Serum level of Brain-derived Neurotropic Factor in major depression disorder

Thesis

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بسم الله الرحمن الرحيم

﴿ وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ وَسَتُرَدُّونَ إِلَى عَالِمِ الْغَيْبِ وَالشَّهَادَةِ فَيُنَبِّئُكُمْ بِمَا كُنْتُمْ تَعْمَلُونَ ﴾

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Dedication

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List of Abbreviations

AKT: Enzyme that encoded by AKT gene

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropnic acid

BDNF: Brain derived neurotropic factor.

BMI : Body mass index

CBP: CREB binding protein

CE : Capillary electrophoresis.

Cpg: The cpg sites are regions of DNA where cytosine nucleotide is followed by a guanine in a linear sequences of bases along its $5\rightarrow 3$ direction. Methylated sequences of DNA.

CPE : Cytopathic effect

CRHR1: Corticotrophin-releasing hormone receptor 1

CREB: cAMP response element-binding protein.

CT : computerized tomography

DD-NOS: Depressive disorder not otherwise specified

DEDC : department of education

DNMT: DNA methyl transferase.

DSM V: Diagnostic and statistical manual of mental disorder five.

ECT : Electroconvulsive therapy

EGFP : Protein (EGFP) downstream of specific promotor

ELISA: Enzyme linked immunoassay.

ERK: Extra cellular receptor coupled kinase

FGF: Fibroblast growth factor.

GABA: Gamma amino butyric acid.

GAD: Generalized Anxiety disorder

List of Abbreviations

GCA : giant cell arteritis

HAT: Histone acetyl transferase.

HDACs: Histone deactylase.

HMTs: Histone methyl transferase.

HPA : Hypothalamic pituitary axis

IL6 : Interleukin 6

Kda: kilo Dalton

LNGFR : Low affinity nerve growth factor receptor.

mAB : monoclonal antibody

MDD: Major depressive disorder

Met: Methionine

NF-KB: Nuclear factor kappa

NGF: Nerve growth factor.

NFKB: Nuclear factor kappa-light-chain enhancer of activated B cell.

NGFR: Nerve growth factor receptor

NMDA: N-methyl-D-aspratate.

NT-3 : Neurotrophin 3

NT-4 : Neurotrophin 4

NTRK2: Neurotropic tyrosine kinase receptor type 2

NSC|NPC : Neural stem cell\neural proliferation cell

PDZ : Domain is a common structural domain of 80-90 amino acid

PFC: Prefrontal cotex

PKC : Protein kinase

List of Abbreviations

PMD: Psychotic major depression

PPD : Postpartum depression.

PSD-95 : Postsynaptic density 95

PTEN: is a gene encoded for Phosphate and tensin homolog protein

RBD : Recurrent brief depression

RIA : Radioimmunoassay

ROIs : Region of interest

RT-PCR : Reverse transcription polymerase chain reaction

SAD : Seasonal affective disorder.

SVZ: Subventicular zone

Trk : Tyrosine kinase.

Trk A: Tyrosine receptor kinase A

TrkC: Tyrosine receptor kinase C

Val: Valine

5-HTTLPR: Serotonin-transporter-linked polymorphic region

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Introduction

Depression is one of the most important mental disorders with a state of sad mood and aversion to activities that exerts a negative effect on a person's thoughts and behavior. It is a complex disease having both genetic and environmental components as contributing factors *(Sheikh. et al 2010)*. Major depressive disorder is one of the leading causes of disability and mortality in the world *(Fuchikami., et al 2011 and Roy., et al 2014)*.

Neurotropic factors had been implicated in the pathophysiology of depression. Among neurotrophins, Brain derived neurotropic factor (BDNF) is the matter of researches nowadays *(Molendijk., et al 2016)*. Brain derived neurotropic factor is particularly abundant in the hippocampus and cerebral cortex. Postmortem studies revealed that the brain of depressed patients showed smaller hippocampi than healthy individuals .Studies done on experimental animals revealed a significant positive correlation between cerebral and blood BDNF *(Fuchikami., et al 2011 and Rawson., et al 2015)*.

Aim of the Work

The aim of the present study was to assess serum BDNF among major depression disorder (MDD) patients in comparison to healthy controls .In addition to investigate the role of anti-depressant therapy on BDNF levels.

I.Major Depression Disorder:

Healthy persons experience wide range of moods that can be normal, elevated or depressed thus they have equally large reports of affective expression so, they feel in control *(American psychiatric Association,2018)*. Major depression disorder is one of the mood disorders. That is a pervasive and sustained feeling experienced internally and influences a person's behavior and perception of the world *(Wu and Len GW .,2014).*

Mood disorders include the followings:

- Major depressive disorder.
- Bipolar disorder (type1,2) .
- Cyclothymic disorder.
- Mood disorders due to general medical condition.
- Substance –induced mood disorder
- General category of depressive and bipolar disorder not otherwise specified *(Sheikh. et al 2010*).

Major depression disorder (MDD) is characterized by a persistent feeling of sadness or a lack of interest to the outside stimuli *(Roy et al., 2014).* It is a mental disorder characterized by at least two weeks of low mood that is present across most situations. It is often accompanied by low self-esteem, loss of interest in normally enjoyable activities, low energy, and pain without a clear cause *(Wu and Len GW .,2014).*

The MDD is also known as unipolar. It differs from bipolar disorder in that the latter is an oscillating state between depression and mania. Instead, unipolar depression is solely focused on the "lows" or the negative emotions and

symptoms that experienced *(American psychiatric Association,2018)*.

A.Causes of Major Depression Disorder:

The cause of major depression disorder is unknown. Biological, psychological, and social factors may play a role in causing depression. The diathesis–stress model specifies that depression results when a preexisting vulnerability, or diathesis, is activated by stressful life events *(Rawson et al., 2015)*.There is evidence that MDD can be inherited and that there is a genetic vulnerability to develop the illness. In psychiatric issues many disorders can co-occur with the depression disorder such as anxiety or drug abuse *(Fuchikami., et al 2011).*

1.Genetics:

A family history of depression may increase the risk. It's thought that depression is a complex trait, meaning that there are probably many different genes that each exert small effects, rather than a single gene that contributes to disease risk *(American psychiatric Association,2018).*

The serotonin transporter promoter gene's short allele (5-HTTLPR) has been associated with increased risk of depression. Other genes have been linked to a gene environment interaction. These include corticotropin releasing hormone receptor 1 (CRHR1), (FKBP5) also known as FKBP5, (a protein that encoded by the FKBP5 gene) and brain derived neurotropic factor (BDNF), the first two proteins are related to the stress reaction of the hypothalamic pituitary axis(HPA) axis, and the latter is involved in neurogenesis *(Roy et al., 2014)*.

2.Other Health Problems

Depression may also be secondary to chronic or terminal medical conditions such as HIV/AIDS, or asthma in this condition depression is termed "secondary depression" *(American psychiatric Association,2018)*. It is unknown if the underlying diseases induce depression through effect on quality of life, or through shared etiologies such as degeneration of the basal ganglia in Parkinson's disease or associated with other immune deregulation *(Caldeira et al., 2007)*.

Drug abuse in early age is also associated with increased risk of developing depression later in life *(Foulds et al.,2015)*. Depression that occurs as a result of pregnancy is called postpartum depression, and is thought to be the result of hormonal changes associated with pregnancy *(Kaplan et al., 2016*).MDD may also be iatrogenic, such as drug induced depression. Therapies associated with depression include interferon therapy, beta blockers, isotretinoin, contraceptives pills, cardiac agents, anticonvulsants, anti-migraine drugs, antipsychotics, and hormonal agents such as gonadotropin-releasing hormone agonist *(Ray et al., 2018)*.

B.Types of Major Depression Disorder:

1. Persistent Depression Disorder

Depression that lasts for 2 years or longer is called typical depressive disorder. This term is used to describe two conditions previously known as dysthymia (low-grade persistent depression) and chronic major depression *(American psychiatric Association,2018*).

Symptoms include changes in appetite (not eating enough or overeating), sleep too much or too little, lack of energy, or fatigue ,low self-esteem, trouble concentrating or making decisions and feel hopeless *(Sheikh. et al 2010)*.

2. Seasonal Affective Disorder (SAD)

Seasonal affective disorder is a period of major depression that most often happens during the winter months, when the days become short and get less sunlight. It typically goes away in the spring and summer. Diagnosis is based on at least two episodes that occur in winter months *(Kaplan et al.,2016).*

3. Psychotic Depression

People with psychotic depression have the symptoms of major depression along with "psychotic" symptoms, such as:

- Hallucinations (seeing or hearing things that aren't there).
- Delusions (false fixed beliefs).
- Paranoia (wrongly believing that others are trying to harm you). *(Kaplan et al., 2016).* .

4. Peripartum (Postpartum) Depression

Women who have major depression in the weeks and months after childbirth may have peripartum depression disorder *(Fuchikami et al., 2011).*

5. Premenstrual Dysphoric Disorder (PMDD)

Women with PMDD have symptoms of depression before the start of their period *(Rich et al., 2011).*

6. Situational Depression

It is the depressive mood when having trouble managing in a stressful life event, such as a death in family, a divorce, or losing job. It's also called "stress response syndrome." If persists more than two months, it is considered major depression disorder *(Briones et al., 2013).*

7. Atypical Depression

On the contrary to persistent depression, a patient of atypical depression may have a temporarily improvement of the