 4. The maximum score is 60. Score is interpreted as follows:

- < or equal to 12 = remission
- 13-19 = minimal symptoms
- 20-25 = mild mania
- 26-37 =moderate mania
- 38-60 = severe mania

Brief Psychiatric Rating Scale (BPRS)[92]

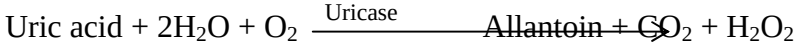
It comprises a total of 18 items, each of which is scored in between 1 to 7. A rating of "1" is given when a particular item is "not present", "2" for "very mild", "3" for "mild", "4" for "moderate", "5" for "moderately severe", "6" for "severe", and "7" for "extremely severe."

Uric Acid estimation

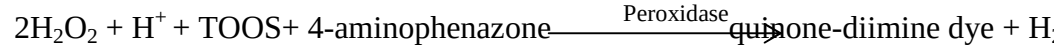
Serum uric acid estimation was done in vitro on Roche/Hitachi cobas c systems based on an enzymatic colorimetric test.

Steps of reaction:

1. Uric acid is cleaved by uricase enzyme to form allantoin and hydrogen peroxide.



2. Hydrogen peroxide oxidizes 4-aminophenazone in the presence of peroxidase enzyme and N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methylaniline (TOOS) to form a quinone-diimine dye that produces a red color, intensity of which is measured via photometrical analysis.



Normal reference range of serum uric acid was stated to be the following:

a) Males: 3.4 - 7.0 mg/dL
b) Females: 2.4 - 5.7mg/dL

Data Analysis

Data obtained was tabulated in Microsoft excel and subjected to appropriate statistical analyses. Descriptive statistics in the form of socio-demographic profile were presented as percentages, mean and standard deviation. The strength of association (p value) was calculated using fisher's exact test for qualitative data, and using unpaired t test and ANOVA for quantitative data. Pearson's correlation coefficient(r) was used to find the correlation between uric acid and other variables such as agitation, manic symptom severity, and psychotic symptom severity. Statistical significance was set at p value less than 0.05.

DISCUSSION

The main purpose of the study was to compare serum uric acid level among two sets of agitated patients, one with mania and other with non-affective psychotic disorders. Out of the 100 agitated patients that were admitted in the hospital, 50 individuals were those who were diagnosed with mania and the remaining 50 were those who were diagnosed with non-affective psychosis. Correlation of uric acid levels with the severity of agitation and severity of manic and psychotic symptoms was also attempted. The findings of the study are organized under the following headings of discussion.

1. Findings related to socio-demographic variables
2. Diagnostic subtypes among the two groups
3. Comparison of serum uric acid levels among the two groups
4. Comparison of serum uric acid levels among the males and females
5. Association of serum uric acid levels with body mass index among males and females
6. Correlation of serum uric acid levels with severity of agitation
7. Correlation of serum uric acid levels with severity of manic symptoms in individuals with mania
8. Correlation of serum uric acid levels with severity of psychotic symptoms in individuals with non-affective psychosis

1. Findings related to socio-demographic variables (refer Table 1)

A) Age

The mean age of individuals with mania was 32.42±12.47 years and those with non-affective psychosis was 33.3±9.17 years. The age difference between the two groups was not found to be statistically significant as p value was found to be 0.6886. As per the NMHSreport of 2015-16, current prevalence of bipolar disorder and schizophrenia was found to be maximum in the age group of 40-49 years.[82] Our study thus had a younger population of individuals affected than otherwise expected.

B) Gender

Among those who were suffering with mania, 68% were males who formed the majority and remaining 32% were females. NMHS report also highlighted slightly higher prevalence in males (0.3%) with respect to females (0.2%). However, our study reported a much higher proportion of males than females. This difference might be owing to the small sample size.

Among those suffering with non-affective psychotic disorder almost an equal number of males (48%) and females (52%) were found with females being a little more in number. However, when compared to the NMHS report a slight difference was noted as slightly higher prevalence among males (0.5%) was noted with respect to females (0.4%) as per its findings.[82] This again can be attributed to the small sample size of the population taken up in our study. Overall, no statistical significance was noted in the gender distribution among the two groups in our study, based on the data tabulated (p=0.0676).

C) Body Mass Index (BMI)

Our study revealed higher mean BMI in individuals belonging to the non-affective psychosis group (24.04±3.57 kg/m^2) than the manic group (22.93±3.76 kg/m^2). However, no statistical significant difference was noted since the p value was found to be 0.1333.

Table 3 further lays down the BMI distribution among males and females in the study sample. In both the sexes, maximum number of individuals belonged to the normal BMI category- 68.96% and 50% for males and females respectively. Among males, underweight BMI category, and among females, obese BMI category formed the minority with the percentage distribution being 5.17% and 2.38% respectively.

Studies conducted in the past have highlighted a positive association between uric acid levels and body mass index, details of which are discussed below.

D) Religion

Our study revealed that in both the groups Hindus formed the majority of the population. The percentages of Hindus (82%) and Muslims (18%) were found to be the same among the two groups, which is a chance finding, since it was not statistically significant (p=1.207).

E) Place of residence

Majority of the population were found belonging to the urban areas which was in line with the NMHS report. [82]56% of manic patients and 64% of the non-affective psychotic disorder patients belonged to the urban region, whereas 44% of manic patients and 36% of non-affective psychotic disorder patients belonged to the rural

region as per the results of our study. The inference based on our data regarding the domicile status is statistically insignificant (p=0.5406).

2. Diagnostic subtypes among the two subgroups (refer Table 2, Figure 1)

Under the manic group, our study included both patients who presented with first episode mania and those who had bipolar disorder- individuals with more than one episode of mania in the past. 74% of individuals in this group presented with bipolar disorder and hence formed the majority, out of which 44% were those who presented with psychotic symptoms and 30% were those who presented without psychotic symptoms. On the other hand, 26% of the individuals in this group presented with first manic episode, out of which 22% presented with psychotic symptoms and 4% presented without psychotic symptoms.

Under the non-affective psychosis group, our study included patients who presented with either acute psychosis or with chronic psychosis such as schizophrenia. Majority of individuals who were apart of this subgroup were cases of paranoid schizophrenia (60%), whereas acute psychosis without schizophrenic symptoms, acute psychosis with schizophrenic symptoms and undifferentiated schizophrenia were 20%, 12%, and 8% of the population respectively.

3. Comparison of serum uric acid levels among the two groups (refer Table 4, Figure 2)

Our study revealed higher serum uric acid levels in individuals suffering from mania (5.64±1.60 mg/dL) than those suffering from non-affective psychosis (4.99±1.49 mg/dL) and the difference between the two values was found to be statistically significant (p=0.0381).

Albert et al. (2014) compared uric acid levels in 150 bipolar disorder patients (cases) with 150 individuals with other psychiatric illnesses such as schizophrenia, obsessive compulsive disorder and major depressive disorder. This study revealed mean serum uric acid levels to be significantly higher in cases (5.06±1.45 mg/dl) with respect to controls (4.17±1.05 mg/dl).[113]

A mediation analysis by Bartoli et al. (2016) that compared the association between serum uric acid levels and various mental disorders revealed there being a significant association existing only with bipolar disorder patients and not with schizophrenia spectrum disorder patients.[125]

The results that were obtained in our study was hence corroborates well with the data that has been collected over the years. Kraeplin in 1921 had identified a link between bipolar disorder and purinergic dysfunction, stating that such patients had higher risk of developing gout because of hyperuricemia.[7] Similar findings were noted by Chung et al. (2010) who found a 1.14-fold higher risk of development of gout in bipolar disorder patients than the healthy controls.[126]

Table 5 and Figure 3 compare serum uric acid levels among various diagnostic subtypes under the two groups. Among manic individuals, those who presented with first episode mania without psychotic symptoms had the highest serum uric acid levels (7.15±0.07 mg/dL) and those who presented without psychotic symptoms had the lowest serum levels (5.16±1.58 mg/dL). Studies done by Salvadore et al. (2010) and Chatterjee et al. (2018) on first episode, treatment-naïve individuals with mania found serum uric acid levels to be elevated when compared to healthy controls. Their results further added to the preliminary evidence of underlying purinergic system dysfunction existing early on in the illness and not being associated with its longstanding course. The possible influence of drugs given in bipolar disorder patients

on uric acid, such as valproate, resulting in hyperuricemia was also hence ruled out.[42, 108, 35]

The results in our study further revealed that among individuals with non-affective psychosis, those who suffered from paranoid schizophrenia had the highest serum uric acid levels (5.20±1.52 mg/dL), whereas those suffered from undifferentiated schizophrenia had the lowest serum levels (3.77±0.69 mg/dL).

4. Comparison of serum uric acid levels among males and females

a) In the entire study population (refer Table 6, Figure 4)

In our study higher mean serum uric acid levels were found in males (5.75±1.62 mg/dL) than females (4.65±1.27 mg/dL) and the result was statistically significant (p=0.0004). This finding was in accordance to the available literature, and the reason put forward was the more muscle mass and hence increased turnover of purines seen in males with respect to females. Likewise, a study conducted by Bartoli F et al. (2018) which compared subjects with major affective disorders with healthy controls found mean serum uric acid to be significantly higher in males than females (5.43±1.23 mg/dL vs. 4.08±1.39 mg/dL; p <0.001).[80] Similar findings supportive of the results obtained in our study was noted in other studies as well.[115]

b) Those suffering from mania and non-affective psychosis (refer Table 7, Figure 5)

Since a significant statistical difference was noted between serum uric acid levels among the two groups (table 4), and among males and females of the sample as a whole (table 6), an attempt to further tabulate and compare males and females among the two groups was made in table 7.

Higher serum uric acid levels were noted among males when compared to females in both the groups (5.89±1.82 mg/dL vs.5.16±0.859 mg/dL and 5.58±1.32 mg/dL vs. 4.44±1.44 mg/dL in males and females of manic and non-affective psychosis group respectively). When the two sexes were compared individually, higher serum levels were found in the gender that belonged to the manic group than the non-affective psychosis group. The result was found to be statistically significant (p=0.0029).

5. Association of serum uric acid levels with body mass index (BMI) among males and females

The available literature points towards the male gender having higher uric acid levels, an attempt to find whether a significant correlation existed between the two sexes individually with uric acid levels existed in our study sample or not.

a) Males (refer Table 8, Figure 6)

Our study revealed that males who fell in the underweight BMI category (<18.5kg/m^2), had the lowest mean serum uric acid levels (4.4±1.05 mg/dL), whereas those in the normal BMI category (18.5-24.9 kg/m^2), had the highest mean serum uric acid levels (5.88±1.75 mg/dL). The findings were not statistically significant (p=0.5012). Figure 7 shows a bar graph with a rising trend of serum uric acid levels (plotted on the y-axis) as we move from the underweight BMI towards the normal BMI (plotted on the x-axis). However, subsequently we see a falling trend instead as we move towards the overweight and obese category. This is in contrast to the expected outcome which claims there to be a positive association between uric acid levels and BMI. The possible explanation to this finding could be the small population

sample of the overweight and the obese groups, which were 11 and 4 individuals respectively. A larger population would have hence helped generate better and more reliable results.

b) Females (refer Table 9, Figure 7)

Our study revealed that females who fell in the underweight BMI category (<18.5kg/m^2) had the lowest mean serum uric acid levels (4.27$\pm$0.26 mg/dL) whereas those in the obese category ($\geq$30 kg/m^2) had the highest mean serum uric acid levels (5.6$\pm$0.28 mg/dL). The findings were not statistically significant (p=0.7112). Figure 8 shows a bar graph with a progressive rising trend of serum uric acid levels (plotted on the y-axis) as we move from the underweight BMI category towards the obese BMI category (plotted on the x-axis).

Following studies reflect on the available literature on BMI and serum uric acid:

A study conducted by Reddy et al.(2003) revealed a positive correlation between plasma uric acid levels and body mass index, however no statistical significance was found.[9] Bartoli et al. (2018), found a positive correlation between uric acid levels and BMI which was found to be statistically significant.[80]

6. Correlation of serum uric acid levels with severity of agitation

a) In the study sample as a whole (refer Table 10, Figure 8)

In the present study it was found that when the mean serum uric acid levels were correlated with agitation, a weak positive correlation with ABS scores was found which was statistically significant (r=0.3095, p=0.0017). This meant that more severe the agitation, i.e. higher scores on ABS were associated with higher uric acid levels.

Our findings corroborated with the studies mentioned below:

A longitudinal study conducted by Sutin et al. (2014) on non-clinical community samples (n=6883) that attempted to find a link between serum uric acid levels and impulsivity related traits. Uric acid samples were tested twice in these individuals at a time interval of 3-5 years. The results showed that higher uric acid levels were found in individuals who had rated themselves higher for impulsiveness and excitement seeking under the impulsivity-related traits as per the Revised NEO Personality Inventory.[2]

A prospective study by Mrug et al. (2016) on a group of adolescents, primarily of African-American origin, found uric acid to be a predictor of aggression. In this study, patients were interviewed twice (wave 1 and wave 2) over a span of one and a half years, and uric acid samples were collected within one week of baseline interview. The results revealed higher 12-hour excretion of uric acid in urine in individuals that were older and in those who had higher self-reported aggression in the previous month in the second wave (r=0.28, p=0.014).[4]

However, a study conducted by Nurmedov et al. (2016) on 80 patients diagnosed with substance use disorder highlighted uric acid levels and impulsivity scores to be higher when compared to the healthy volunteers, however a statistically significant negative correlation was found between uric acid levels and impulsivity scores ($r=-0.278$, $p<0.05$).[79]

The above mentioned studies were either a longitudinal study conducted in healthy adults in a community (who showed a positive correlation) or a cross-sectional study conducted in substance use disorder patients (who showed a negative correlation).

However, no study tested for correlation of uric acid with psychiatric illness (other than substance use disorder until Bartoli et al. (2018) who in his cross-sectional study on subjects with major affective disorder (such as bipolar disorder and depression), found no significant correlation between uric acid levels with the previously tested behavioral manifestations on healthy animal and human models.[80]

b) In individuals with mania (refer Table 11, Figure 9)

Our study found a weak positive correlation between uric acid levels and agitation as measured using ABS scores in the manic group which was not found to be statistically significant ($r=0.2186$, $p=0.1272$). A study conducted by Chatterjee et al.(2018) on bipolar subjects that rated impulsivity in these individuals, however found uric acid levels to significantly correlate with scores on Barrett's Impulsivity Scale ($r=0.604$, $p<0.01$).[108]

c) In individuals with non-affective psychosis (refer Table 12, Figure 10)

Our study found a weak positive correlation that existed between serum uric acid levels and agitation as measured using ABS scores in the non-affective psychosis group which was statistically significant (r=0.2949, p= 0.0376).

7. Correlation of serum uric acid levels with severity of manic symptoms in individuals with mania (refer Table 13, Figure 11)

Our study has shown that there existed a weak positive correlation between uric acid levels and symptom severity as measured by YMRS scores in the manic subgroup as a whole. This however was found to be statistically significant (r=0.3433, p=0.0147). The interpretation of this result is that more severe the mania, higher will be the uric acid levels.

A study conducted by Gultekin et al. (2014) put the manic patients through repeated YMRS evaluation at baseline and weekly subsequently for four weeks thereafter, after the onset of treatment. No correlation was noted with symptom severity, however a correlation was found with clinical improvement. There was a significant correlation that was detected between the fall in serum levels and simultaneous reduction in YMRS scores at the baseline, and after one week. The significance was lost thereafter. Further weekly assessment revealed a falling trend in YMRS scores, which lost significance third week onwards.[110] A cross-sectional study conducted by Salvadore et al. (2010) found a negative correlation between YMRS scores and severity of manic symptoms in manic individuals which was not statistically significant (r=-0.20, p=0.39).[42] A cross-sectional study by Chatterjee et al. (2018) that attempted to correlate baseline YMRS scores and uric acid levels found no significant correlation between the two (r=0.047, p=0.80).[108]

8. Correlation of serum uric acid levels with severity of psychotic symptoms in individuals with non-affective psychosis (refer Table 14, Figure 12)

The results in our study showed a very weak positive correlation that existed between serum uric acid levels and psychosis symptom severity as measuring using BPRS scores in the non-affective psychosis group which was not statistically significant (r=0.1822, p=0.2053).

Strengths of the study

There have been mixed evidences in the past regarding the relationship between uric acid and agitation in psychiatric illnesses. This study further adds to the evidence of there being a positive correlation between the two. Our study also helps understand the relationship of uric acid and mania better. Unlike the previous studies that showed a correlation between fall in uric acid levels and reduction of YMRS scores, suggesting clinical improvement, our study adds on to the existing literature, by highlighting the correlation of uric acid levels with manic symptom severity. It hence suggests a future possibility of its use as a possible biomarker for early detection and severity assessment of mania.

Limitations of the study

a) Comparison with healthy controls would have helped understand the difference better- whether the rise in uric acid was due to agitation alone or whether it was due to the underlying pathophysiology.
b) A bigger sample size would have helped obtain results that would have been more generalizable.
c) The design of our study is cross-sectional, hence a causal association between uric acid and bipolarity cannot be drawn from our results.

d) Our study includes individuals who had first episode of mania or psychosis and those who were chronic cases of bipolar disorder or schizophrenia. The ones with a long standing course of illness were the ones likely to be on multiple psychotropics, the effect of which on uric acid wasn't considered in our study. Lithium for example is known for its uricosuric action; hence the individuals who were already on it at the time admission would have had lesser than the expected serum levels. Also, many individuals were simultaneously on treatment for other comorbidities as well such as hypertension, diabetes etc. but the influence of those drugs wasn't taken into account.

Future directions

This study opens us to the other possible underlying pathophysiologies that can result in an outward manifestation of agitation in individuals with mania and non-affective psychosis. Further studies adding more evidence on this subject will help us understand the relationship better which will further help detect and treat agitation earlier, hence minimizing the overall care-giver burden and the duration of hospital stay of the patient.

CONCLUSION

Our study revealed that uric acid levels are found to be significantly higher in individuals suffering from mania than individuals suffering from non-affective psychosis. A statistically significant correlation between agitation and serum uric acid levels was found in the overall study sample, however among the two groups, correlation was found to be significant only for the non-affective psychosis group. Uric acid levels were found to correlate well with severity of manic symptoms which meant that more severe forms of mania correlated with higher serum levels. However, correlation between uric acid levels and psychotic symptoms severity in non-affective psychotic disorder subgroup was not statistically significant.

SUMMARY

Purinergic dysfunction and subsequent rise in uric acid levels has a close association with agitation that can manifest itself in the form of verbal or physical aggression, disinhibition, impulsivity etc. Hyperuricemia is seen in all individuals, those healthy and those with organic or functional illnesses who present with acute agitation. Psychiatric illnesses such as bipolar disorder and schizophrenia have been proposed to have heterogeneous underlying etiopathologies that ultimately lead to their precipitation. Purinergic dysfunction and reduced anti-oxidant defense mechanisms are two of such mechanisms and since uric acid is related to both of these, altered uric acid levels are suspected in these illnesses.

The present study was a one year comparative cross-sectional study which was conducted in the Department of Psychiatry, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi from 1st January 2018 to 31st December 2018. A total of 100 agitated patients were admitted, 50 of them were diagnosed cases of mania and the remaining 50 were diagnosed cases of non-affective psychotic disorders. ABS was applied to the entire study sample to measure the severity of agitation. YMRS and BPRS were applied to the two groups to measure severity of mania and psychotic symptoms respectively. Fasting blood samples were collected and sent to biochemistry laboratory for serum uric acid estimation. Appropriate statistical tools were used to analyze uric acid levels were compared among the two groups and were correlated to ABS, YMRS and BPRS scores.

The mean age in manic subgroup was found to be 32.42±12.47 years and in the non-affective psychosis subgroup was found to be 33.3±9.17 years. 68% were males and 32% were females in the manic subgroup and 48% were males and 52%

were females in the non-affective psychosis subgroup. Mean BMI was found to be higher in the non-affective psychosis group (24.04±3.57 kg/m^2) than the manic group (22.93±3.76 kg/m^2). Both groups had Hindus in majority forming 82% of the total sample and Muslims who were the remaining 18%. The place of residence was rural in 44% of people with mania and 36% of people with non-affective psychosis. The p value across the two groups for the aforementioned parameters under socio-demographic profile was not statistically significant.

Mean serum uric acid levels in the manic subgroup (5.64±1.60 mg/dL) were found to be higher than the non-affective psychosis subgroup (4.99±1.49 mg/dL) with the p value being 0.0381. In the overall sample, significantly higher uric acid levels were found in males (5.75±1.62 mg/dL) with respect to females (4.65±1.27 mg/dL) (p=0.0004). The overall sample showed a moderate positive correlation between uric acid levels and agitation (r=0.3095, p= 0.0004). However, a weak positive correlation was found in mania (r=0.2186, p=0.1272) and non-affective psychosis when estimated separately (r=0.2949, p=0.0376).

Under manic subgroup, serum uric acid levels and manic symptom severity when correlated, showed a weak positive correlation (r= 0.3433, p=0.0147). Under non-affective psychosis subgroup, serum uric acid levels and psychotic symptom severity showed a very weak positive correlation (r=0.1822, p=0.2053).

Our study hence reveals that, uric acid level is found to be significantly higher in individuals suffering from mania and correlates well with manic symptom severity, which means that more severe the mania higher are the uric acid levels. However, even though uric acid levels are insignificant for severity of psychosis in non-affective psychotic disorder subgroup, it had a significant correlation with agitation.

More studies need to be done to further highlight and establish significance of uric acid as a biomarker for mania for its early detection and severity assessment. This will eventually help in shortening the duration of hospital stay, better treatment outcomes and lesser care-giver burden.

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ANNEXURE I

Title: "ASSESSMENT OF URIC ACID LEVELS IN AGITATED MANIA AND OTHER AGITATED NON-AFFECTIVE PSYCHOTIC DISORDERS- A ONE YEAR HOSPITAL BASED COMPARATIVE STUDY"

Principal Investigator (PI): Dr. _____

Objective/Purpose of the study:

You/your relative are/is being requested to be a subject in a comparative study, the purpose of which is to assess serum uric acid levels in agitated mania and in other agitated non-affective psychotic disorders which will be conducted between 1st January 2018 and 31st December 2018, by Dr. _____, a post graduate student in the Department of Psychiatry at Jawaharlal Nehru Medical College, KLE University, Belgaum, Karnataka.

You/your relative have/has been requested to participate in this study as you/your relative are/is likely to have a psychiatric illness. This study will help understand the association of uric acid levels in psychiatric disorder which will help us understand its role better and aid in further research.`

Procedure involved: If you/your relative agree to be a part of the study, the PI will interview you/your relative and take the blood sample.

Risks and benefits involved: There are no risks involved. During the period of study, the existence or development of any significant findings in terms of psychiatric disorders will be informed by the PI to you/your relative as well as the parent consultant for the appropriate action

Alternatives: Your/your relative's participation in this study is a completely voluntary decision. If you/your relative do/does not want to be a part of the study, you/your relative may refuse for the same or if you/your relative are/is already a part of the study and if you/your relative want/wants to withdraw from the study for any reason, you/your relative may do so without any hesitation. Discontinuation from the study for any reason will not affect your/your relative's current or future relationship with KLES Dr. Prabhakar Kore Hospital, Belgaum.

Privacy and confidentiality: The information provided by you/your relative will be known to the PI and the members of the research team. This information will remain confidential and will be disclosed to others only with your/your relative's written permission or if required by the law.

Financial incentives for participation: You/your relative will not be paid/offered any gifts for participation in the research. There will not be any remuneration for participating in the research and you/your relative will not be reimbursed for any expenses, such as bus/train travelling /companion/assistant etc.

Authorization to publish results: When the results of the research are to be published or discussed in conferences by the PI, no information will be disclosed that will reveal your/your relative's identity.

If you/your relative have/has any questions about this study, you/your relative may contact:

Dr. _____
Department of Psychiatry,
Jawaharlal Nehru Medical College,
KAHER, Belagavi-590010
Karnataka.

Dr. _____
Associate Professor,
Department of Psychiatry,
Jawaharlal Nehru Medical College,
KAHER, Belagavi-590010
Karnataka.

STATEMENT OF CONSENT

I have read and have completely understood the entire information given in the consent form, which explains all the details of the study, i.e, the purpose, procedure involved, risks & benefits, privacy & confidentiality, incentives and the authorization to publish the results of the study. I have voluntarily agreed to participate in the study. I may withdraw my participation for any reason or may be withdrawn by the investigator from the study for any reason at any time. I am not giving up any of my legal rights by signing this consent form. I will be given a copy of this consent form.

Signature of the participant with date: _____

Name of the participant: _____

Signature of the authorized representative with date:_____

Name of the authorized representative: _____

Signature of the witness with date: _____

Name of the witness:_____

Signature of the Investigator with date: _____

ANNEXURE II.ETHICAL CLEARANCE.

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
(Accredited 'A' Grade by NAAC)

Website: http://www.jnmc.edu
E-Mail : dome@jnmc.edu

Phone: (+ 91-(0)831 Office : 2471350
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 54 **Date: 22/11/2017**

To,

PG student in Psychiatry,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"ASSESSMENT OF URIC ACID LEVELS IN AGITATED MANIA AND OTHER AGITATED NON-AFFECTIVE PSYCHOTIC DISORDERS – A ONE YEAR HOSPITAL BASED COMPARATIVE STUDY"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

3

ANNEXURE III- PROFORMA

"ASSESSMENT OF URIC ACID LEVELS IN AGITATED MANIA AND OTHER AGITATED NON-AFFECTIVE PSYCHOTIC DISORDERS- A ONE YEAR HOSPITAL BASED COMPARATIVE STUDY"

Date and Time: IP/OP No: Serial No:

Name: Age: Sex: M/F

Religion: Hindu/Muslim/Christian/Others Marital Status/UM/WIDOW

Place: Informant:

Phone No: Socio-economic status:

Diagnosis:

Duration of illness:

Past treatment history:

Present treatment history :

Family history: Y/N

Substance use:

Alcohol Nicotine Cannabis Any other drugs

General Physical Examination:

BP: PULSE: RR: TEMPERATURE:

Height: Weight: BMI:

Systemic Examination:

CNS:

CVS:

RS:

P/A:

Mental Status Examination:

Consciousness

Orientation

Speech

Thought

Mood

Affect

Perception

Insight

Serum Uric Acid levels:

On Application of Scales:

YMRS Score:

BPRS Score:

ABS Score:

ANNEXURE IV

AGITATED BEHAVIOR SCALE

Patient_____ **Period ofObservation:**

Observ.Environ._____ **From:**_____ **a.m. p.m.**____/____/____

Rater/Disc._____ **To:**_____ **a.m. p.m.**____/____/____

At the end of the observation period indicate whether the behavior described in each item was present and, if so, to what degree: slight, moderate or extreme. Use the following numerical values and criteria for your ratings.

1 = absent: the behavior is not present.

2 = present to a slight degree: the behavior is present but does not prevent the conduct of other, contextually appropriate behavior. (The individual may redirect spontaneously, or the continuation of the agitated behavior does not disrupt appropriate behavior.)

3 = present to a moderate degree: the individual needs to be redirected from an agitated to an appropriate behavior, but benefits from such cueing.

4 = present to an extreme degree: the individual is not able to engage in appropriate behavior due to the interference of the agitated behavior, even when external cueing or redirection is provided.

DO NOT LEAVE BLANKS.

_____1. Short attention span, easy distractibility, inability toconcentrate.

_____2. Impulsive, impatient, low tolerance for pain orfrustration.

_____3. Uncooperative, resistant to care,demanding.

_____4. Violent and or threatening violence toward people orproperty.

_____5. Explosive and/or unpredictableanger.

_____6. Rocking, rubbing, moaning or other self-stimulatingbehavior.

_____7. Pulling at tubes, restraints,etc.

_____8. Wandering from treatmentareas.

_____9. Restlessness, pacing, excessivemovement.

_____ 10. Repetitive behaviors, motor and/orverbal.

_____ 11. Rapid, loud or excessivetalking.

_____ 12. Sudden changes ofmood.

_____ 13. Easily initiated or excessive crying and/orlaughter.

_____ 14. Self-abusiveness, physical and/orverbal.

____Total Score

ANNEXURE V - Young Mania Rating Scale (YMRS)

Instructions: For each item below, circle the response that best describes how you felt or behaved during the past 48 hours.

1. Elevated Mood

0 Absent
1 Mildly or possibly increased on questioning
2 Definite subjective elevation; optimistic; selfconfident; cheerful; appropriate to content
3 Elevated, inappropriate to content; humorous
4 Euphoric; inappropriate laughter, singing

2. Increased Motor Activity/Energy

0 Absent
1 Subjectively increased
2 Animated; gestures increased
3 Excessive energy; hyperactive at times; restless (can be calmed)
4 Motor excitement; continuous hyperactivity (cannot be calmed)

3. Sexual Interest

0 Normal; not increased
1 Mildly or possibly increased
2 Definite subjective increase on questioning
3 Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
4 Overt sexual acts (toward patients, staff, or interviewer)

4. Sleep

0 Reports no decrease in sleep
1 Sleeping less than normal amount by up to one hour
2 Sleeping less than normal by more than one hour
3 Reports decreased need for sleep
4 Denies need for sleep

5. Irritability

0 Absent
2 Subjectively increased
4 Irritable at times during interview; recent episodes of anger or annoyance on ward 6 Frequently irritable during interview; short or curt throughout
8 Hostile, uncooperative; interview impossible

6. Speech (Rate and Amount)

0 No increase
2 Feels talkative
4 Increased rate or amount at times, verbose at times
6 Push; consistently increased rate and amount; difficult to interrupt
8 Pressured; uninterruptible, continuous speech

7. Language/Thought Disorder

0 Absent
1 Circumstantial; mild distractibility; quick thoughts
2 Distractible; loses goal of thought; changes topics frequently; racing thoughts
3 Flight of ideas; tangentiality; difficult to follow; rhyming; echolalia
4 Incoherent; communication impossible

8. Thought Content

0 Normal
2 Questionable plans; new interests
4 Special project(s); hyper-religious
6 Grandiose or paranoid ideas; ideas of reference
8 Delusions; hallucinations

9. Disruptive/Aggressive Behavior

0 Absent, cooperative
2Sarcastic; loud at times, guarded
4 Demanding; threats in ward
6Threatens interviewer; shouting; interview difficult
8 Assaultive; destructive; interview impossible

10. Appearance

0 Appropriate dress and grooming
1 Minimally unkempt
2 Poorly groomed; moderately disheveled; overdressed
3 Disheveled; partly clothed; garish makeup
4 Completely unkempt; decorated; bizarre garb

11. Insight

0 Present; admits illness; agrees with need for treatment
1 Possibly ill
2 Admits behavior change, but denies illness
3 Admits possible change in behavior; but denies illness
4 Denies any behavior change

Scoring the YMRS

The purpose of each item is to rate the severity of that abnormality in the patient. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating. A severity rating is assigned to each of the eleven items, based on the patient's subjective report of his or her condition over the previous forty-eight hours and the clinician's behavioral observations during the interview, with the emphasis on the latter.

Scoring between the points given (whole or half points) is possible and encouraged after experience with the scale is acquired. This is particularly useful when severity of a particular item in a patient does not follow the progression indicated by the keys.

In scoring the YMRS, the following items are graded on a 0 to 8 scale:

- Irritability
- Speech
- Thought content
- Disruptive/aggressive behavior

The following items are graded on a 0 to 4 scale:

- Elevated mood
- Increased motor activity/energy
- Sexual interest
- Sleep
- Language/thought disorder
- Appearance
- Insight

ANNEXURE VI- Brief Psychiatric Rating Scale (BPRS)

Please enter the score for the term which best describes the patient's condition.
0 = not assessed, 1 = not present, 2 = very mild, 3 = mild, 4 = moderate, 5 = moderately severe, 6 = severe, 7 = extremely severe

1.SOMATIC CONCERN Degree of concern over present bodily health. Rate the degree to which physical health is perceived as a problem by the patient, whether complaints have a realistic basis or not.	10. **HOSTILITY** Animosity, contempt, belligerence, disdain for other people outside the interview situation. Rate solely on the basis of the verbal report of feelings and actions of the patient toward others; do not infer hostility from neurotic defenses, anxiety, nor somatic complaints. (Rate attitude toward interviewer under "uncooperativeness").
2. **ANXIETY** Worry, fear, or over-concern for present or future. Rate solely on the basis of verbal report of patient's own subjective experiences. Do not infer anxiety from physical signs or from neurotic defense mechanisms.	11. **SUSPICIOUSNESS** Brief (delusional or otherwise) that others have now, or have had in the past, malicious or discriminatory intent toward the patient. On the basis of verbal report, rate only those suspicions which are currently held whether they concern past or present circumstances.
3. **EMOTIONAL WITHDRAWAL** Deficiency in relating to the interviewer and to the interviewer situation. Rate only the degree to which the patient gives the impression of failing to be in emotional contact with other people in the interview situation.	12. **HALLUCINATORY BEHAVIOR** Perceptions without normal external stimulus correspondence. Rate only those experiences which are reported to have occurred within the last week and which are described as distinctly different from the thought and imagery processes of normal people.
4. CONCEPTUAL DISORGANIZATION Degree to which the thought processes are confused, disconnected, or disorganized. Rate on the basis of integration of the verbal products of the patient; do not rate on the basis of patient's subjective impression of his own level of functioning.	13. **MOTOR RETARDATION** Reduction in energy level evidenced in slowed movements. Rate on the basis of observed behavior of the patient only; do not rate on the basis of patient's subjective impression of own energy level.
5. **GUILT FEELINGS** Over-concern or remorse for past behavior. Rate on the basis of the patient's subjective experiences of guilt as evidenced by verbal report with appropriate affect; do not infer guilt feelings from depression, anxiety or neurotic defenses.	14. **UNCOOPERATIVENESS** Evidence of resistance, unfriendliness, resentment, and lack of readiness to cooperate with the interviewer. Rate only on the basis of the patient's attitude and responses to the interviewer and the interview situation; do not rate on basis of reported resentment or uncooperativeness outside the interview situation.
6. **TENSION** Physical and motor manifestations of tension "nervousness", and heightened activation level. Tension should be rated solely on the basis of physical signs and motor behavior and not on the basis of subjective experiences of tension reported by the patient.	15. **UNUSUAL THOUGHT CONTENT** Unusual, odd, strange or bizarre thought content. Rate here the degree of unusualness, not the degree of disorganization of thought processes.
7. MANNERISMS AND POSTURING Unusual and unnatural motor benavior, the type of motor behavior which causes certain mental patients to stand out in a crowd of normal people. Rate only abnormality of movements; do not rate simple heightened motor activity here.	16. **BLUNTED AFFECT** Reduced emotional tone, apparent lack of normal feeling or involvement.
8. **GRANDIOSITY** Exaggerated self-opinion, conviction of unusual ability or powers. Rate only on the basis of patient's statements about himself or self-in-relation-to-others, not on the basis of his demeanor in the interview situation.	17. **EXCITEMENT** Heightened emotional tone, agitation, increased reactivity.
9. **DEPRESSIVE MOOD** Despondency in mood, sadness. Rate only degree of despondency; do not rate on the basis of inferences concerning depression based upon general retardation and somatic complaints.	18. **DISORIENTATION** Confusion or lack of proper association for person, place or time.

VII- KEY TO MASTER CHART

SEX

1. Male
2. Female

RELIGION

1. Hindu
2. Muslim

OCCUPATION

1. Unemployed
2. Student
3. Housewife
4. Farmer
5. Businessman
6. Ex-service man
7. Driver
8. Coolie

AREA

1. Rural
2. Urban

DIAGNOSIS

30.1 Mania without psychotic symptoms

30.2 Mania with psychotic symptoms

31.1 BPAD mania without psychotic symptoms

31.2 BPAD mania with psychotic symptoms

20.0 Paranoid schizophrenia

20.2 Catatonic schizophrenia

20.3 Undifferentiated schizophrenia

23.0 ATPD APPD without symptoms of schizophrenia

23.1 ATPD APPD with symptoms of schizophrenia

Age	Sex	Religion	Occupation	Area	Height	Weight	BMI	Diagnosis	Uric Acid	ABS	YMRS	BPRS
19	1	1	2	2	169	55	19.25	30.2	4.9	37	43	0
28	1	1	5	2	177	75	23.94	31.2	7.8	46	54	0
30	1	1	2	1	171	63	21.54	31.2	11	43	49	0
18	1	2	2	2	170	58	20.07	30.2	7.7	42	48	0
20	1	1	5	2	159	62	24.52	31.1	6.6	24	30	0
20	1	1	2	1	166	69	25.04	30.1	7.1	34	35	0
24	1	1	2	1	174	54	17.83	31.2	4.5	49	42	0
30	1	1	5	2	165	72	26.44	30.2	4.8	44	33	0
59	1	1	6	2	164	64	23.79	30.2	3.2	30	36	0
30	2	1	3	2	138	36	18.9	31.2	6.6	43	30	0
18	1	2	2	2	160	55	21.48	31.2	4.8	38	41	0
18	2	1	2	2	152	41	17.74	30.2	4.5	47	44	0
28	1	1	4	1	171	63	21.54	31.2	5.4	53	43	0
32	2	1	3	1	149	64	28.82	31.2	4.5	44	44	0
67	1	1	4	1	165	72	26.44	31.2	4.33	38	19	0
24	1	1	8	2	166	73	26.49	31.1	6.3	28	33	0
23	1	1	4	1	174	63	20.8	31.1	4.6	24	31	0
65	1	1	3	1	157	63	25.55	31.1	7.1	41	40	0
51	2	1	3	1	163	52	19.57	31.2	4.1	23	49	0
24	2	1	1	1	159	90	35.59	31.1	5.8	27	27	0
43	1	2	1	2	166	54	19.59	31.1	6.3	42	42	0
30	1	1	5	2	159	57	22.54	31.2	4.2	24	32	0
42	1	1	1	2	176	82	26.47	30.2	4.2	26	34	0
23	2	2	3	2	154	65	27.4	31.2	5	30	32	0
20	2	1	1	1	159	46	18.19	31.1	4.5	23	28	0
26	1	1	4	1	181	67	20.45	31.1	5.5	30	41	0
25	1	1	8	2	166	57	20.68	30.2	6.2	29	34	0
53	2	1	3	2	152	51	22.07	31.2	4.1	51	39	0
42	2	2	1	2	163	52	19.57	31.1	6.1	39	42	0
34	1	1	4	2	166	69	25.03	31.1	6.6	24	30	0
56	1	1	1	2	172	63	21.29	31.2	4.8	38	41	0
43	1	1	4	1	169	68	23.8	31.1	4.6	24	31	0
19	1	2	1	2	172	55	18.59	30.2	4.2	26	34	0
23	1	1	4	2	174	58	19.15	30.2	7.7	42	48	0
28	1	1	4	1	165	72	26.44	30.2	3.2	30	36	0
39	2	1	3	1	159	62	24.52	31.2	4.5	44	44	0
41	2	1	3	2	159	46	18.19	31.2	4.1	23	49	0
35	2	1	3	2	152	51	22.07	31.2	5	30	32	0
45	2	1	3	2	154	65	27.4	31.1	6.1	39	44	0
21	1	1	1	1	168	60	21.25	30.1	7.2	34	35	0
42	1	1	1	2	160	79	30.85	31.2	5.4	53	43	0
40	2	1	3	1	159	57	22.54	31.1	5.9	27	27	0
25	1	2	1	1	170	62	21.45	30.2	6.2	29	34	0
28	1	2	5	2	163	59	22.2	31.2	4.5	49	42	0
26	1	1	4	2	160	79	30.85	31.2	4.33	38	19	0
30	1	1	4	2	163	60	22.58	31.1	7.1	42	48	0
28	2	1	3	1	152	46	19.9	31.2	5.8	30	32	0
30	1	1	2	1	168	62	21.96	31.2	10.9	43	49	0
34	2	1	3	1	154	55	23.19	31.2	6	36	40	0
22	1	2	1	1	168	60	21.25	31.1	6.2	27	34	0
23	1	1	7	2	157	46	18.66	23	8.3	28	0	74
28	1	1	1	2	159	44	17.4	20	5.4	49	0	60
42	1	1	4	1	167	54	19.36	20.3	3.6	32	0	52
45	1	1	1	2	160	79	30.85	20	5.4	37	0	74
50	2	1	3	2	156	70	28.76	20	5.8	30	0	65
40	2	1	3	2	149	64	28.82	20	4.1	39	0	46
59	2	1	3	2	146	45	21.11	20	7.2	33	0	52
21	2	2	1	2	147	35	16.19	20	4	26	0	56
28	1	1	4	1	163	60	22.58	23	5.5	28	0	74
30	2	2	3	2	149	56	25.22	23.1	6.9	24	0	51
30	2	1	5	2	151	53	23.24	20	4.8	22	0	42
33	1	1	5	1	167	52	18.64	20	5.6	29	0	65
30	1	1	1	2	168	50	17.71	20.3	3.3	25	0	80
28	2	1	1	2	150	63	28	20	3.5	25	0	86
25	2	1	3	2	152	57	24.67	20	3.9	21	0	56

32	2	1	3	2	154	75	31.62	20	5.4	21	0	62
33	2	1	3	2	158	60	24.03	20	4.9	29	0	65
31	2	1	3	1	155	52	21.64	20	2.3	24	0	56
38	1	1	1	2	179	87	27.15	20	7.3	33	0	74
37	1	1	5	2	170	90	31.41	20	6.9	25	0	60
38	2	1	3	1	154	51	21.5	23.1	3.6	27	0	52
21	1	1	1	1	173	88	29.4	20	6.5	23	0	55
47	2	1	1	2	141	53	26.65	20.3	3.4	21	0	80
18	1	1	2	1	167	54	19.36	23	3.9	21	0	46
26	2	1	3	2	151	64	28.06	23	3.7	24	0	38
35	1	1	4	1	170	69	23.87	20	5.6	29	0	65
42	1	1	4	1	159	55	21.75	20	7.3	31	0	70
24	1	1	5	2	164	59	21.93	20	6.5	23	0	55
32	1	2	3	2	173	65	21.71	23	5.5	28	0	74
22	2	1	1	2	160	60	23.43	20	3.9	21	0	56
25	2	1	1	2	150	55	24.44	23	3.7	24	0	38
38	2	2	3	2	155	65	27.05	23.1	6.9	24	0	51
18	2	1	1	2	149	58	26.12	23	3.6	27	0	52
28	1	1	4	1	165	60	22.03	23.1	3.9	21	0	46
45	2	2	3	2	149	55	24.77	20	4.8	22	0	42
34	2	1	1	2	153	60	25.63	20	3.5	25	0	86
30	2	1	4	1	159	55	21.75	20	2.3	24	0	56
40	1	2	3	2	166	68	24.67	20	5.3	29	0	65
42	1	1	1	2	163	60	22.58	20	7.1	31	0	70
35	1	1	1	1	171	65	22.22	20	6.5	23	0	55
25	1	1	4	1	165	70	25.71	23	5.5	28	0	74
22	2	1	1	2	150	55	24.44	23.1	3.6	27	0	52
28	1	1	4	1	168	60	21.54	23	3.9	21	0	46
42	2	1	4	1	142	55	27.27	20	2.3	24	0	56
30	2	2	3	1	155	60	24.97	20	5.4	21	0	62
40	1	2	3	2	166	68	24.67	20	5.5	24	0	65
45	2	2	3	2	149	55	24.77	20.3	4.8	22	0	42
51	2	1	3	2	146	55	25.8	20	7.2	33	0	52
25	1	1	4	1	163	60	22.58	23	4	26	0	46
34	1	1	3	1	150	55	24.44	23.1	5.8	40	0	65