

بسم الله الرحمن الرحيم





شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



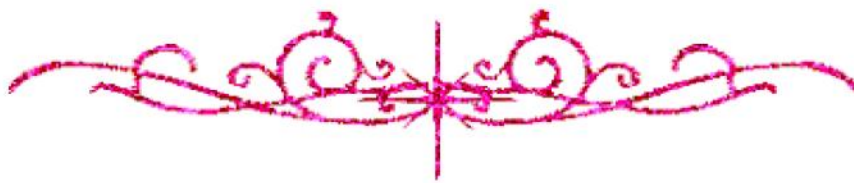
يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



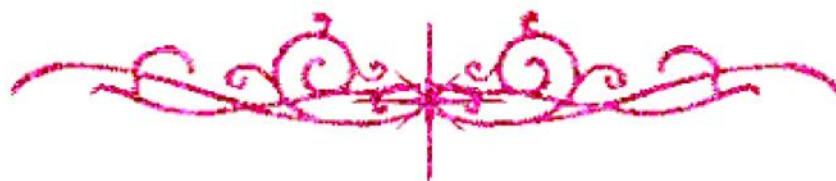


بعض الوثائق الأصلية تالفة





بالرسالة صفحات
لم ترد بالأصل





The Role of Serum Uric Acid as a Biomarker in Patients with Mood Disorders and Schizophrenia

Thesis

*Submitted for Partial Fulfillment of
Master Degree in Neuropsychiatry*

By

Riham Hossam ELDin Mahfouz
M.B.B.Ch

Supervised by

Prof. Nermin Mahmoud Shaker

*Professor of Neuropsychiatry
Faculty of Medicine – Ain Shams University*

Ass. Prof. Doha Mostafa ElSerafi

*Assistant Professor of Neuropsychiatry
Faculty of Medicine – Ain Shams University*

Dr. Mohamed Hossam Eldin Abdelmonem

*Lecturer of Neuropsychiatry
Faculty of Medicine – Ain Shams University*

Faculty of Medicine - Ain Shams University

2020

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سُبْحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

Acknowledgments

*First and foremost, I feel always indebted to **Allah** the Most Beneficent and Merciful.*

*I wish to express my deepest thanks, gratitude and appreciation to **Prof. Mermin Mahmoud Shaker**, Professor of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Ass. Prof. Doha Mostafa ElSerafi**, Assistant Professor of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for her sincere efforts, fruitful encouragement.*

*I am deeply thankful to **Dr. Mohamed Hossam Eldin Abdelmonem**, Lecturer of Neuropsychiatry, Faculty of Medicine, Ain Shams University, for his great help, outstanding support, active participation and guidance.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Riham Hossam Eldin Mahfouz

List of Contents

Title	Page No.
List of Tables.....	5
List of Figures	6
List of Abbreviations.....	7
Introduction	- 1 -
Hypothesis and Rationale	12
Aim of the Study	13
▪ The Purinergic Pathway, Serum Uric Acid and Major Mental Illness	14
▪ The Link between Purinergic Pathway and Major Mental Illness	29
▪ Clinical Implications of Purinergic Pathway on Major Mental Illness	34
Subjects and Methods.....	60
Results.....	68
Discussion	81
Conclusion	87
Strengths & Limitations.....	88
Recommendations	89
Summary.....	90
References	92
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table 1a:	Socio-demographic data of Schizophrenia, Bipolar disorder and Major Depression Disorder (MDD) cases and healthy control group.....	69
Table 1b:	Socio-demographic data of Schizophrenia, Bipolar disorder and Major Depression Disorder (MDD) cases and healthy control group.....	62
Table 2:	The Severity of symptoms in bipolar patients by Young Mania Rating Scale (YMRS), Hamilton depression scale (HAM-D) and Positive and Negative Syndrome Scale (PANSS) in the sample:	72
Table 3:	Uric acid values in Bipolar in relation to control.....	74
Table 4:	Uric acid values in MDD in relation to control.....	74
Table 5:	Uric acid values in Schizophrenia in relation to control.	75
Table 6:	Uric acid values in relation to sociodemographic data	76
Table 7a:	The difference in serum uric acid in major mental illness and controls.	78
Table 7b:	The difference in serum uric acid in major mental illness and controls with controlling of gender as a confounding factor.....	71
Table 8:	Correlation between Uric acid level and severity of symptoms in each illness.....	80

List of Figures

Fig. No.	Title	Page No.
Figure 1:	Metabolism and receptors of extracellular adenosine derivatives.....	17
Figure 2:	Schematic model of the sources of extracellular adenosine.....	19
Figure 3:	Uric acid	23

List of Abbreviations

Abb.	Full term
ADA	Adenosine deaminase
AMP	Adenosine monophosphate
ATP	Adenosine-5'-triphosphate
BD	Bipolar disorder
BIS-11.....	Barratt Impulsiveness Scale-11
CAT	Catalase
CFCN	Cerebrospinal fluid-contacting neurons
CNS	Central nervous system
E-5'NU	Ecto-5'nucleotidase
E-ADA	Adenosine deaminase
E-NPPases	Ecto-NPPases
E-NTPDases	Ecto-NTPDases
GHQ-28	General health Questionnaire
GSHPx	Glutathione peroxidase
HAM-D	Hamilton Depression Rating Scale
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HPST	Hypoxanthine-guanine phosphoribosyltransferase
IMP	Inosine monophosphate
MDD	Major depressive disorder
NMDA receptor	N-methyl-D-aspartate receptor
NTPDases	Nucleoside triphosphate diphosphohydrolases
PANSS	Positive and Negative Syndrome Scale
PNP	Purine nucleoside phosphorylase
RC	Rapid cycling
ROS	Reactive oxygen species
SAHH	S-adenosylhomocysteine hydrolase
SCID-I	Structured Clinical Interview for DSM-IV Axis I Disorders
SD	Standard deviation
SNP	Single nucleotide polymorphism

List of Abbreviations cont...

Abb.	Full term
<i>SOD</i>	<i>Superoxide dismutase</i>
<i>SPSS</i>	<i>Statistical package for Social Science</i>
<i>SSRIs</i>	<i>Selective Serotonin Re-Uptake Inhibitors</i>
<i>UA</i>	<i>Uric acid</i>
<i>VTA</i>	<i>Ventral tegmental area</i>
<i>XO</i>	<i>Xanthine-oxidase</i>
<i>YMRS</i>	<i>Young Mania Rating Scale</i>

INTRODUCTION

Uric acid is an end product from the purinergic metabolism of both adenosine and guanosine. It has been hypothesized that uric acid might be a marker of dysfunctions in adenosine transmission and antioxidant system, in different mental disorders, increased serum levels of uric acid may be a sign of an amplified purinergic turnover and a reduced adenosine transmission, opposite variation in serum levels of uric acid in Major depressive disorder and bipolar disorder. a reduced adenosinergic activity, mostly at A1 receptors (with an increase in uric acid levels), is associated with the complex network of changes on neurotransmitters pathways related to manic behavior (*Bartoli et al., 2018; Bartoli et al., 2016; Albert et al., 2015*) as the purinergic system was found involved in the regulation of mood, motor activity, cognitive function, sleep, and behavior, individuals with increased uric acid levels who do not have any psychiatric diagnosis were found to have high impulsivity and hyperthymic and irritable temperaments (*Asit et al., 2014*).

Studies found that the purinergic modulator allopurinol, a xanthine oxidase inhibitor used for the treatment of gout and hyperuricemia, is effective in treating acute mania when used adjunctively with mood stabilizers, besides its antimanic effect as an add-on treatment, it has been reported to reduce aggressive behavior in patients with dementia and refractory

aggression in psychiatric inpatients (*Oliveira et al., 2019; Bartoli et al., 2018*).

Circulating uric acid levels are dependent mainly on the nucleotide catabolism and cell turnover. However, uric acid can be oxidized non- enzymatically, and has proven to be a selective antioxidant. Membrane pathology, similar to that of RBC in response to free radicals was found in brains of schizophrenic patients, and so, the membrane dysfunction has been linked to free radical-mediated pathology and may contribute to specific aspects of schizophrenic symptomatology and complications of its treatment (*Yao et al., 1998*).

As evidence indicates that dysfunction in the purinergic system is involved both in bipolar disorder (BD) and in the pathophysiology and treatment of schizophrenia, However, uric acid levels were found to be lower in both chronic schizophrenia patients and newly diagnosed schizophrenia patients than healthy individuals, despite increased uric acid levels shown in both chronic BD patients and first episode mania patients (*Asit et al., 2014*).

Purinergic system dysfunction was incriminated in major depressive disorder (MDD) as well. studies conducted with these patients reported lower serum uric acid levels than healthy controls. Additionally, it was reported that those levels returned to normal ranges after 5 weeks of antidepressant treatment. In the former study, a strong inverse relation was