بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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Clinical correlates of elevated C-reactive protein (CRP) in Major Depressive disorder (MDD)

A Thesis

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in Psychiatry

By

Tamer Mohamed Sedky Zeidan

M.B.B.CH., M.SC.

Under Supervision of

Prof. Ahmed Saad Mohamed

Professor of Psychiatry, Psychiatry Department
Faculty of Medicine, Ain-Shams University

Prof. Nermin Mahmoud Shaker

Professor of Psychiatry, Psychiatry Department
Faculty of Medicine, Ain-Shams University

Prof. Marwa Abdel-Rahman Sultan

Professor of Psychiatry, Psychiatry Department
Faculty of Medicine, Ain-Shams University

Assist. Prof. Hanan Hany Elrassas

Assistant Professor in Psychiatry Department
Faculty of Medicine, Ain-Shams University

Faculty of Medicine

Ain-Shams University

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✍ **Tamer Mohamed Sedky Zeidan**

List of Contents

List of Abbreviations

Abbr.	Full-term
BBB	**:** Blood-brain barrier
BDI-II	**:** Beck Depression Inventory II
BDNF	**:** Brain-derived neurotrophic factor
COX	**:** Cyclooxygenase
CRP	**:** C-reactive protein
DHA	**:** Docosahexaenoic acid
DSM	**:** Diagnostic and Statistical Manual of Mental Disorders
EPA	**:** Eicosapentaenoic acid
fMRI	**:** Functional magnetic resonance imaging
GABA	**:** Gamma-aminobutyric acid
GWAS	**:** Genome-wide association studies
HAM-A	**:** Hamilton Anxiety Rating Scale
HPA	**:** Hypothalamic-pituitary-adrenal
ICD	**:** International Classification of Diseases
IFN	**:** Interferon
IL	**:** Interleukin
LBP	**:** Lipopolysaccharide binding protein
LOX	**:** Lipoxygenase
LPS	**:** Lipopolysaccharide
MAOA	**:** Monoamine oxidase A
MAOIs	**:** Monoamine oxidase inhibitors
MAPK	**:** Mitogen-activated protein kinases
MBC	**:** Measurement-based care

MCP-1 : Monocyte chemoattractant protein-1
mCRP : Monomeric (or modified) C-Reactive Protein
MDD : Major depressive disorder
MRI : Magnetic resonance imaging
MRS : Magnetic resonance spectroscopy
n-3 : Omega-3
n-6 : Omega-6
NICE : National Institute for Health and Care Excellence
NIRS : Near-infrared spectroscopy
NMDA : N-methyl-D-aspartate
NSAIDs : Nonsteroidal anti-inflammatory drugs
OxLDL : Oxidized low-density lipoprotein
PC : Phosphocholine
pCRP : Pentameric C-Reactive Protein
PET : Positron emission tomography
PHQ-9 : Patient Health Questionnaire-9
PUFA : Polyunsaturated fatty acids
QIDS-SR : Quick Inventory of Depressive Symptomatology
SCFAs : Short-chain fatty acids
SCID-I : Structured clinical interview for DSM-IV
SD : Standard deviation
SDS : Self-rating Depression Scale
SNRIs : Serotonin–noradrenaline reuptake inhibitors
SPSS : Statistical Package for Social Sciences
SSRIs : Selective serotonin reuptake inhibitors
SSS-8 : Somatic Symptom Scale-8
STAR*D : Sequenced treatment alternatives to relieve depression

TCAs **:** Tricyclic antidepressants
TNF **:** Tumor necrosis factor
TRD **:** Treatment-resistant depression
TSPO **:** Translocator protein 18 kDa
VMAT2 **:** Vesicular monoamine transporter 2
YLDs **:** Years lived with disability

List of Tables

List of Figures

Rationale and Hypothesis

Although many antidepressant drugs are currently available, they are far from optimal. Approximately 50% of patients do not respond to initial first line antidepressant treatment, while approximately one third fail to achieve remission following several pharmacological interventions. Most of the commonly used antidepressants have been primarily designed to increase synaptic availability of serotonin and/or noradrenaline and although they are of therapeutic benefit to many patients, it is clear that other therapeutic targets are required if we are going to improve the response and remission rates ***(O'Leary et al., 2015).***

The rationale to this study is to help find/confirm a different pathological mechanism contributing to depression and thus paves the way for utilizing other out-of-the-box medication either mono or as add-on if we are going to improve the response and remission rates.

Hypothesis

The research team hypothesizes that; there would be an association between CRP and MDD.

Introduction

Major Depressive disorder (MDD) is a common illness worldwide, with more than 264 million people affected. At its worst, depression can lead to suicide. Close to 800 000 people die due to suicide every year which is the second leading cause of death in 15-29-year-olds ***(World Health Organization, 2020).***

Disturbances in four spheres **(mood, psychomotor activity, cognitive, and vegetative)** should be ordinarily present for a definitive diagnosis of MDD. Mood disturbances includes painfully aroused mood typically experienced as worse than the severest physical pain, thus depressed mood has a somatic quality. In psychomotor disturbances, there may be either psychomotor agitation (pressured speech, restlessness, hand wringing, and hair pulling) or psychomotor retardation, which underlie diminished efficiency or those patients' inability to work. The cognitive view of depression considers negative evaluations of the self, the world, and the future (the negative triad). Faulty thinking patterns are clinically expressed as ideas of deprivation and loss, low self-esteem, helplessness, hopelessness, and pessimism; and recurrent thoughts of death and suicide. Some of the thoughts may verge on the delusional. For vegetative disturbances, the mood change in depressive disorder is accompanied by measurable alterations of biorhythms that implicate midbrain dysfunction. The biological concomitants of melancholia include profound reductions in appetite, sleep, and sexual functioning, as well as alterations in other circadian rhythms, especially matinal worsening of mood

and psychomotor performance. An equally prominent subgroup of depressed persons exhibits a reversal of the vegetative and circadian functions, with increases in appetite and sleep—and sometimes in sexual functioning—and an evening worsening of mood ***(Akiskal, 2017).***

Inflammation is a key component of the innate immune system's ability to clear infection and repair injured tissue. Inflammation results from the release of pro-inflammatory cytokines from innate immune cells. In addition to their effects in the periphery, cytokines can communicate with the brain, can have a negative effect on neurotransmission and result in a host of emotional, cognitive, and behavioral changes collectively termed "sickness behaviors" ***(Dantzer et al., 2008)***.

Peripheral cytokines can, directly and indirectly, affect brain circuits, behavior and mood. They can be transported through the blood–brain barrier to act directly on CNS-resident cells, including astrocytes, microglia and neurons. In addition, inflammatory signals can be conveyed to the CNS through cellular mechanisms (CNS infiltration by peripheral immune cells) or signaling via the vagus nerve (the 'inflammatory reflex') ***(Hodes et al., 2015)***

Among peripheral biomarkers associated with MDD, the inflammation biomarkers are the most promising and easy to measure. Several evidences implicate that elevated levels of systemic inflammation have been associated with depression ***(Howren et al., 2009),***and studies have shown

that patients with MDD on an average have higher levels of plasma inflammatory markers compared to nondepressed individuals ***(Dowlatiet al., 2010).*** It was also found that lack of therapeutic benefit of antidepressants is associated with increased inflammatory markers ***(Haroon et al., 2018).***

C-reactive protein (CRP) is an acute-phase protein that is widely used in clinical practice and has also been measured in many prior studies of MDD. A high-sensitivity assay for CRP is well-validated and accessible. CRP synthesis is induced in the liver by proinflammatory cytokines – especially interleukin 6 (IL-6) – in response to infection, inflammation and tissue damage ***(Haapakoski et al., 2015).***

Several studies identified associations between depression and a high level of CRP ***(Lee et al., 2019; Tabatabaeizadeh et al., 2018).***

Few studies have investigated if there is a relationship between inflammatory markers and specific mood symptoms and their severity ***(Hafner et al., 2008; Kohler et al., 2016b; Köhler-Forsberg et al., 2017)***. However they were not without limitations like inclusion of bipolar patients ***(Hope et al., 2013; Kohler et al., 2016b)***, inclusion of few sample size ***(Hafner et al., 2008)***, did not investigate specific symptoms ***(Hafner et al., 2008)***, or CRP levels were not measured in all individuals ***(Köhler-Forsberg et al., 2017).***