Republic of Iraq

Ministry of Higher Education and Scientific Research

University of Babylon / College of Science

Department of Biology

A study of Immunogenetic and Physiological Parameters Among Patients with Some Psychological Stress

A Thesis

Submitted to the Council of the College of Science, University of Babylon, in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Science /Biology-Zoology

By

Qasim Hamadi Abid Fhdil

B.Sc. Biology / College of Science
University of Kerbala(2013)
M.Sc. Biology/ College of Science
University of Kerbala(2016)

Supervised By

Prof. Dr. Alaa Jawad Hassan

College of Science

University of Babylon

2023 A.D. **1444 A.H.**

بسم الله الرحمن الرحيم

فَتَعَالَى اللَّهُ الْمَلِكُ الْحَقُّ ۗ وَلَا تَعْجَلْ
بِالْقُرْآنِ مِن قَبْلِ أَن يُقْضَىٰ إِلَيْكَ وَحْيُهُ ۖ
وَقُل رَّبِّ زِدْنِي عِلْمًا

صدق الله العلي العظيم

سورة طه

ايه ١١٤

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Supervisor Certification

I certify that this thesis entitled "**A study of Immunogenetic and Physiological Parameters Among Patients with Some Psychological Stress"** was prepared under my supervision at the College of Science, University of Babylon , Department of Biology, as a partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Biology/ Zoology.

Accordingly, I recommended this study for discussion.

Signature
Prof. Dr. Alaa Jawad Hassan
Department of Biology - Collage of Science
University of Babylon
(Supervisor)
Date: / /2023

In view of the available recommendation, I forward this thesis for debate by the examining committee.

Signature
Assis.Prof. Dr. Adi Jassim Abd AL-Rezzaq
Head of Department of Biology - Collage of Science
University of Babylon
Date: / /2023

Certification of the Examining committee

We, the members of examining committee, certify that we have read the dissertation entitled **(A study of Immunogenetic and Physiological Parameters Among Patients with Some Psychological Stress)** and examined the student **(Qasim Hamadi Abid Fhdil)** in its contents, and that in our opinion, it is accepted as a dissertation for degree of Doctor of Physiology in biology/ Zoology with **(Excellent)** estimation .

Signature:…

Prof. Dr. Ihsan Idan Abdul Kareem Al-Saimary

College of Medicine/ University of Basrah

Date: / / 2023

(Chairman)

Signature:……

Prof. Dr. Shakir Hammad Mohammed Al-Alwany

College of sciences/ University of Babylon

Date: / / 2023

(Member)

Signature:……

Prof. Dr. Hussein Jasim Obaid Al-Harbi

College of sciences / University of Babylon

Date: / / 2023

(Member)

Signature:……

Prof. Dr. Frial Gemeel Abd Atiae

College of sciences / University of Babylon

Date: / / 2023

(Member)

Signature:……

Prof. Dr. Maysaa Adil Hadi

College of sciences / University of Babylon

Date: / / 2023

(Member)

Signature:……

Prof. Dr. Alaa Jawad Hassan

College of sciences/ University of Babylon

Date: / / 2023

(Member and Supervisor)

Approved for the College Committee of Graduate Studies

Signature:……

Prof. Dr. Mohammed Hadi Shinen Alshammeri

Dean of College of sciences/ University of Babylon

Date: / / 2023

DEDICATION

To My Dears

My Father,

My Mother,

My Brothers,

My Sister,

QASIM

Acknowledgment

First and foremost, I wish to express my sincere gratefulness and deep cordial thanks to ALLAH, The Originator of Heavens and Earth, Who provides me the strength and the patience to complete this work.

It is indeed sense of pleasure and pride that I extend my thanks and gratitude to my supervisor **Prof. Dr. Alaa Jawad Hassan** , College of Science / University of Babylon, for his valuable guidance, unceasing help, unerring supervision and critical suggestions.

I am also grateful to **Prof. Dr. Shakir Al-Alwany**, College of Science/ University of Babylon for his help in viral diagnosis.

I would like to offer my thanks to **Assist Prof. Dr. Wassen Modher** and **Assist Prof**. **Dr. Sura Ihsan** College of Science/ University of Babylon, for her help in facilitating the tasks of my higher studies and offering facilities to finish this work.

I would like to offer my thanks to **Prof. Dr. Waffa AL-Wazni** , College of Science/ University of Karbala for their guidance in planning and precious advices during this work.

My thanks to **Assist lecture Iman** for their help to finish this work.

My thanks to **my dear sisters Gasson and Najah** for their help to finish this work.

Qasim 2023

Summary

There are many of Psychological diseases associated with stress such as Alzheimer's disease (AD) is considered a degenerative neurological disorder. Around 50 million people worldwide will be affected by this illness in 2020, while, schizophrenia is a mental condition that affects about 1% of people worldwide and major depression disease is a global concern roughly 7% of adults experience a severe depressive episode each year.

The present study was conducted in Imam Al-Hasan Almjtaba Hospital and Imam AL- Hussein Medical City in Karbala city from February (2022) to August (2022). Ninety persons included in this study with ages ranged from 19-92 years and the study population was divided into four groups: first group includes 30 of apparently healthy control(AHC) and three patients groups which include 60 of patients with psychological stress distributed into 20 patients for each Alzheimer, schizophrenia and major depression diseases. A total of 90 blood and stool samples were collected from patients and AHC groups.

Demographic characteristics of the study appeared that age distributed in Alzheimer, schizophrenia and Major depression patients was (>60, 30-60 and 30-60) years in percentage (95%, 60% and 50%) respectively compared with AHC group. Alzheimer, schizophrenia Major depression patients that distributed by duration of disease are (5-20, 5-20 and <5) year in percentage (75%,60% and 80%) respectively. The distribution of Alzheimer, schizophrenia and Major depression patients according to sex was (female, female and male) in percentage (60%, 60% and 55%) respectively compared with AHC group. Smoking status revealed that Alzheimer, schizophrenia and Major depression patients was(non-smoker, smoker and smoker) in percentage (80%,65% and 70%) respectively compared with AHC group.

Summary

According to the results revealed that Alzheimer, schizophrenia and depression patients was (married, married and single and married) in percentage (100%, 45% and 65%) respectively compared with AHC group.

The results of immunological parameters appeared that significant rise ($p \leq 0.05$) in the levels IL-1β and GAD65 in all patients groups compared with AHC group. In addition , the results of physiological parameters showed that there are significant decrease ($p \leq 0.05$) in serotonin and dopamine hormones levels in patient groups in comparison with AHC group.

Results of correlation coefficient between study parameters (IL-1β, serotonin, dopamine and GAD-65) showed that there are a positive significant association ($P \leq 0.05$) between IL-1β and serotonin levels in AHC group.

The molecular study of *IL-1β* gene polymorphism appeared that *IL-1β* genotype (GA) in Alzheimer patients are formed (60%) compared with AHC group, while, the percent of schizophrenia patients and Major depression patients are(70%) and (45%) respectively in *IL-1β* genotype (GG) compared with AHC group. Results of *5-HT1A* gene polymorphism showed that Alzheimer and schizophrenia patient groups was in percent (50%) of *5-HT1A* genotype(GC) compared with other groups, but the major depression patients was reached to (50%) in *5-HT1A* genotype (CC) compared with other groups. While, relationship of *IL-1β* gene polymorphism with IL-1β level in psychological stress patients and AHC groups appeared that there are a significant rise($p \leq 0.05$) in schizophrenia patients in genotype (GA) of *IL-1β* gene and IL-1β levels in comparison with genotype (GG) of *IL-1β* gene and schizophrenia patients don't have genotype (AA) of *IL-1β* gene in their chromosome.

Summary

Percent of infection in HSV-1is (50% and 50%) in HSV-1 positive and negative test for Alzheimer and schizophrenia patients respectively, while, the Major depression patients formed (60% and 40%) in HSV-1 test positive and HSV-1 test negative respectively. there was a significant change ($p \leq 0.05$) in Alzheimer and major depression patients between HSV-1 infection(positive and negative) and IL-1β levels .

Percent of bacterial infections showed that Alzheimer, schizophrenia and Major depression patients are formed (35%, 25% and 40%) respectively in *H. pylori* test positive compared with AHC group.

In conclusion, the psychological stress diseases increased pro inflammatory cytokines (IL-1β and GAD-65). Also, physiological parameters (serotonin and dopamine) induced by psychological stress diseases. Also, there was association between genotypes (GA, GG) for *IL-1β* (rs16944) and genotypes (GC, CC) for (*5-HT1A*) **(**rs6296) gene polymorphisms with psychological stress diseases. Finally microbial infection (HSV-1and *H. pylori*) was associated with psychological stress diseases, because the stress leads to minimize the activity and efficiency of immune response against foreign antigens.

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List of Abbreviation

Abbreviation	Description
ACS	Acute Coronary Syndrome
A	Adenine
AD	Alzheimer's Disease
APP	Amyloid Precursor Protein
Aβ	Amyloid-β
ANOVA	Analysis of Variance
Ag	Antigen
AN-FEP	Antipsychotic Naive First-Episode Psychosis
APOE	Apo lipoprotein E
AHC	Apparently Healthy Control
AAAD	Aromatic Amino Acid Decarboxylase
bp	Base Pair
BD	Bian Disease
BP	Bipolar Disorder
BBB	Blood-Brain Barrier
BSCB	Blood-Spinal Cord Barrier
BDV	Borna Disease Virus
BDNF	Brain-Derived Neurotropic Factor
BDH	British Drug Houses
CO2	Carbon Dioxide
CAIDE	Cardiovascular Risk Factors, Aging And Dementia
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CCL11	Chemokine(C-C motif) Ligand 11
CIRS	Compensatory Immune-Regulatory Reflex System
CRH	Corticotropin-Releasing Hormone
CRP	C-Reactive Protein
CXCL8	C-X-C Motif Chemokine Ligand8
COX-2	Cyclo-Oxygenase- 2
CSP	Cysteine String Protein
CMV	Cytomegalovirus
C	Cytosine
DA	3,4-Dihydroxyphenethylamine or Dopamine
DAT	DA Transporter
Deaf-1	Deformed epidermal autoregulatory factor-1
DDC	DOPA Decarboxylase
ELISA	Enzyme Linked Immuno Sorbent Assay
EBV	Epstein Barr Virus
EDTA	Ethylene Diamine Tetra Acetic Acid
FST	Forced Swim Test

GABA	**Gamma-Aminobutyric Acid**
GI	**Gastrointestinal Tracts**
GWEIS	**Genome-Wide by Environment Interaction Studies**
GAD1 gene	**Glutamic Acid Decarboxylase 1 gene**
GAD2 gene	**Glutamic Acid Decarboxylase 2 gene**
GAD 65	**Glutamic Acid Decarboxylase 65**
GAD67	**Glutamic Acid Decarboxylase 67**
G	**Guanine**
HCs	**Healthy Controls**
HSC70	**Heat Shock Cognate 70**
H. pylori	***Helicobacter pylori***
HIV	**Hepatitis I Virus**
HSV	**Hepatitis S Virus**
HSV-1	**Herpes Simplex Virus Type1**
HSV-2	**Herpes Simplex Virus Type-2**
HRP	**Horse Radical Peroxidase**
HHV 6-8	**Human Herpes Viruses 6, 7 and 8**
HLA	**Human Leukocyte Antigen**
NFTs	**Hyperphosphorylated Neurofibrillary Tangles**
HPAA	**Hypothalamus–Pituitary–Adrenal Axis**
5-HT	**5-Hydroxytryptamine or Serotonin**
5-HTR1A	**5-Hydroxytryptamine Receptor 1A or Serotonin Receptor**
5-HIAA	**5-Hydrxoy Indole Acetic Acid**
IRS	**Immune-Inflammatory Responses System**
IgG	**Immunoglobulin**
ITG	**Inferior Temporal Gyrus**
IFN-γ	**Interferon-γ**
IL	**Interleukin**
iGluR	**ionotropic Glutamate Receptors**
LOS	**Length of Stays**
L-DOPA	**Levodopa or L- 3,4-Dihydroxyphenethylamine**
MRI	**Magnetic Resonance Imaging**
MDD	**Major Depression Disease**
MDA	**Malondialdehyde**
mGluR	**metabotropic Glutamate Receptors**
Mcc	**Microcin E492**
MCI	**Mild Cognition Impairment**
MAPK	**Mitogen Activated Protein Kinase**
MDs	**Mood Disorders**
NCBI	**National Center for Biotechnology Information**
NUDR	**Nuclear DEAF-1 Related protein**
OCD	**Obsessive-Compulsive Disorder**
OR	**Odds Ratio**

OD	**Optical Density**
5-HT1A	**5-Hydroxytryptamine 1A or Serotonin Receptor**
PD	**Parkinson's Disease**
PUD	**Peptic Ulcer Disease**
PGC-1α	**Peroxisome proliferator-activated receptor Gamma Coactivator 1-α**
PBS	**Phosphate Buffer Solution**
pTau	**Phosphorylated Tau protein**
PA	**Physical Activity**
PUFA	**Poly Unsaturated Fatty Acid**
PCR	**Polymerase Chain Reaction**
PET	**Positron Emission Tomography**
PTSD	**Post-Traumatic Stress Disorder**
PLP	**Pyridoxal-Phosphate**
RPM	**Round Per Minute**
SCZ	**Schizophrenia**
SSRIs	**Selective Serotonin Reuptake Inhibitors**
SERT	**Serotonin**
SNP	**Single Nucleotide Polymorphism**
STHs	**Soil-Transmitted Helminths**
sIL-1RA	**soluble IL-1 Receptor Antagonist**
sIL-2R	**soluble IL-2 Receptor**
sIL-6R	**soluble IL-6 Receptor**
sTNFR	**soluble TNF Receptor**
SE	**Standard Error**
SPSS	**Statistical Program Social System**
SNS	**Sympathetic Nervous System**
Th	**T helper**
Treg	**T regulatory**
TGF-β	**Transforming Growth Factor-β**
TRS	**Treatment-Resistant Schizophrenia**
TBE Buffer	**Tris-Borate-EDTA-Buffer**
TRYCATs	**Tryptophan Catabolites**
TPH	**Tryptophan Hydroxylase type**
TM	**Tryptophan Monooxygenase**
TNF-α	**Tumor Necrosis Factor-α**
T1D	**Type 1 Diabeties**
T2DM	**Type 2 Diabetes Mellitus**
TH	**Tyrosine Hydroxylase**
UV	**Ultraviolet**
VZV	**Varicella-Zoster Virus**
VGAT	**Vesicular GABA Transporter**
WHO	**World Health Organization**

CHAPTER ONE

INTRODUCTION

1:Introduction

Stress is unavoidable in today's world. Stressful situations include bereavement, providing care for a family member with a chronic illness, interpersonal issues, juggling several chores and responsibilities, job stress, unemployment, financial worries, over-exercising, and many others. Previous study appeared that psychological stress has an impact on immunological function (Segerstrom and Miller, 2004). The conception of stress, defined as "the body's general reaction to every change request" (Selye, 2013). Stress reaction will lead to neuroendocrine response which involved hypothalamus–pituitary–adrenal axis (HPAA) and the sympathetic nervous system stimulation that will result in the secretion of glucocorticoids and catecholamine. Subsequently, this response will be followed by a sharp increase in oxidative stress (Chrousos, 2009).

Stress alters immune system responses, which in turn impacts the digestive system, reproductive system, and developmental processes (Maeda and Tsukamura, 2006). Stress was associated with certain psychological diseases such as Alzheimer's disease (AD) which is a degenerative neurological disorder categorized by neuron degeneration, major changes in personality and behavior, memory loss and learning impairment (Deture and Dickson, 2019). Despite the fact that few occurrences among children have been found, AD is an age-linked condition that affects 10% of persons between the ages of 65 and 75 and roughly 32% of those over the age of 80 (Askarova *et al.,* 2020), also AD is associated with significant burden on caregivers and the healthcare system due to increased medical needs and expenditures required to protect from AD disease (Morris *et. al.,* 2015).

Other investigations have discovered a link between IL-1β polymorphism and AD (Du *et al.,* 2000). Another disease related to psychological stress was Schizophrenia which is a mental illness described by negative signs like reduced expressiveness and motivation as well as cognitive deficiencies like

poor mental processing speed, executive functions and memory. It also exhibits psychotic signs like disorganized speech, delusions, and hallucinations (Hany *et al.,* 2021).

One of the top ten causes of impairment globally and one that affects about 1% of the world's population is schizophrenia. While some people with schizophrenia are profoundly disabled, others are able to function at a high level, showing that persons with schizophrenia have a wide variety of abilities in their daily lives (Maj *et al.,* 2021). It was discovered that schizophrenia and the C(x1019)G polymorphism in the human 5-HT1A receptor gene promoter region were significantly correlated, providing evidence for the involvement of the 5-HT1A receptor gene in the pathophysiology of schizophrenia, previous study discovered a higher prevalence of the C allele in schizophrenia, which is connected to higher expression in cell lines (Tauscher *et al.,* 2002).

In addition, major depression disease (MDD) was also related to the psychological stress that are a global concern and the top source of burden and impairment worldwide (Ferrari *et al.,* 2013. Certainly, major depression is associated with a shorter lifespan, in part due to suicide and in part due to a greater susceptibility to serious illnesses such cancer, diabetes, autoimmune disease, cardiovascular disease, and stroke (Bortolato *et al.,* 2017).

In MDD patients, while some studies found no changes, some found elevated serum levels of cortisol, MDA, IL-1β, IL-6 , IL-15, IL-18, TNF-α, IL-10 and CRP (Nishuty et al., 2019). Some studies have found a relation between these indicators and the degree of depression (Farooq et al., 2017). It would have been excellent to evaluate the relationship between the frequency of the rs16944 SNP and the expression of the IL-1β gene, this approach could potentially to improve comprehension of the IL-1β SNP functional role (Battle and Montgomery, 2014). HSV-1 is neurotropic and primarily replicates in the frontal and temporal regions of the brain, where it may cause memory changes and cognitive impairments resembling those seen in schizophrenia

patients(Pramod et al., 2013). HSV-1 interactions with oxidative stress are crucial since it is anticipated that oxidative damage will manifest early in the pathogenesis of AD (Bonda et al., 2010).

Aim of the study

The aim of the current study was to measure the levels of some immunological, physiological parameters , in addition to study the genetic tendency of patients and apparently healthy control, as well as finding the relationship of microbial infection with psychological stress diseases in a sample of Iraqis. This aim would be achieved by using the following objectives:

1.Estimating the serum levels of interleukin- 1β(IL-1β) and glutamic acid decarboxylase (GAD 65).

2.Estimating the serum levels of serotonin or 5-hydroxytryptamine (5-HT) and dopamine (DA).

3.Investigating the polymorphism of *interleukin-1β(IL-1β)* (rs16944) and *serotonin receptor (5-HT1A)* **(**rs6296).

4.Finding the relationship between microbial infections include viral infections such as HSV-1,bacterial infections such as *H. Pylori* and parasitical infections such as *G. lamblia*, *E. histolytica* and *C. parvum* psychological stress diseases.

CHAPTER TWO

LITERATURE REVIEWS

2:Literature Reviews

2.1:Psychological Stress

2.1.1:Definiton of Psychological Stress

Stress is defined in psychology as a sensation of pressure and strain on the emotions (Mental Health America, Retrieved , 2018). A state of mental pain is stress, Some stress may be advantageous since it can increase drive, physical performance, and receptivity to the environment. However, excessive stress can exacerbate a pre-existing condition, increase the risk of strokes, heart attacks, ulcers, and mental health conditions like depression, and make a pre-existing condition worse (Sapolsky,2004). A person may experience pressure, discomfort, or other unpleasant feelings in response to a situation that they later label as stressful because of internal beliefs, or stress may also be external and related to the environment (Fiona *et al.*, 2018).

2.1.2: Classification of Stressful Stimuli

There are three types of stressors to consider (Majzoub, 2006)

1.Physical fitness (for example, restraint, foot shook, and exercise)

2.Psychological, such as anxiety, fear, or mental anguish.

3.Metabolic problems, such as heat exhaustion, hypoglycemia, and bleeding.

Malhotra (2007) categorized stress into two categories depending on its duration:

1.Severe (single, intermittent, and time-limited exposures).

2.Chronic (exposures that are both intermittent and long-term or continuous).

2.1.3: Stress Effects

Stress syndrome leads to muscular atrophy, depressed mood, gastric ulceration, immune system inhibition , weight gain, hypertension, lack of appetite and lack of sexual capicity (Vermetten and Bremner, 2002). Chronic stress can cause females to experience induced abortion, higher infant death

rates, irregular ovulation cycles and late maturation (Pacak and Palkovits, 2001), while in men, long-term stress inhibits testosterone release, which is linked to defective sperm production and lower desire in men (Eskiocak *et al.*, 2006). Another illustration of the adverse effects of continuous mental stress is psychiatric dwarfism (Majzoub, 2006). There is now evidence that aberrant stress responses are implicated in the development of a variety of diseases and disorders. Anxiety disorders, depression, hypertension, and cardiovascular disease, as well as age- related processes, various gastric disorders and some cancers. Stress also appears to increase the frequency and severity of migraine headaches, asthma attacks, and blood sugar fluctuations in diabetics. Furthermore, scientific evidence suggests that people who are under psychological stress are more susceptible to colds and other infections than their less-stressed counterparts. Overwhelming psychological stress can result in both momentary (transient) and long-term (chronic) symptoms of post-traumatic stress disorder (PTSD), a serious psychiatric illness (Panzarino *et al.*, 2007).

2.1.4: Stress Response

The stress response, sometimes known as the "fight-or-flying" response, is the body's natural and rapid shift into "high gear." It is simple to see how this reaction aids the body's response to a physical threat (Guyton and Hall, 2000a). When an individual is confronted with such a threat, the hypothalamus (located near the brain's base) activates the body's warning mechanism. This system causes the adrenal glands, which are located on the top of the kidneys, to release a flood of hormones, the most abundant of which are adrenaline and cortisol, via a combination of nerve and hormonal impulses (Matsuwaki *et al*., 2004). Adrenaline raises blood pressure, raises heart rate, and enhances energy levels. Cortisol, the principal stress hormone, raises

blood sugar (glucose), increases the availability of substances that heal cells and enhances the brain's use of glucose (Anonymous, 2006). Also cortisol suppresses processes that aren't necessary or beneficial in a fight-or-flying location. It suppresses the digestive system, reproductive system, and development processes through altering immune system reactions (Maeda and Tsukamura,2006). Long-term activation of the stress-response system, as well as subsequent overexposure to cortisol and other stress hormones, can disrupt nearly all body processes, raising the risk of obesity, insomnia, digestive issues, heart disease, depression, memory impairment, immune suppression, physical illnesses, and other complications (Guyton and Hall, 2000).

2.1.5: Types of Stress

2.1.5.1: Acute Stress

Acute stress is a fairly typical phenomenon that can be induced by a variety of factors (examples include receiving a chronic sickness diagnosis, losing a loved, being in a road accident and seeing or experiencing an attack. It's vital to realize that severe stress can result from seeing a distressing incident just as much as it can from experiencing one firsthand (Kivi, 2018). When people are seeing the doctor or dentist or looking forward to significant moments or when they are getting ready for a business meeting or a report or significant life events (For instance, the delivery of a child, children leaving for college or university, traveling , beginning a new work, resigning and a marriage night) they can experience acute stress(Healthline Editorial Team,2020). Acute stress rarely has long-term negative effects on mental and physical health. However, following a stressful event, acute stress disorder is classified as a transitory stress disorder in the diagnostic and statistical manual. After an incident, this can continue anywhere from three days to a month (Eske, 2019).

2.1.5.2: Periodic Adverse Stress

Chronic acute stress is characterized as repeated, recurrent episodes of stress in which the stressful experience happens occasionally or on a daily basis. When you experience multiple stressors at the same time, or when you are frequently concerned about a harmful experience or incident that may occur in the future. Non-periodic severe stress can occasionally be seen in episodes of episodic acute stress. They include anxiety about upcoming professional presentations, frequent doctor's appointments, and meetings to discuss a divorce, among other things. Individuals who describe themselves as close, naturally worried or agitated are more likely to experience this form of stress, as even slight stressors might be misinterpreted as big stresses (Healthline Editorial Team,2020).

2.1.5.3: Chronic Stress

Chronic stress is defined as a state of continual tension with little (or no) release. Chronic stress is common in people who are dealing with long-term medical problems or injuries, or those who are providing care for someone who is experiencing such problems; additionally, People who are dealing with or having witnessed neglect, tall remarriage or baby custody disputes, high-stress or high-danger occupations (such as medical emergency service employees, fire services, policemen, military members and naval force, rapid response employees) are all at risk for developing chronic stress (Healthline Editorial Team,2020).

2.2: Alzheimer's Disease

2.2.1: Definition of Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurological illness that begins slowly and worsens with time (WHO,2020). It is the cause of 60–70% of dementia cases (Simon *et. al.,* 2018; WHO,2020). The trouble recalling recent events is the most prevalent early symptom (Knopman *et al.*,2021). Language problems, disorientation (including getting lost easily), mood changes, loss of desire, self-neglect, and behavioral concerns are all possible signs as the condition progresses (Simon *et al.,* 2018). When a person's health deteriorates, they frequently retreat from family and society. Bodily functions deteriorate with time, eventually leading to death. While the rate of progression varies, the average life expectancy after diagnosis is three to nine years (National Institute on Aging,2021).Intracellular structures of hyperphosphorylated neurofibrillary tangles (NFTs) and extracellular amyloid-(A) protein accumulation are features of AD, which is the primary cause of dementia and a growing universal public health concern (Apostolova,2016). Previous research has found biochemical changes in lymphocytes from AD and mild cognitive impairment (MCI), include disruption of the cell cycle, mitochondrial dysfunction and significant oxidative stress. These metabolic changes in MCI and AD cells appear to affect their immunological and physiological capabilities (Wojda ,2016). Additionally, activation status in blood platelets and amyloid precursor protein (APP) synthesis levels have been connected to AD, which may influence AD etiology (Gorelick *et al.*,2014). Patients with AD have deteriorated superior cortical functioning, resulting in memory loss, confusion, difficulties understanding, math, learning capacity, language, and judgment, making it difficult to complete daily activities (Araojo *et al.*,2015).

2.2.2: Neuroinflammation

Neuroinflammation known to occur in the AD brain and can be induced in the periphery through an accumulation of degenerative tissue and deposits of insoluble abnormal peptide formations, such as Aβ peptide and neurofibrillary tangles (NFTs) in plasma (Cai *et al.*,2014).As neuroinflammation is a major contributor to cell damage and neuronal loss, and is a prominent feature in AD, a pharmacological intervention that targets these inflammatory processes may slow the progression of AD (Aso and Ferrer, 2014). Furthermore, as post-mortem and ante mortem studies have demonstrated associations between agitation, and Aβ plaques and NFTs (Ruthirakuhan *et al.,* 2018).

2.2.3: Epidemiological Profile

Females with Alzheimer's disease are more common than males with Alzheimer's disease in terms of deaths per million people in 2012, however this difference is largely attributable to women's higher life spans. Both sexes are afflicted by Alzheimer's disease at the same rate when age is taken into account (Simon *et al.*,2018). The prevalence of Alzheimer's disease in populations is determined by a variety of criteria, including incidence and survival. Because AD incidence increases with age, prevalence is calculated by the average population age. In 2020, the prevalence of Alzheimer's dementia in the United States was projected to be 5.3 percent in people aged 60 to 74, 13.8 percent in those aged 74 to 84, and 34.6 percent in people over 85 (Rajan *et al.*,2021). By 2050, the disease's prevalence is anticipated to triple as both its incidence and prevalence continue to climb(Li *et al.*,2021). There are 50 million AD patients globally as of 2020, and by 2050, that is expected to reach 152 million (Breijyeh and Karaman,2020).

2.2.4: Etiology and Risk Factors

The emergence of psychological stress illnesses is accompanied by a number of environmental and genetic risk factors. The most potent genetic risk factor comes from an (APO lipoprotein E) APOE allele (Long and Holtzman,2019; National Institute Fact Sheet,2021). A history of head trauma, severe depression, and high blood pressure are additional risk factors (WHO,2020). Amyloid plaques, neurofibrillary tangles, and a loss of neuronal connections in the brain are all major contributors to the disease process. While initial symptoms are frequently misdiagnosed as signs of normal aging, a definitive diagnosis can only be made after the patient has passed away and brain tissue has been examined. Healthy eating, regular exercise, and social interaction are all recognized to be advantageous as people age and may help lower the risk of cognitive decline and Alzheimer's disease(NIA,2021). The two primary pathological hallmarks of AD neurofibrillary tangles (NFTs) and amyloid plaques, although no drugs or dietary supplements have been demonstrated to lower risk (Hsu and Marshall,2017). According to some theories, a buildup of amyloid β proteins (Aβ) causes neuronal malfunction and death in the brain, which was considered to be brought on by the overall amyloid load's harmful effects. The cleavage of amyloid precursor proteins (APP) into amyloid β (Aβ) peptides (Aβ1- 40 and Aβ1-42), for example, is one example of particular changes in Aβ processing that have been shown (DeTure and Dickson, 2019).

2.2.5: Inflammatory and Immunological Factors

While some risk factors for AD are inherited in origin, others are influenced by environmental or lifestyle variables, may be modifiable, and have been linked to a developed risk of dementia, including AD. They comprise vascular morbidity, such as silent cerebral infarction, hypertension

and diabetes mellitus as well as smoking and alcoholism, obesity, and high levels of total cholesterol. These factors are also prone to aging-related biological processes that may be associated with AD (Povova *et al.,* 2012). Additionally, research showed that a grouping of risk variables was seen to add to the likelihood of developing AD. Using information from the CAIDE study, a dementia risk score was developed that, over a 20-year follow-up period, predicted dementia with a negative predictive value of 0.98, specificity of 0.63 and sensitivity of 0.77. This score took into account factors including age (47 years), a lack of education, hypertension, high cholesterol, and obesity (Gallagher *et al.,* 2011).

2.3: Depression

2.3.1: Definition of Depression

The word "affective" or "mood disorders" refers to a group of psychological and behavioral issues, including depression. One of the main causes of disease liability globally and a significant public health issue has been depression (Bagalman *et al*., 2014). Clinical signs include alterations in mood and cognition as well as major neurovegetative functions (such as changes in hunger, fatigue, sleep difficulties, and difficulty to perform sexual activities)(Iwata *et al*., 2013). According to Kiecolt-Glaser *et al*., (2015), inflammatory illnesses are commonly co-occurring with chronic and recurrent major depressive disorder (MDD), which raises the possibility that inflammation has a role in the onset or persistence of MDD. Pro-inflammatory cytokines, a family of proteins that mediates immunological responses to injury, infection, and other organism stress, have been linked to increased levels in serum and cerebral spinal fluids in people with MDD, according to several studies (Noto *et al*., 2015). Over 400 million people worldwide suffer from chronic mood disorders (MDs) such MDD and bipolar disorder

(BP)(WHO, 2016). It is becoming more widely recognized that inflammatory processes affect cognition, may be another mechanism through which cardiovascular risk develops into disease in MDD (Rosenblat *et al*., 2014), and interact with brain health (Charlton *et al*., 2014).

2.3.2: Epidemiology

According to Bauer *et al.,* (2013), MDD is a serious mood disease that affects people of all ages and races and is linked to significant morbidity and mortality. Arabic women are more likely than women from other cultures to have postpartum depression (Ramasubramaniam *et al*., 2014). In USA, around 18.6% of adults aged 18 and above is estimated to experience mental illness for 12 months; this statistic excludes substance-use disorders. Meanwhile, excluding substance use disorders, it is estimated that 4.1% of individuals have significant mental illness within a 12-month period (Bagalman and Napili, 2014). According to the global Mental Health Survey, which was a 17-country research, 5% of those polled had a depressive episode within the preceding year (WHO, 2012). After excluding drug addiction disorders, the estimated annual prevalence of mental illness among adults was 4.1%. (Bagalman *et al*., 2014). In the United States, roughly 7% of adults experience a severe depressive episode each year (Hedden *et al*., 2015). Major depression is the second most incapacitating medical condition in the United States, according to the World Health Organization, accounting for more years of disability than heart disease, stroke, or diabetes (Murray *et al*., 2013). Both disability and death are influenced by major depression. In the United States, there are more than 49,000 suicide fatalities every year (Johnson *et al*., 2014).

2.3.3: Prognosis

According to research by Hannestad *et al.,* (2011), depression frequently coexists with acute coronary syndrome (ACS), and elevated inflammation has

been shown to decrease prognosis. Additionally, a worse prognosis is predicted by depression co-occurring with ACS (Lichtman *et al.*, 2014). Since depression was found to be strongly connected with a high mortality risk in T2DM patients, this population's mortality risk may be significantly decreased by conducting a more comprehensive surveillance of T2DM patients to identify depression risk factors (Jeong *et al.*, 2017).

2.3.4: Etiology of Depression

Norepinephrine plays a significant and determinant role in an executive function that regulates cognition, mood, interest, and intelligence; these processes are fundamental in social relationships (Moret and Briley, 2011). The etiology of depression is still unknown, its diagnosis is ambiguous, and medication is unsuccessful despite the extensive research efforts made in previous decades. This can be the result of a lack of knowledge about the molecular pathophysiology of depression(Postal *et al.*, 2015).The pathophysiology of depression has generally been viewed primarily in terms of the monoamine depletion hypothesis. It implies that the pathophysiology of depression is primarily driven by an imbalance in serotonergic and noradrenergic neurotransmission (Massart *et al.*, 2012). It links the monoamine theory to additional biological variables and contends that elevated immunological activation is the cause of depression (Maes *et al.*, 2013). In order to achieve rapid synapses-crossing transmission, glutamate must bind to metabotropic glutamate receptors (mGluR) and ionotropic glutamate receptors (iGluR), which are found on both neurons and non-neuronal cells (Dore *et al.*, 2014). Patients with depression have higher amounts of glutamate (or glutamine) in their brains, cerebrospinal fluid, and plasma (Hashimoto, 2011).

2.3.5: Depression and Immune Response

The discovery that depression is associated with increased expression of pro-inflammatory cytokines, such as cyclo-oxygenase-2 (COX-2), makes it possible to create novel medications that focus on the aforementioned molecular pathways(Maes *et al.,* 2013). COX-2 inhibitors are also being considered as complementary treatments for depression (Faridhosseini *et al.,* 2014). Aspirin, curcumin, celecoxib, N-acetylcysteine and statins are examples of medications with possible antidepressant characteristics that also have immunological effects related to the pathophysiology of depression (Berk *et al.,* 2013), according to recent meta-analyses have potential antidepressant properties (Fernandes *et al.,* 2016).

Maximizing the amounts of muscle-derived protein (peroxisome proliferator-activated receptor gamma coactivator-1 [PGC-1]), Physical Activity (PA) modifies the course of MD neuropathology (Agudelo *et al.*, 2014). According to certain studies, pro-inflammatory cytokines may help healthy volunteers who receive immune-stimulating substances like endotoxin develop (Grigoleit *et al.*, 2011). TNF-α may influence how antidepressants work in a number of different ways (Duseja *et al.*, 2015) , First, anti-TNF-α does raise SERT expression in astrocytes, which may increase the efficacy of the medications or otherwise be permissive for drug action (Malynn *et al.*, 2013).

Anti-TNF- may have effects through the regulation of other neurotransmitter receptors, such as the 5-HT1A auto-receptor, which can also determine responsiveness to antidepressants (Cai *et al.*, 2013) , Changes in glutamate signaling are thought to be important in depression and the response to antidepressants (Richardson *et al.,* 2010).

2.4: Schizophrenia

2.4.1: Definition

The name "schizophrenia" was originally used in 1908 by Eugen Bleuler, and it comes from the Greek words "schizo" (splitting) and "phren" (mind) (Engmann, 2021). Delusional beliefs, hallucinations, and changes in thought, perception, and behavior are all features of the functional psychotic condition schizophrenia (Hany *et al.,* 2021). Hallucinations, delusions, disorganized speech and behavior, and a flattened affect are some examples of the positive, negative, and cognitive symptoms that groups categorize it as having (Correll and scoller, 2020). According to studies by Espregueira *et al.* in 2020 and Moreno-Küstner *et al.* in 2021, serious mental illness is associated with an increased risk of suicide and violent death as well as cardiovascular disease, cancer, and diabetes. As a result, life expectancy may be reduced by nearly 15 to 25 years(Espregueira *et al.,* 2020 and Moreno-Küstner *et al.,* 2021). Additionally, Schizophrenia is often related to a decline in socioeconomic conditions, a decline in job rates and several issues with the ability to live independently (Fu *et al.,* 2020). The disruption of such basic areas of life can be crushing for many people with schizophrenia, leading to a lifetime of incapacity, recurrent hospitalizations, and the breakdown of social and familial ties (Espregueira *et al.,*2020 and Moreno-Kustner *et al.,* 2021).

2.4.2: Epidemiology

One of the top 10 global causes of disability, schizophrenia affects close to 1% of the world's population. The ability of someone with schizophrenia to operate in daily life varies greatly, with some being profoundly incapacitated and others being able to function at a high level (Goldman *et al.,* 2020 and Maj *et al.,* 2021). Over 21 million people worldwide suffer with schizophrenia (WHO, 2018), and it is predicted that seven people out of every 1000 will

experience the disease at some point in their lifetime, with symptoms typically appearing in the second or third decade (Remington *et al.,* 2016). Genetic, sociodemographic, and environmental factors may all play a role in the development of a disease (Orrico-Sánchez *et al.,* 2020). Schizophrenia state tends to be more prevalent in lower socioeconomic , on the other hand recent meta-analyses have confirmed the assumption that males have a higher lifetime risk of developing SCZ 1.4 times than women (Chong *et al.,* 2016). There is, however, a high degree of inconsistency in the findings of studies regarding the prevalence of schizophrenia, reporting up to 13-fold variation from 0.12 to 1.6 per 100 (Orrico-Sánchez *et al.,* 2020), Several systematic reviews have revealed high variability of schizophrenia incidence rates among sites, ranging from 8 to 43 per 100,000 people.

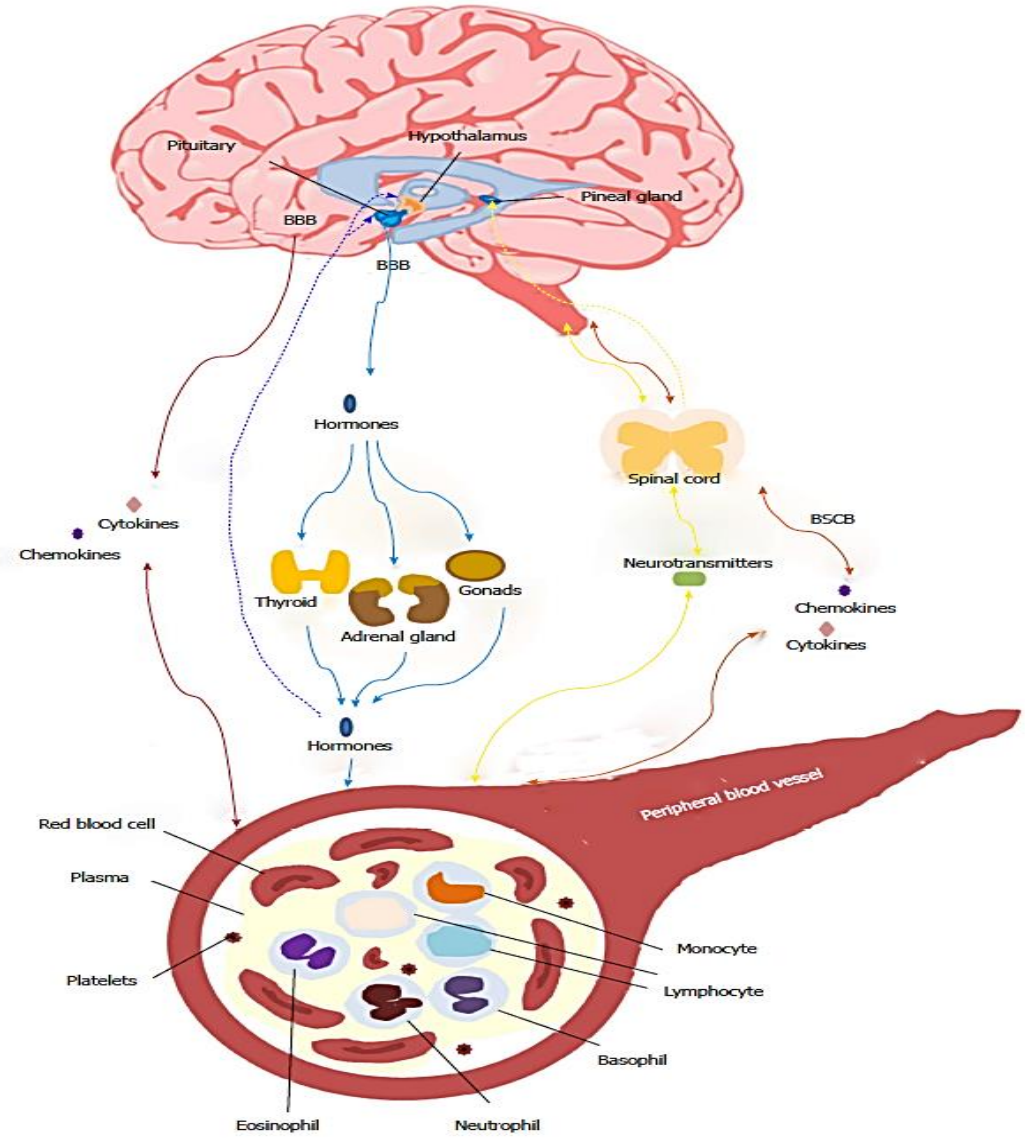
2.4.3: Etiology

The exact cause of schizophrenia is still a mystery, and this unclear etiology has impeded the treatment of the disease (Kumar *et al.,* 2019). In addition , to the dopaminergic disorder hypothesis, which is the most prominent explanation of schizophrenia, there are various theories on the origins of schizophrenia (Howes *et al.,* 2017). One of the most well-known theories is the aberrant neuron-developmental hypothesis. It is based on perinatal and prenatal conditions, as well as the existence of genetic anomalies that, when combined with specific environmental circumstances, could lead to schizophrenia at some time during development (Sneeboer *et al.,* 2020). One of the main causes of schizophrenia is complex experiences with the neurological system and immune system disruptions, which may offer a fresh perspective on the pathogenesis of this mental illness (Xu *et al.,* 2020).

2.4.4:The relationship Between Immune Response and Schizophrenia

Inflammation is currently considered a potential mechanism in the development and progression of schizophrenia (Scheinert *et al.,* 2015 and Gómez-Rubio and Trapero, 2019). There are elevated levels of inflammatory cytokine in patients with schizophrenia, and more importantly, this increase may be related to the negative symptoms of the disorder (Noto *et al.,* 2015). An insufficient balance between pro-and anti-inflammatory cytokines will therefore induce dysfunction of the immune system, impair neurodevelopment and deregulate brain neurotransmission in schizophrenia patients (Rodrigues-Amorim *et al.,* 2018 and Gómez-Rubio and Trapero, 2019).

Also, Neuron inflammation early in life followed by chronic over-activation has been hypothesized to contribute to the etiology of schizophrenia; high levels of inflammation may play a role in treatment-resistant schizophrenia (TRS). The inflammatory cytokine profiles have been associated with both treatment-responsive schizophrenia and TRS, in addition the levels of these proteins can be present from illness onset and thus do not represent a downstream effect of psychosis (Potkin e*t al.,* 2020). With different transportation methods, Through the use of neurotransmitters, hormones and cytokines CNS stress may have an impact on DNA methylation, cellular metabolism and expression of genes in the peripheral circulation.‹ as seen in figure (2.1).



Figure(2.1): A schematic representation of central nervous system-peripheral blood tissue interactions. The BBB and BSCB allow cytokines and chemokines to travel from the central nervous system to peripheral blood tissue as well as the other way around. The circulatory system carries the hormones over the BBB to the target tissue (blue lines), where they exert their influence and regulate the central nervous system through negative feedback (blue dashed lines). The parasympathetic or sympathetic nervous system of the spinal cord stimulates (yellow line) or inhibits (yellow dashed line) another link. It is observed that different blood cell types and their characteristics can be found in peripheral blood vessels. BSCB: Blood-spinal cord barrier; CNS: Central nervous system; BBB: Blood-brain barrier (Lai *et al.*, 2016).

Meta-analyses showed that schizophrenia and BD both have a pro-inflammatory condition(Marcinowicz e*t al.,* 2021) , while some cytokines such as IL-1β, IL-6, and TGF-β may be altered during acute exacerbations (state markers), other cytokines (or receptors) including soluble IL-2 receptors (sIL-2R) , IL-12, IFN-γ and TNF-α as schizophrenia trait markers (Krynicki *et al.,* 2021; Maes *et al.,* 2021 and Misiak *et al.,* 2021). Even before receiving antipsychotic medication, changes in cytokine profiles may already be seen in the early stages of psychosis. Recent investigations revealed that antipsychotic naive first-episode psychosis (AN-FEP) patients had significantly higher levels of pro-inflammatory cytokines and their receptors (TNF-α, IL-1β, sIL-2R and IL-6) (Upthegrove *et al.*, 2014; Noto *et al.*, 2015).

M1 macrophage activation, elevated levels of IL-6,TNF-α, soluble IL-6 receptor (sIL-6R) and IL-1β as well as Th1 helper and Th17 responses with elevated levels of IL-17, IL-2 and IFN-γ are all associated with affective disorders. Increased plasma concentrations of the immune-regulatory proteins sTNFR-80(sTNFR2), sTNFR-60 (sTNFR1) and soluble IL-1β receptor antagonist (sIL-1RA) as well as activated Th2 and T regulatory (Treg) phenotypes with increased IL-4 and IL-10 levels, are all signs of the compensatory immune-reflex system (CIRS) being activated in schizophrenia(Al-Hakeim *et al.,* 2015; Roomruangwong *et al.,* 2020). M1 macrophage activation is indicated by elevated sIL-1RA levels, although elevated levels are hostile to the immune-inflammatory responses system (IRS) because they reduce IL-1β pro-inflammatory signaling (Maes *et al.,* 2020).

Following pro-inflammatory signals such as TNF-α, IL-1β, IL-6, sTNFR2 and sTNFR1 are released into the serum as a result of motivation (Kudo *et al.,* 2018; Gohar *et al.,* 2019 and Al-Hakeim *et.al.*,2020). Examples include

increased production of interferon- γ associated with Th1 cells and tryptophan catabolites (TRYCATs), pro-inflammatory cytokines like TNF-α, IL-1β, IL-4 and IL-6, chemokines like CCL11(eotaxin) and Th2-related cytokines(Maes *et al.,* 2018; Roomruangwong *et al.,* 2020 and Maes *et al.,* 2020).

2.5:Association of Psychological Stress Diseases with Immunological Parameters

2.5.1:Effect of Psychological Stress Diseases on The level of IL-1β

Interleukin-1beta (IL-1β) also known as leukocytic pyrogen, leukocytic endogenous mediator, mononuclear cell factor, lymphocyte activating factor and other names, is a cytokine protein that in humans is encoded by the IL1β gene"(Giuliani *et al.,* 2017). IL-1β is a powerful pro-inflammatory cytokine that must be converted from its inactive precursor by the cysteine protease inflammasomes caspase-1 to its active secreted p17 fragment. Numerous research have outlined the connection between IL-1β and conditions including AD, depression, Parkinson's disease and schizophrenia etc. (Li *et al.,* 2021; Reale *et al.,* 2021).

According to Zhu *et al.,* (2018), This cytokine stimulates dopaminergic neuronal differentiation of neural stem cells and controls the formation of dopamine neurons and contributes in the selective sensitivity of the nigrostriatal pathway connected to dopaminergic neurotoxicity. Additionally, One of the cytokines most frequently associated with Alzheimer's, schizophrenia, and serious depressive disorders is IL-1β. (Çakici *et al.,* 2020). The pathophysiology and etiology of schizophrenia are assumed to be significantly influenced by IL-1β, according to a number of studies (Reale *et al.,* 2021). Schizophrenia patients characterized by raised peripheral monocyte IL-1β release before to therapy, which was afterwards normalized by antipsychotic medication (He *et al.,* 2020). Additionally, IL-1β levels in the

serum were noticeably greater in schizophrenia patients with negative signs in comparsion with positive signs (Dai *et al.,* 2020). Another study demonstrated that serum IL-1β levels were greater in schizophrenia patients in comparison with healthy controls. These proteins can be thought of as precise predictors of the therapeutic results in schizophrenia patients(He *et al.,* 2020). A growing corpus of research indicates that people with schizophrenia may have immune system problems. Between the treated patients and the healthy group, there was no discernible variation in the levels of IL-1β or TNF-α (Esfandiar *et al.,* 2019).

There have been conflicting findings regarding the relationship between IL-1β and depression, and some meta-analyses have not discovered a common connection between major depressive disorder and IL-1β(Köhler *et al.,* 2017). However, given that IL-1β levels in blood are extremely low, it has been hypothesized that this may be because to measurement difficulties (Haapakoski *et al.,* 2015). Additionally, there were no discernible variations in the baseline levels of IL-1β in depression patients , but the proteins that are necessary for IL-1β synthesis were raised (Syed *et al.*, 2018).

2.5.2:Effect of Psychological Stress Diseases on The levels of Glutamic Acid Decarboxylase (GAD65)

Gamma-aminobutyric acid (GABA) and carbon dioxide(CO2) are produced when glutamate is decarboxylated by the enzyme glutamic acid decarboxylase (GAD). GAD requires pyridoxal phosphate (PLP) as a cofactor. GAD67 and GAD65, two distinct isoforms of GAD with molecular weights of 67 and 65 kDa, are found in mammals. Two distinct genes on two distinct chromosomes express these isoforms (GAD2 and GAD1 genes, chromosomes 10 and 2 in humans, respectively). Both the brain, where GABA is a neurotransmitter, and the pancreatic beta cells, which produce insulin, express

GAD67 and GAD65. These two enzymes work in tandem to maintain mammals' main physiological source of GABA(Langendorf *et al.*, 2013), even though it can also be produced from putrescine by diamine oxidase and aldehyde d-aspartate in the brain, enteric nervous system, and other places(Kim *et al.*, 2015). Because it generates GABA for neurotransmission, GAD65 is necessary at synapses and nerve terminals. GAD65 forms a compound with heat shock cognate 70 (HSC70), cysteine string protein (CSP), and vesicular GABA transporter(VGAT) to help with neurotransmission. For release during neurotransmission, this complex helps GABA become packaged into vesicles(Jin *et al.*, 2003).

2.6:Association of Psychological Stress Diseases with Physiological Parameters

2.6.1:Effect of Psychological Stress Diseases on the Levels of Serotonin

A monoamine neurotransmitter is serotonin, also known as 5-hydroxytryptamine (5-HT). Its biological effects are varied and complex, affecting a diversity of physiological processes such as vomiting and vasoconstriction in addition to mood, reward, learning, and memory (Young,2007). Serotonin is one of the neuromediators, and acts on the functioning of immune, central nervous system (CNS),cardiovascular, gastrointestinal and renal systems. Any disorder in the synthesis, metabolism and reuptake of serotonin leads to symptoms and diseases such as learning disability, depression, obsessive-compulsive disorder(OCD)and schizophrenia (Amiri *et al.*, 2016; Solati *et al.*, 2017a). The serotonin hormone affects many physiological activities, including mechanisms of anxious, appetite, sexual behavior, sleep-wake cycle and peristalsis (Oláh *et al.*, 2005). Serotonin aids in mood regulation and memory in the brain, a crucial organ, but the

neurotransmitter also plays crucial roles in other parts of the body (Lv and Liu, 2017). According to reports, your gut contains the majority of the body's serotonin and not your brain. In addition intestine producing almost all of the body's serotonin, because the intestine need serotonin to support good digestion (Yano *et al.,* 2015).

2.6.2:Effect of Psychological Stress Diseases on The level of Dopamine

Dopamine is a neurotransmitter that facilitates neurochemical transmission in the mammalian tuberoinfundibular, mesolimbic, nigrostriatal, and mesocortical dopaminergic systems. These brain regions are crucial for the execution of psychomotor, cognitive, and neuroendocrine processes (Belkaid and Krichmar, 2020). Dopamine, which is expressed in the regions of the brain that regulator movement, emotion, and feeling, is another neuromediator connected to depression. Dopamine acts as a stabilizing agent in the brain and regulates the transmit of information from the brain to different regions of the body.

It also greatly affects how thoughts and movements are controlled (Solati *et al.,* 2017b). Dopamine, short for 3,4-dihydroxyphenethylamine, is a neuromodulator molecule with a variety of crucial functions in living things. It is a chemical compound that comes from the same family as phenethylamine and catecholamine. About 80% of the catecholamines in the brain are dopamine. L-DOPA, a precursor chemical produced in plants, the brain, the kidneys, and the majority of animals, is changed into an amine by the removal of a carboxyl group from the molecule. Dopamine acts as a neurotransmitter in the brain, a substance released by neurons (nerve cells) to interact with other neurons. Although they are produced in certain parts of the brain, neurotransmitters have a systemic impact on numerous areas. Dopamine levels

in the brain are frequently raised when rewards are anticipated, and many addictive substances either boost dopamine release or prevent its absorption into neurons after release (Wise and Robble, 2020). Motor control and hormone release are both regulated by additional brain dopamine pathways. The dopamine system, a neuromodulator, is made up of these routes and cell types (Wise and Robble, 2020). Dopamine affects circulatory system, bone marrow and immune cells in the spleen via acting on immune cells' receptors, particularly those on lymphocytes (Sarkar *et al.,* 2010). Additionally, immune cells themselves have the ability to produce and release dopamine (Buttarelli *et al.,* 2011). Dopamine primarily affects lymphocytes by lowering their level of activation. It may be connected to various autoimmune diseases and is hypothesized to offer a potential channel for interactions between the immune system and the nervous system (Sarkar *et al.,* 2010).

2.7:The relationship Between Psychological Stress Diseases and Genetic Parameters

2.7.1:Association of *IL-1β* Gene Polymorphism with Psychological Stress Patients

According to Liu *et al.,* (2010), schizophrenia patients' siblings also had raised levels of IL-1β in their peripheral blood mononuclear cells, suggesting that genetic factors may be at play. Additionally, earlier research revealed that IL-1β might be connected to a potential association between prenatal infection exposure and schizophrenia (Gilmore *et al.,* 2004). On 2q14, there is a region where the *IL-1β* gene is found. Positive linkage results in schizophrenia have repeatedly been found in this region (DeLisi *et al.,* 2002). Additionally, Lewis *et al.,* (2003) demonstrated that 2p12-q22.1 was connected to a genome-wide significant P value, according to a meta-analysis of 20 genome scans. There has also been information linking this area to schizophrenia in Asian (Faraone

et al., 2006). Numerous genetic association studies have connected the *IL-1β* gene variation to the probability of developing schizophrenia. *IL-1β* gene polymorphism rs16944 was associated with schizophrenia in three studies in Caucasian populations, but this connection was not supported by other research (Hanninen *et al.,* 2008), However, additional research did not support this association (Shirts *et al.,* 2006; Betcheva *et al.,* 2009). Additionally, no previous research in Asian populations has shown any proof of a link between schizophrenia and *IL-1β* gene (Watanabe *et al.,* 2007).

2.7.2:Association of Serotonin Receptor *(5-HT1A)* Gene Polymorphism with Psychological Stress Patients

Three protein-coupled receptor families—Gi/o (5-HT1A, 1B, 1D, 1E, 1F, 5A, 5B), Gq/11 (5-HT2A, 2B, 2C), and Gs (5-HT4, 6) protein-coupled receptors and one ligand-gated ion channel—represent the 14 different types of serotonin receptors that have been found (the 5-HT3 receptor). While the other receptors are excitatory, Gi/o protein-coupled receptors are inhibitory. Postsynaptically is where most serotonin receptors are expressed (Nichols and Nichols, 2008). The 5-HT1A receptors are expressed in the soma and dendrites of serotonergic neurons, where they also function as auto receptors, and they are located in several regions of the brain. They appear to be involved in the regulation of body temperature, eating behavior, depression, and anxiety disorders (Lesch and Gutknecht,2004). The most prevalent 5-HT receptor is the 5-HT1A receptor. The cerebral cortex, hippocampus, septum, amygdala, and raphe nucleus of the central nervous system contain high concentrations of 5-HT1A receptors; in addition, basal ganglia and the thalamus have fewer 5-HT1A receptors. In the raphe nucleus, somatodendritic auto-receptors make up the majority of 5-HT1A receptors, while postsynaptic

receptors are found in other regions, such as the hippocampus (de Almeida and Mengod, 2008).

2.8:Association of Psychological Stress Diseases with Microbial Infection

2.8.1:Association of Psychological Stress Diseases with Viral Infection

There are eight different varieties of herpes viruses, which are DNA viruses, that are known to infect people. The human herpes viruses 6, 7, and 8 as well as cytomegalovirus (CMV) (HHV 6-8), varicella-zoster virus (VZV), and epstein-barr virus(EBV)are among them. As seen in picture, herpes viruses are big, enclosed, and contain double-stranded DNA that is encased in an icosadeltahedral capsid (2.2). Both viral and cellular nuclear factors control the transcription of herpes viruses, which controls whether the infection is latent, lytic or chronic. Herpes viruses are desirable candidates for a function in schizophrenia disorder because of their capacity to develop latency in the human body. Without the development of clinical signs, The majority of herpes viruses are most commonly first infected in infancy (Murray *et al.*,2002).

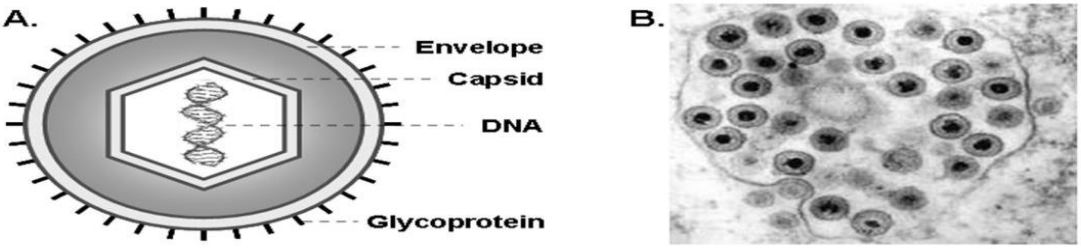


Figure (2.2) Herpes viruses, A. The herpes virus' structure. B. Virions are depicted in a thin section as they leave the nucleus of an infected cell in this micrograph from F. A. Murphy's School of Veterinary Medicine at the University of California, Davis, in the United States(magnification: roughly 40.000x)(Murray *et al.*,2002).

2.8.2:Association of Psychological Stress Diseases with Bacterial Infection

The stomach's mucous layer, which shields stomach cells from acid and also protects the delicate *Helicobacter pylori* , is the perfect place for this bacteria to live. *H. pylori* can cause both chronic and acute gastritis (Su *et al.,* 2018). *H. pylori* causes gastritis by infecting the stomach lining and releasing a cytotoxin called vacuolating cytotoxin A (Vac-A), which can result in the progress of ulcers (Floch *et al.,* 2017). Several interleukins (ILs), especially the pro-inflammatory cytokine Interleukin-1beta (IL-1β), which is created by activated macrophages, have been shown in epidemiological studies to regulate the inflammation brought on by *H. pylori* infection (Salimzadeh *et al.,* 2015). It has been proposed that the cytokine gene interleukin-1β affects the pathophysiology of inflammation brought on by *H. pylori* infection (Salimzadeh *et al.,* 2015). The inflammatory responses to *H. pylori* infection are initiated and amplified by IL-1β, which also inhibits stomach acid output. However, IL-1β ultimately permits *H. pylori* colonization to spread from the gastric antrum to the corpus, which further advances severe atrophic gastritis (Valenzuela *et al.,* 2015). Mucosa-associated lymphoid tissue lymphoma, chronic gastritis, Peptic ulcers and stomach cancer are all caused by *H. pylori*. Prolonged infection also causes chronic inflammation, oxidative stress, and DNA damage (Johnson and Ottemann,2018).

CHAPTER THREE

MATERIALS AND METHODS

3:Materials and Methods

3.1:Materials

3.1.1:Chemicals and Biological Materials

Table (3.1) revealed the chemical and biological materials that used in current study .

Table (3.1): Chemicals and biological materials and their suppliers.

Chemicals and biological materials	Suppliers
Acetone	Merk /Germany
Agarose	Promega /USA
Amyl Alcohol	Merk /Germany
Anhydrous Sodium Carbonate	Syrbio /Switzerland
Copper Sulphate	Syrbio /Switzerland
Distilled water	Drugs and medical appliances/Iraq
DNA Ladder(100bp)	BioNeer /Korea
DNA loading dye	BDH / England
Ethanol	Merk /Germany
Ethidium bromide solution	USA
Hydrogen peroxide (H2O2) 70%	SDI /Iraq
Iodide Solution	Merk /Germany
KOH	SDI /Iraq
Master mix(pcr pre mix)	BioNeer /Korea
Methanol	GCC /UK
Methyl red	BDH /England
Methylene blue	BDH /England
Normal saline	Haidylena /Egypt
Nuclease free water	Biolabs – EnglandAWQQ2
PBS	BDH /England
P-dimethyl amine Benz aldehyde	BDH /England
Primer pairs	ALPHA DNA /Canada
Proteinase K	Biolabs – England

Sodium Carbonate Decahydrate	Syrbio /Switzerland
Sodium Chloride(NaCl)	Syrbio /Switzerland
Sodium Citrate	Syrbio /Switzerland
TBE Buffer	Promega / USA
Urea Solution	Mastdiagnostic /UK

3.1.2: Instruments and Equipment

Tables (3.2) and (3.3) contain a list of the tools and instruments used in this study .

Table (3.2): Instruments and their Suppliers in current study .

Instruments	**Suppliers**
Beakers	Iwaki glass/Japan
Bunsen burner	Shndon/England
Conical flask	Marienfeld/Germany
Cool box	Eskemo /(India)
Digital camera	Canon/ Japan
Disposable gloves without powder	Bioneer/Korea
Disposable plastic cup (50 ml)	Changazhou medical appliances /China
Disposable syringe	Changazhou medical appliances /China
Disposable tips	CAPP/Denmark
Disposable tips with filter	Bioneer/Korea
EDTA Tubes	AFCO-DISPO /Jordan
Eppendrof rack	Eppendrof rack
Eppendrof tube (1.5)ml	Heittch/Germany
Eppendrof tubes(0.5)	Merk /Germany
Gel Tubes	Lassco /India
Graduated Tube	Merk /India
Loop	Shndon/England
Micropipettes (different volumes)	Slamid/Germany
PCR tubes	Gilson /France

Petri dishes Plates	Sterilin /England
PH meter	Radiometer /Denmark
Pipette tips	Gilson /France
Plain tube	Gilson /France
Slides	Sail Brand/China
Sterile Mask	Bioneer/Korea
Swabs	Arth Al-Rafidain/China
Test tubes	Arth Al-Rafidain/China

Table (3.3): Equipment with their Suppliers in current study.

equipment	**Suppliers**
Autoclave	Hirayamy/Japan
ELISA Reader and washer	Biotek / USA
Exispin vortex centrifuge	Bioneer/ Korea
Hood(laminar air flow)	LabTech/ Korea
Hot plate	LabTech/ Korea
Oven	Hirayama /Japan
Thermocycler (PCR)	Biobase/China
UV- Trans illuminator	Techen/ England
Vortex mixer	Memmert /Germany
Water bath	Techen/ England

3.1.3: Kits

Table (3.4) showed that the kits with their suppliers that used in current study.

Table (3.4): Kits with their suppliers that used in this study.

Kits	**Suppliers**
Add Prep Genomic DNA Extraction Kit From Blood	Addbio/Korea
Human dopamine (DA) ELISA Kit	Sunlong /China
Human GAD 65 Kit instruction	Sunlong /China
Human herpes simplex virus	Sunlong /China

ELISA Kit	
Human serotonin or 5-hydroxytryptamine (5-HT) ELISA Kit	Sunlong /China
Human Interleukin1-β (IL-1β) ELISA Kit	Sunlong /China
One Step *H. Pylori* Feces Test	Healgen/ China

3.2: Methods

3.2.1:The Studied Groups

The present study was done in Imam Al-Hasan Almjtaba Hospital and Imam AL- Hussein Hospital City in Karbala city from February (2022) to August (2022). The number of persons included in this study was 90 with ages ranged from 19-92years. The study population was divided into four groups: first group include 30 of apparently healthy control(AHC) and three patients groups which include 60 of patients with psychological stress distributed into 20 patients for each Alzheimer, schizophrenia and major depression diseases .These groups divided according to their sex , age, education , smoking status, marital status and duration of stress.

3.2.2: Medical Ethics

The approval were obtained by the patients and also agreed to study scientifically and morally by the medical committee in the Imam Al-Hasan Almjtaba Hospital and Imam AL- Hussein Hospital City .

3.2.3: Questionnaire

A questionnaire was taken from the patients and case sheets including ; gender , age, education , smoking status, marital status and duration of stress.

3.2.4: The Study Design

The study design of current study were illustrated in figure (3.1).

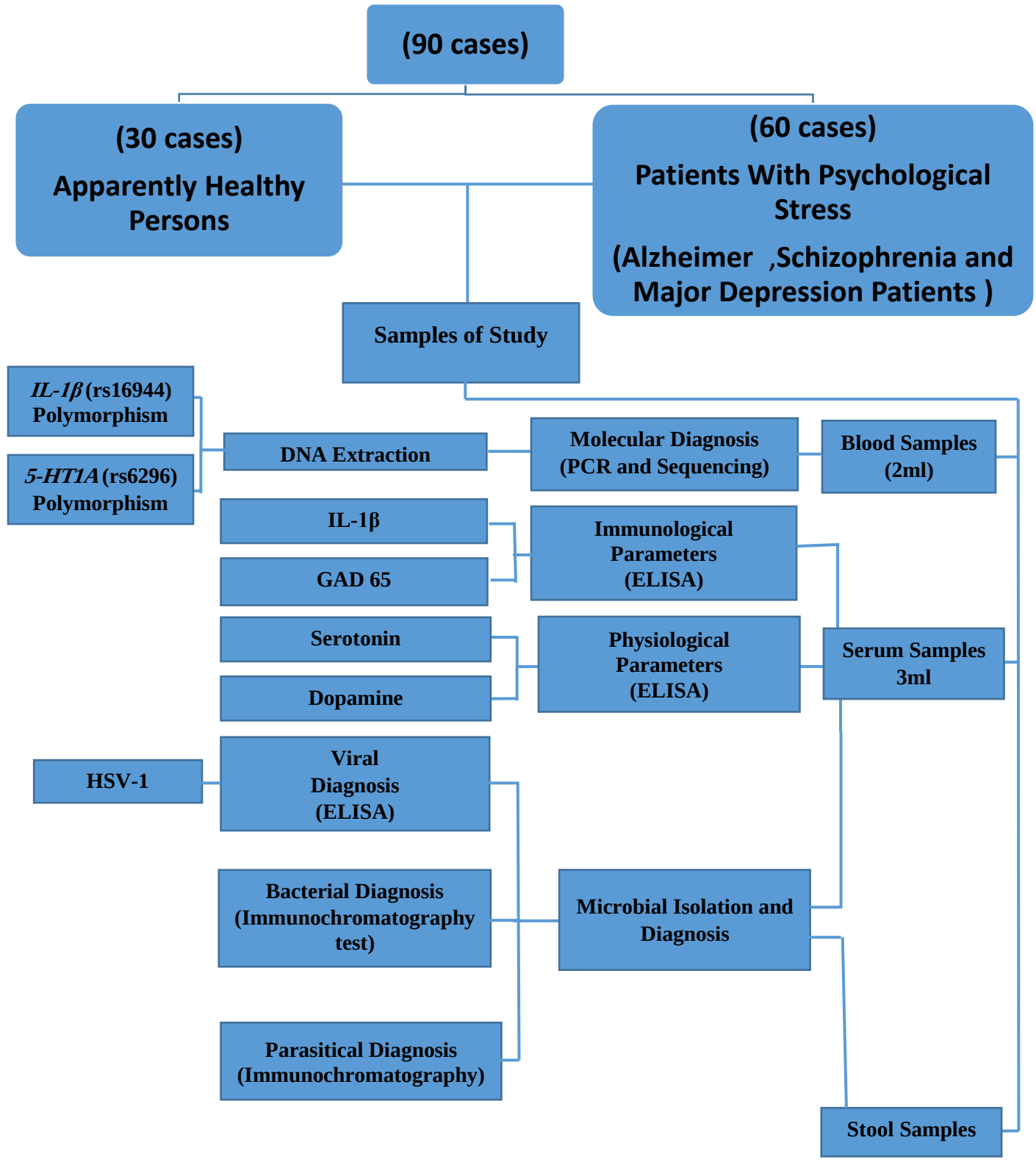


Figure (3.1): Study design

3.2.5:Exclusion Criteria

The exclusion criteria from current study was patients with severely psychological stress diseases associated with chronic diseases such as cardiovascular diseases, diabetes mellitus and renal failure etc.

3.2.6:Inclusion Criteria

The inclusion criteria from current study was patients with severely psychological stress diseases only.

3.2.7:Blood Samples Collection

A total of 90 blood samples were collected from persons included 60 cases of patients and 30 of apparently healthy persons. Five ml of blood was obtained by venipuncture by using disposable syringe(5ml) ,then 2ml of blood placed in EDTA tube for genetic tests , while the remaining blood (3 ml) was transferred to gel tube and put in centrifuge for 10 minutes at 3000rpm in order to obtain serum. Then, serum was collected and spread into aliquots of 0.25 ml in eppendorf tubes for immunological ,physiological tests and viral diagnosis which were frozen at -20°C until laboratory measurements (Dacie and lewis,2005).

3.2.8: Stool Samples Collection

The stool samples were collected from patients and apparently healthy groups. Samples were transferred to the laboratory on ice in sealed bag. A fresh liquid or unformed stool sample is collected in a sterilized container. Once it has been collected, the stool sample should be taken to the laboratory directly or refrigerated and taken to the laboratory immediately possible for bacterial diagnosis (Santiago *et al.,* 2014).

3.1: Immunological Parameters

3.1.1: Human Interleukin-1β (IL-1β) ELISA Kit

3.1.1.1:Principle of The assay

The levels of IL-1β in serum was estimated by using Human Enzyme-Linked Immunosorbent Assay Kit (China/Sunlong) and their items, principles, reagent preparation and calculations were explained in appendix 1 .

3.1.1.2:Assay Procedure

1.All reagents were prepared before starting the assay technique.

2.Standards were added, set up standard wells and test sample wells. The well should receive 50µl of standard.

3.Samples were added to the testing sample well, add 10µl of sample along with 40 µl of sample diluent; the blank well receives no additions.

4. Hundred µl of HRP-conjugate reagent was added to each well before pouring, covering with an adhesive strip, and incubating at 37 °C for 60 minutes.

5. Wash solution was aspirated into each well, then wash a total of five times (four more times if necessary). Wash each well with 400µl of wash solution using an auto washer, manifold dispenser, or spray bottle. Each phase of the performance must be fluid-free in order to be successful. Aspirate or decant any lingering wash solution after the last wash. The plate should be turned over and blotted with fresh paper towels.

6.Fifty µl each of chromogen solution A and B was poured into each well. 15 minutes of mild incubation and mixing at 37 °C. shield against light

7.Fifty µl of Stop Solution was added to each well . The wells must switch from blue to yellow in color. If the color change is not uniform or the wells are green, lightly tap the plate to ensure that it is thoroughly mixed.

8. Optical density (O.D.) was reed Within 15 minutes at 450 nm using a micro titer plate reader as shown in figure (3.2) .

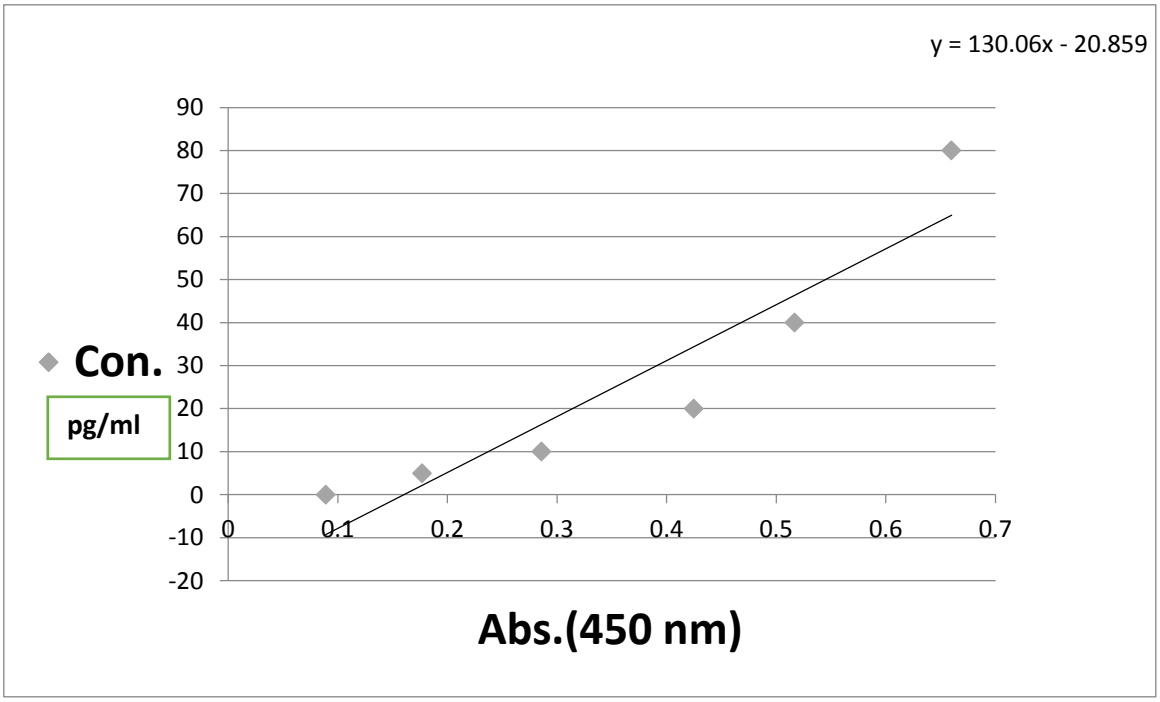


Figure (3.2):Standard curve for determine the level of IL-1β

3.1.2: Human Glutamic Acid Decarboxylase (GAD 65) ELISA Kit

3.1.2.1:Principle Of The assay

The levels of GAD 65 in serum was estimated by using Human Enzyme-Linked Immunosorbent Assay Kit(China/Sunlong) and their items, principles, reagent preparation and calculations were explained in appendix 1

3.1.2.2:Assay Procedure

The procedure was similar to the IL-1β ELISA kit and at 450 nm, examine the optical density (O.D) as illustrated in figure (3.3).

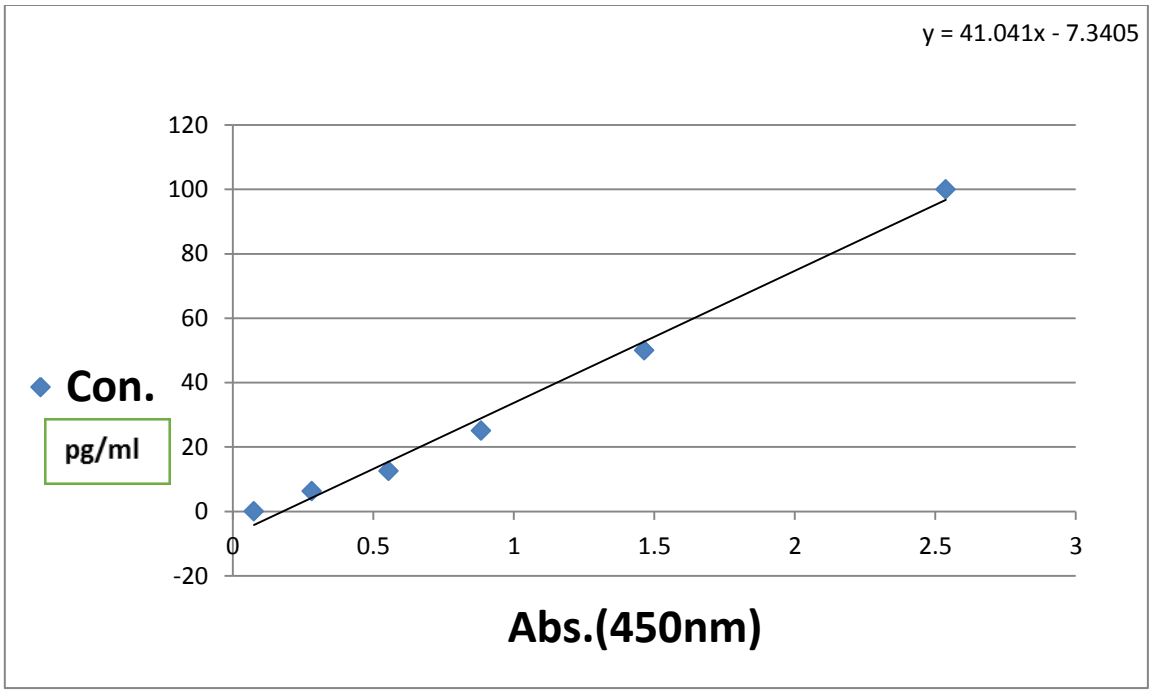


Figure (3.3): Standard curve for determine the serum level of GAD 65

3.2:Physiological Parameters

3.2.1:Human Serotonin or 5-Hydroxytryptamine (5-HT) ELISA Kit :

3.2.1.1:Principle of The assay

The serum levels of serotonin was estimated by using Human Enzyme-Linked Immunosorbent Assay Kit (China/Sunlong) and their items, principles, reagent preparation and calculations were explained in appendix 1.

3.2.1.2:Assay Procedure

The procedure was similar to the IL-1β ELISA kit and at 450 nm, examine the optical density (O.D) as illustrated in figure (3.4).

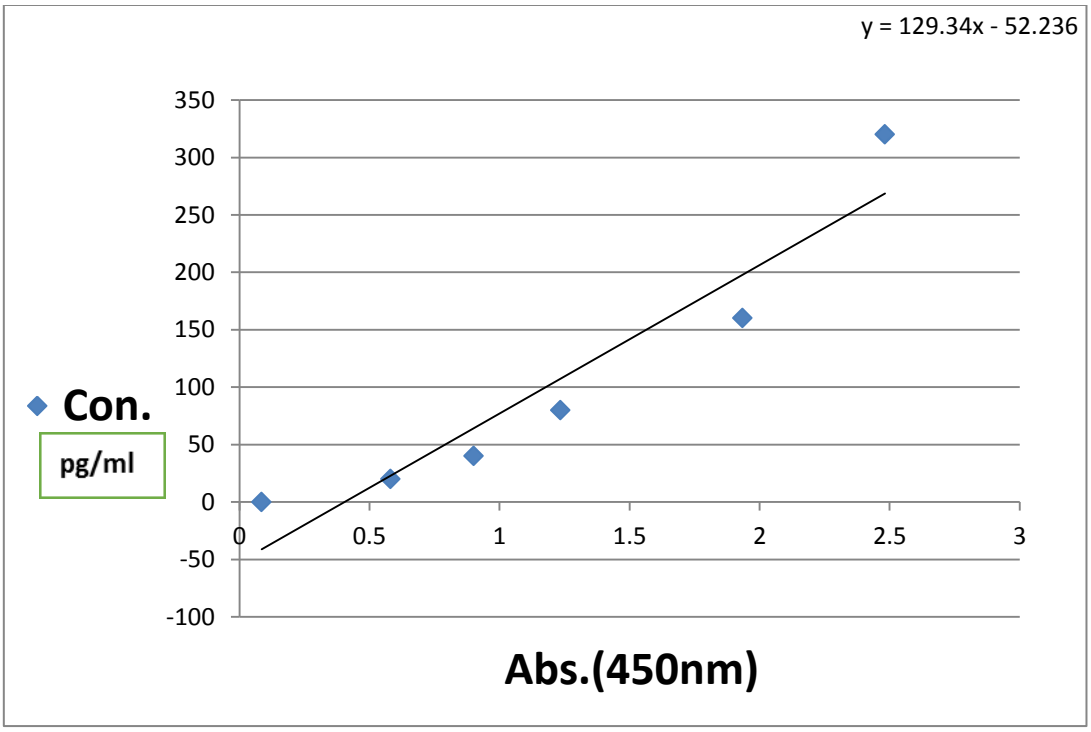


Figure (3.4):Standard curve for determine the serum level of serotonin

3.2.2:Human Dopamine (DA) ELISA Kit

3.2.2.1:Principle of The assay

The serum levels of dopamine hormone was estimated by using Human Enzyme-Linked Immunosorbent Assay Kit (China/Sunlong) and their items, principles, reagent preparation and calculation were explained also in appendix1.

3.2.2.2: Assay Procedure

The procedure was similar to the IL-1β ELISA kit and at 450 nm, examine the optical density (O.D) as illustrated in figure (3.5).

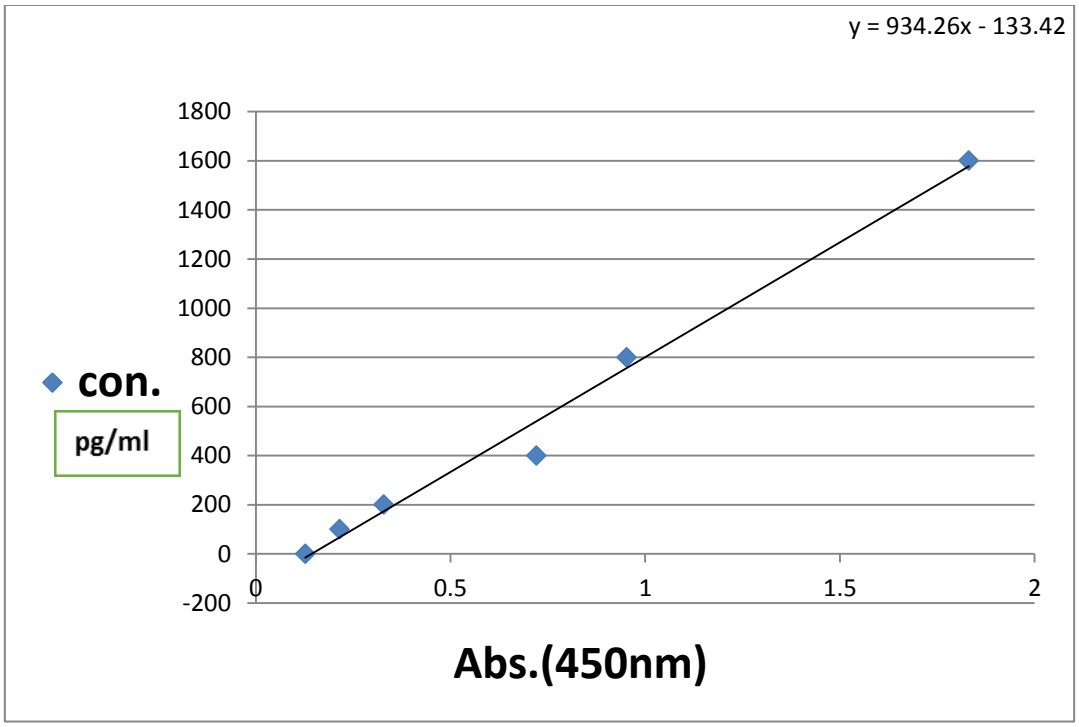


Figure (3.5):Standard curve for determine the serum level of dopamine

3.3: Viral Diagnosis

3.3.1: Human Herpes Simplex Virus ELISA Kit

3.3.1.1: Principle of The assay

The levels of HSV-1 in serum was estimated by using ELISA kit(China / Sunlong) and their items, principles, reagent preparation and calculations were explained also in appendix 1.

3.3.1.2: Assay Procedure

The procedure of this kit was similar to (IL-1β) ELISA kit except add 50µl each of the positive and negative controls to the positive and negative wells and at 450 nm, examine the optical density (O.D).

3.3.1.3:Determine The results

1. The average of the wells serving as positive controls was 1.00, while the average of the wells serving as negative controls was 0.15.

2. Added 0.15 to the average of the negative control wells to get the critical (CUT OFF) value.

The outcome of the Sample OD Calculate Critical (CUT OFF) was negative.

The Sample OD Calculate Critical (CUT OFF) yielded a successful outcome.

3.4: Molecular Study

3.4.1: DNA Extraction

The Add Prep Genomic DNA Extraction Kit (Korean origin) provides a quick, easy, and affordable way to isolate genomic DNA from blood. This kit is made to quickly prepare genomic DNA, such as entire blood, from up to 200 µl of blood, and it can be used with whole blood that has been treated with EDTA.. Kit components was explained in appendix 2 .

3.4.1.1:Extraction Protocol For Blood

1.Twenty µl of Proteinase K solution (20 mg/ml) was placed in a 1.5 ml micro centrifuge tube (Not provided).

2.PBS should be add if the sample volume is less than 200 µl. Whole blood sample 200 µl should be transferred to a 1.5 ml of Proteinase K solution in a micro centrifuge tube.

3.Treatment with RNase A is optional. The addition of 20µl of RNase A Solution (10 mg/ml, not provided) is necessary if RNA-free genomic DNA is needed.

4.Pulse-vortexing was used to thoroughly swirl the sample tube for 15 seconds after 200 µl of Binding Solution has been added.

5.The quantity or quality of the pure DNA were unaffected by a ten-minute incubation period at 56°C.

6.Tow hundred µl of 100% ethanol was added, and it should be forcefully mixed for 15 seconds using a pulse-vortex. Once you've finished doing this, quickly spin the container to get the drips stuck to the lid.

7.Utilizing a 2.0 ml collection tube, delicately transfer the lysate into the spin column's upper reservoir, taking care not to wet the rim.

8. After centrifuging for one minute at 13,000 rpm, utilizing the 2.0 ml collecting tube, complete the spin column assembly. The flow-through should be emptied.

9. Five hundred of Washing 1 Solution was added to the spin column in the 2.0 ml collecting tube, then centrifuge for one minute at 13,000 rpm. Reassemble the spin column after emptying the flow-through.

10. Five hundred of Washing 2 Solution was added to the spin column in the 2.0 ml collecting tube, then centrifuge for one minute at 13,000 rpm. Reassemble the spin column after emptying the flow-through.

11.To get rid of any remaining ethanol, perform extra centrifugation on the spin column at 13,000 rpm for one minute.

12 .Filled a new 1.5 ml micro-centrifuge tube with the spin column (Not provided).

13. The spin column was Placed inside the micro centrifuge tube and added 100 to 200 µl of the elution solution. Allow to stand for at least one minute.

14.The genomic DNA was centrifuged for 1 minute at 13,000 rpm.

3.4.2:Agarose Gel Electrophoresis

3.4.2.1:Preparation of Agarose Gel

1. Cellophane tape over both of the gel tray's edges was used to secure the comb in the top slot of the tank insert.

2.To prepare agarose gel, 100 ml of TBE buffer were combined with 1.5 g of agarose gel powder, and the mixture was microwaved for 3 minutes.

3.Ethidium bromide was added to the gel after it had cooled to 50°C and was agitated for 15 seconds. Onto the tray that had been taped, the gel was then poured.

4.Agarose gel was given 30 minutes to cool and solidify. Then it was removed from the comb.

5.The gel tray in the tank was covered with a TBE buffer. B - Loading DNA and Electrophoresis DNA (7µl) and bromophenol blue (1µl) were combined, and the mixture was loaded in the wells of the 1% agarose gel. For 30 minutes, the electrical power was turned on at 60 volts. Under a UV Trans illuminator, the DNA was examined.

3.4.3:(20X) Tris Borate EDTA (TBE) Buffer

It to make the TBE, the concentrated TBE buffer was diluted (20X). It was employed in the electrophoresis process and to dissolve agarose powder. To get a 1X TBE concentration, to 800 ml of distilled water, 200 ml of TBE (20X) was added (Sambrook and Russell, 2001).

3.4.4:Polymerase Chain Reaction (PCR) of *IL-1β* and *Serotonin Receptor*

3.4.4.1:Preparation of Reaction Mixture to PCR

3.4.4.1.1:Primers Selection

Primers were designed according to the genome sequences near these SNP sites and all amplicons could generate about 500 bp fragments in which containing the corresponding SNPs (rs6296 G/C) and (rs16944 G/A) according to the website https://www.ncbi.nlm.nih.gov/ and using software primer designer open-source GUI program (PerlPrimer version 5.36) appendix (3&4). These primers were provided from (Oligo^{TM}, Korea).

3.4.4.1.2:The preparation of Primers

Every primer utilized in this work, were created in line with the manufacturer's instructions by combining the necessary amount of lyophilized primers with nuclease-free water to produce a stock solution containing 100 pmol/l. By using dilution techniques, a workable solution with a final concentration of 10 pmol/L was created.

3.4.4.1.3:PCR Master Mix Preparation

Add Bio Master Mix (Korea) was used to create the PCR master mix, and it carried out two reactions for each sample in accordance with the guidelines provided by the manufacturer.

Following that, the PCR master mix components listed in the tables in appendixes(5,6,7,8) were added to a standard Accu power PCR premix Kit, which also included all other necessary components for the PCR reaction. All of the PCR tubes were then placed in the PCR Thermo cycler after being transferred to an Exispin vortex centrifuge at 3000 rpm for 3 minutes(Biobase/china).

3.4.4.1.4:PCR Thermo Cycler Conditions

1.PCR Thermo cycler conditions for *IL-1β* gene (appendix 5).

2. PCR Thermo cycler conditions for *serotonin receptor* gene (appendix 7).

3.4.4.1.5: PCR Product Electrophoresis

PCR product was subjected to electrophoresis on 1% agarose gel. Six micro liters of the ladder DNA(100bp) were applied to the first well of the gel. five micro liters of PCR sample was applied to each well of the gel. The lid of electrophoresis tank was placed and the power was run for 30 minutes at 60 volts.

3.4.4.1.6:Sequencing

A total of 6 samples were included in sequencing, three samples for *IL-1β* (rs16944) gene and three samples for *serotonin receptor* (rs6296) gene. One sample

for each Alzheimer, schizophrenia and depression diseases and each sample done allele forward sequence and allele reverse sequence by sequencer system (sanger), all six PCR product were sent to Korea for sequences analysis and the obtaining results were analyzed according to NCBI (https://www.ncbi.nlm.nih.gov/).

3.5:Bacterial Diagnosis

3.5.1: *Helicobacter Pylori* Ag Cassette

A rapid method for the qualitative detection of *Helicobacter pylori* in faces was created by Shimoyama and Kato, (2009).

3.5.1.1:Principle Assay

To detect *Helicobacter pylori* antigen in human feces, a lateral flow chromatographic immunoassay known as the Linear *H. pylori* Ag cassette is utilized. It is intended to be used as both a screening test and a tool to aid in the diagnosis of *H. Pylori* infection. Any sample that tests positive for the *Helicobacter pylori* Ag cassette needs to be supported by other testing and clinical data. A sandwich lateral flow chromatographic immunoassay is used to detect linear *Helicobacter pylori* Ag. A monoclonal anti-*H. pylori* antibody conjugated with colloid gold, a conjugate pad in burgundy, a nitrocellulose membrane strip with a test band (T band) and two control bands (b and C band), are all included in the test strip (anti-*H.Pylori* conjugates). While the C band has a pre-coated goat anti-mouse IgG antibody, the T band has a pre-coated monoclonal anti-*H.Pylori*. antibody. When enough liquid is injected into the sample well, the extracted fecal specimen spreads out by capillary action throughout the test cassette. If *H.Pylori*. antigen is present, the anti-*H.Pylori* conjugates in the samples will attach to it. The pre-coated antibody then binds to the immunological combination on the membrane, forming a burgundy-colored T band that denotes a positive *H.Pylori* test result. An *H.Pylori* negative result means that this band is absent, indicating that the specimen's

concentration of *H.Pylori* is below the detection threshold. The lack of the T band indicates a poor result. No matter how the T band's color changes, A burgundy band comprised of a goat anti-mouse IgG/mouse IgG-gold conjugate immunological complex should be seen as the test's internal control (C band). If the test outcome is incorrect, the sample must be retested using a different equipment.

3.5.1.2:Procedure

Before testing, let the controls, stool samples, and assays warm up to room temperature (15–30 ^{O}C). When you are prepared to perform the assay, wait to open the pouches.

1.The test gadget was taked by opening the pouch at the notch when it's time to conduct the test. Placing the test instrument on a spotless, level surface.

2.The feces collection device was shaken to ensure a homogeneous liquid suspension.

3.The toilet paper dispenser was positioned vertically, then twist the top off. dispense 2 drops of the solution into the sample well of the test device while holding the stool collecting device vertically. Avoid oversampling your sample.

4.The timer was Sat in step four.

5.Fifteen minutes after the material was applied, the results was reed. Optimism is a possibility.

3.5.1.3:Interpretation of Results

Negative Results: The test reveals that there is no detectable *H. Pylori* antigen in the samples if just the C band forms. The outcome is subpar.

Positive Results: The test verifies the presence of *H. Pylori* antigen in the specimen if both the C and T bands have developed. The outcome is favorable.

invalid: As illustrated below, regardless of color development on the T line, the assay is invalid if there is no C line development. Rerun the test using a different piece of test equipment.

3.6:Statistical Analysis

1-Performing a one-way analysis of variance using the Statistical Program Social System (SPSS) ANOVA Duncan used the post hoc test to determine the difference between means that was statistically significant (SPSS, 2001).

2. To evaluate the relationship between any two categorical variables, the chi-square test, p-value ≤ 0.05 was significant, was utilized (Armitage *et al.*, 2008).

CHAPTER FOUR

RESULTS

4:Results

4.1: Demographic Characteristics

4.1.1: Age

Apparently healthy control (AHC) group was in percent of 50% in age <30 year , while the Alzheimer patients group the largest percent (95%) was shown in age category >60 year, whereas in Schizophrenia and major depression patients groups the percent are (60%) and (50%) respectively in age category 30-60 year as shown in table(4.1).

4.1.2:Duration of Disease

The data revealed that the percent of major depression patients group was (80%) in duration of disease <5 year , while the percent are (75%) and (60%) in Alzheimer and Schizophrenia patients groups respectively in duration of disease 5-20 year as shown in table(4.1).

4.1.3: Sex

The sex of AHC and Schizophrenia patients groups showed that the percent of male was 53.33% and 55% respectively compared with other groups, while in Alzheimer and major depression patients groups the percent of female was (60%) in both groups , in addition the percent of female was 46.67% and 45% in AHC and Schizophrenia patients groups respectively as shown in table(4.1).

4.1.4:Education

The data in AHC, Schizophrenia and major depression patients groups revealed that the educated persons are in percent 83.33%, 65% and 80% respectively, while in Alzheimer patients group the percent of illiterate persons was (60%), but the percent in AHC, schizophrenia and major depression

patients groups reached to 16.67% , 35% and 10% respectively as shown in table(4.1).

4.1.5:Smoking Status

The percent of non-smoker persons are 76.67% and 80% in AHC and Alzheimer patients groups respectively , while, the percent in schizophrenia and major depression patients groups are 35% and 30% respectively. The Schizophrenia and major depression patients groups showed the largest percent in smoker persons which reached to 65% and 70% respectively as shown in table(4.1).

4.1.6: Marital Status

The distribution of AHC and patients groups according to the marital state. The percent of single persons in control group was 56.67% ,while in Alzheimer and Major depression patients groups the percent of married persons are 100% and 65% respectively, but in Schizophrenia patients group the percent was 45% in both single and married persons as shown in table(4.1).

Table(4.1):Distribution of psychological stress patients and AHC groups according to demographical characteristics (age, duration of disease, sex, education, smoking status and marital status)

Demographical characteristics	Study groups(%)					P-value
Age	AHC	Alzheimer Disease	Schizophrenia Disease	Major Depression disease	x^2	
< 30 years	15 (50%)	0 (0%)	6 (30%)	8 (40%)	53.27	0.00001*
30-60 years	10 (33.33)	1 (5%)	12 (60%)	10 (50%)		
> 60 years	5 (16.67%)	19 (95%)	2 (10%)	2 (10%)		
Total	30 (100%)	20 (100%)	20 (100%)	20 (100%)		
Duration of Disease						
< 5 years	0(0%)	5(25%)	7(35%)	16(80%)	15.615	0.015*
5-20 years	0(0%)	15(75%)	12(60%)	4(20%)		
> 20 years	0(0%)	0(0%)	1(5%)	0(0%)		
Total	30(100%)	20(100%)	20(100%)	20(100%)		
Sex						
Male	16(53.33%)	8(40%)	11(55%)	8(40%)	1.232	0.74
Female	14(46.67%)	12(60%)	9(45%)	12(60%)		
Total	30(100%)	20(100%)	20(100%)	20(100%)		
Education						
Illiterate	5(16.67%)	12(60%)	7(35%)	2(10%)	15.442	0.001*
Educated	25(83.33%)	8(40%)	13(65%)	18(90%)		
Total	30(100%)	20(100%)	20(100%)	20(100%)		
Smoking status						
Yes	7(23.33%)	4(20%)	13(65%)	14(70%)	19.016	0.00002*
No.	23(76.67%)	16(80%)	7(35%)	6(30%)		
Total	30(100%)	20(100%)	20(100%)	20(100%)		
Marital status						
Single	17(56.67%)	0(0%)	9(45%)	6(30%)	27.214	0.0012*
Married	12(40%)	20(100%)	9(45%)	13(65%)		
Divorced	1(3.33%)	0(0%)	2(10%)	0(0%)		
Widowed	0(0%)	0(0%)	0(0%)	1(5%)		
Total	30(100%)	20(100%)	20(100%)	20(100%)		

*p-value ≤ 0.05 was significant

4.2:Immunological Parameters

4.2.1:The levels of IL-1β In Psychological Stress Patients and AHC Groups

The data in table (4.2) appeared that a significant rise ($p \leq 0.05$) in the levels of IL-1β in all patients groups in comparison with AHC group. The levels of this cytokine was 10.04±0.75 (pg/ml)in AHC group , whereas it reached to 34.27±3.39 ,31.56±3.02 ,and 24.10±0.98 (pg/ml) in Alzheimer, Schizophrenia and major depression patients groups respectively. In contrast, the results of present study indicated that there were non-significant changes ($P \geq 0.05$) in IL-1β levels between Alzheimer and Schizophrenia patients groups.

Table(4.2): The levels of IL-1β (Mean±SE) in psychological stress patients and AHC groups .

Parameters / Groups N=90	IL-1β pg/ml	p-value
AHC group	A 10.04±0.75	0.0001*
Alzheimer patients	C 34.27±3.39	
Schizophrenia patients	C 31.56±3.02	
Major depression Patients	B 24.10±0.98	

Note: A different letter designates a significant change at($p \leq 0.05$).

4.2.2:Estimation The levels of Glutamic Acid Decarboxylase 65(GAD 65) in Psychological Stress Patients and AHC Groups

Table (4.3) shown that a significant rise ($p \leq 0.05$) in the levels of GAD65 in all patients groups in comparison with AHC group. The levels were 51.08±4.12 , 45.89±2.97 , and 38.94±1.57(pg/ml) in Alzheimer , Schizophrenia

, and major depression patients groups respectively , while it was 19.91± 1.41(pg/ml) in AHC group . The results of current study appeared that there were significant changes (P≤ 0.05) in GAD65 between all patients groups.

Table (4.3): The levels (Means ± SE)of glutamic acid decarboxylase 65 (GAD 65) in psychological stress patients and AHC groups .

Parameter / Groups N=90	GAD 65 pg/ml	p-value
AHC group	A 19.91± 1.41	0.0002*
Alzheimer patients	B 51.08±4.12	
Schizophrenia patients	BC 45.89±2.97	
Major depression patients	C 38.94±1.57	

Note: A different letter designates a significant change at($p \leq 0.05$).

4.3:Physiological Parameters

4.3.1: The levels of Serotonin in Psychological Stress Patients and AHC Groups .

The results in table (4.4) shown that a significant reduction (p≤0.05) in serotonin hormone levels in all patients groups in comparison with AHC group, which reached to 25.26±2.68 , 23.59±1.79 , 22.74±1.69 (pg/ml) in Alzheimer, Schizophrenia and major depression patients groups respectively , while it was 47.25±3.37 (pg/ml) in AHC group and there were non-significant differences(P≥0.05) in serotonin hormone levels in all patients groups .

Table (4.4): The levels of serotonin(5-HT) (means ± SE) in psychological stress patients and AHC groups.

Parameter / Groups N=90	Serotonin pg/ml	
AHC group	B 47.25±3.37	0.0003*
Alzheimer patients	A 25.26±2.68	
Schizophrenia patients	A 23.59±1.79	
Major depression patients	A 22.74±1.69	

Note: A different letter designates a significant change at($p \leq 0.05$).

4.3.2:Estimation The levels of Dopamine in Psychological Stress Patients and AHC Groups .

The data in table (4.5) showed that a significant reduction ($p \leq 0.05$) in dopamine hormone levels in all patients groups (Alzheimer, Schizophrenia and major depression diseases) compared with AHC group, which reached to 145.59±5.46,153.87±6.27,131.39±4.71 and 217.38±9.73(pg/ml) respectively. The results of current study appeared that there were non-significant differences($P \geq 0.05$) in hormone level in all patient groups.

Table (4.5) : The levels of dopamine (means ± SE) in psychological stress patients and AHC groups.

Parameter / Groups N=90	Dopamine pg/ml	p-value
AHC group	B 217.38±9.73	0.0002*
Alzheimer patients	A 145.59±5.46	
Schizophrenia patients	A 153.87±6.27	
Major depression patients	A 131.39±4.71	

Note: A different letter designates a significant change at($p \leq 0.05$).

4.4:Correlation Coefficient Between Study Parameters(IL-1β, Serotonin, Dopamine and GAD-65) in Psychological Stress Patients and AHC Groups.

4.4.1:Correlation Coefficient Between Study Parameters (IL-1β, Serotonin, Dopamine and GAD-65) in AHC Group.

Table (4.6) showed that there are positive significant association ($P \leq 0.05$) between IL-1β and serotonin levels, but there was a negative relationship (non-significant) between the levels of IL-1β and dopamine, whereas , there was a progressive relationship(non-significant) between IL-1β and GAD-65 levels in AHC group. In contrast, the data noted that a negative correlation (non-significant) between serotonin and dopamine levels , but there is a positive correlation between serotonin and GAD-65 levels in AHC group. On the other hand, there are negative non-significant correlation between dopamine and GAD 65

Table(4.6):Correlation coefficient between study parameters (IL-1β, Serotonin, Dopamine and GAD-65) in AHC group.

Parameters		Parameters			
		IL-1β	Serotonin	Dopamine	GAD-65
IL-1β	r p-value	1	0.39* 0.03	-0.16 0.39	0.26 0.17
Serotonin	r p-value	0.39* 0.03	1	-0.09 0.64	0.20 0.28
Dopamine	r p-value	-0.16 0.39	-0.09 0.64	1	-0.24 0.20
GAD-65	r p-value	0.26 0.17	0.20 0.28	-0.24 0.20	1

Note:* At a level of 0.05 (2-tailed), correlation is significant (pearson correlation, sig.(2-tailed))

4.4.2:Correlation Coefficient Between Study Parameters (IL-1β, Serotonin, Dopamine and GAD-65) in Alzheimer Patients Group

The results of present study (table 4.7) revealed that there are a positive association(non-significant) between IL-1β and serotonin levels , but there was a negative association(non-significant) between IL-1β and dopamine levels , in addition a negative relationship(non-significant) between IL-1β and GAD-65 levels.

Also, the data appeared that there was a positive relationship between serotonin and dopamine levels, as well as a positive correlation between serotonin and GAD-65 levels.

The data revealed that a positive correlation between dopamine and GAD-65 levels.

Table(4.7): Correlation coefficient between study parameters (IL-1β, Serotonin, Dopamine and GAD-65) in Alzheimer patients group .

Parameters		Parameters			
		IL-1β	Serotonin	Dopamine	GAD-65
IL-1β	r p-value	1	0.08 0.73	-0.28 0.23	-0.31 0.18
Serotonin	r p-value	0.08 0.73	1	0.34 0.15	0.08 0.74
Dopamine	r p-value	-0.28 0.23	0.34 0.15	1	0.01 0.97
GAD-65	r p-value	-0.31 0.18	0.08 0.74	0.01 0.97	1

(pearson correlation, sig.(2-tailed))

4.4.3:Correlation Coefficient Between Study Parameters(IL 1β,Serotonin, Dopamine and GAD-65) in Schizophrenia Patients Group

Table (4.8) showed that a progressive association between IL-1β and serotonin levels , in addition a progressive relationship between IL-1β and dopamine levels , but there was a negative relationship between IL-1β and GAD-65 levels. Also , there was a positive correlation between serotonin and dopamine levels and a negative relationship between serotonin and GAD-65 levels. Meantime, there was a positive relationship between dopamine and GAD-65 levels.

Table(4.8): Correlation coefficient between study parameters (IL-1β, Serotonin, Dopamine and GAD-65) in Schizophrenia group .

Parameters		Parameters			
		IL-1β	Serotonin	Dopamine	GAD-65
IL-1β	r p-value	1	0.21 0.37	0.16 0.51	-0.08 0.75
Serotonin	r p-value	0.21 0.37	1	0.09 0.68	-0.18 0.44
Dopamine	r p-value	0.16 0.51	0.09 0.68	1	0.29 0.20
GAD-65	r p-value	-0.08 0.75	-0.18 0.44	0.29 0.20	1

(pearson correlation, sig.(2-tailed))

4.4.4:Correlation Coefficient Between Study Parameters (IL-1β, Serotonin, Dopamine and GAD-65) in Major Depression Patients Group

The results of present study as shown in table (4.9) revealed a correlation coefficient between study parameters in major depression patients group . There was negative correlation between IL-1β and serotonin levels, also there was a negative relationship between IL-1β and dopamine levels, but there is a positive relationship between IL-1β and GAD-65 levels.

In addition , a negative relationship between serotonin and dopamine levels, as well as a negative correlation between serotonin and GAD-65 levels.

Furthermore, there is a positive correlation between dopamine and GAD-65 levels.

Table (4.9): Correlation coefficient between study parameters (IL-1β, Serotonin, Dopamine and GAD-65) in major depression patients group.

Parameters		Parameters			
		IL-1β	Serotonin	Dopamine	GAD-65
IL-1β	r p-value	1	-0.13 0.59	-0.05 0.83	0.32 0.16
Serotonin	r p-value	-0.13 0.59	1	-0.26 0.27	-0.39 0.08
Dopamine	r p-value	-0.05 0.83	-0.26 0.27	1	0.23 0.32
GAD-65	r p-value	0.32 0.16	-0.39 0.08	0.23 0.32	1

(pearson correlation, sig.(2-tailed))

4.5:Molecular Diagnosis

4.5.1:Distribution and Association of Allele Frequencies For Polymorphism of *Intrleukim-1β* Gene with Psychological Stress Patients (Alzheimer, Schizophrenia and Major Depression Diseases) and AHC Groups

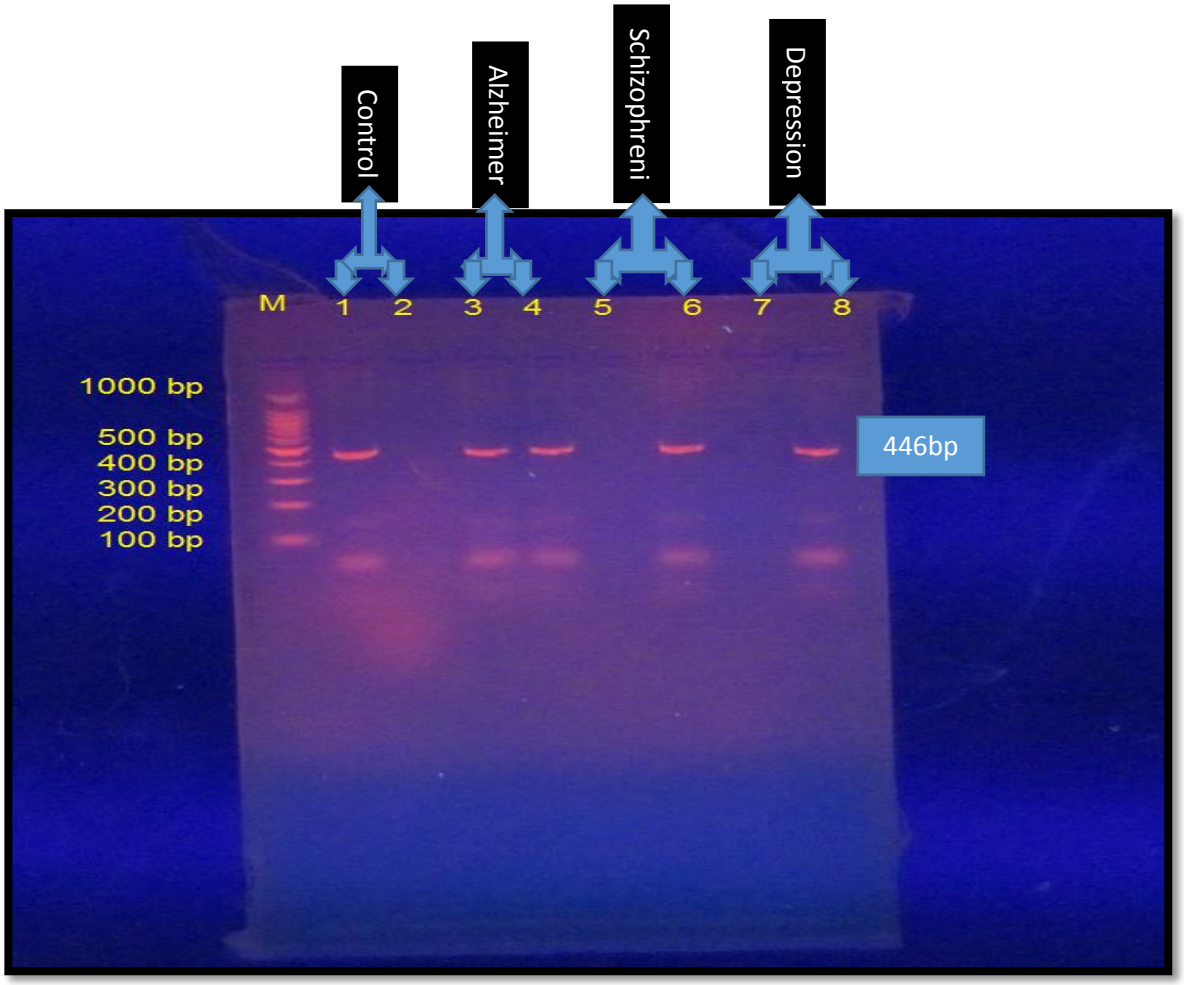
The results of current study (table 4.10 and figure 4.1) showed that AHC group are the highest percent (80%) in *IL-1β* genotype AA in comparison with patients groups, also Alzheimer patients group revealed the highest percent (60%) in *IL-1β* genotype GA compared with other groups .While, Schizophrenia and Major depression patients groups revealed the highest percent (70%) and (45%) respectively in *IL-1β* genotype GG in comparison with other groups. On the other hand, AHC group showed the lowers percent (6.67%) in IL-1β genotype GA compared with other groups, furthermore, *IL-1β* genotype AA showed the lowers percent in patients groups in comparison with AHC group. Also, the results revealed that the AHC group was the highest percent (83.3%) in *IL-1β* allele A compared with other groups, as well as, Alzheimer, Schizophrenia, and major depression patients group revealed the highest percent in *IL-1β* allele G which reached to (70%), (85%) and (65%) respectively

compared with AHC group , but the lowers percent was revealed in *IL-1β* allele A in patients groups in comparison with AHC group. In contrast, The frequency of *interleukin-1 beta* genotype GA was higher in MDD patients group with odds ratio of 32 compared with AHC group (95% CI 2.93 - 64.35) $P<0.05$ $\chi^2= 3.4$, but the frequency of *interleukin-1beta* genotype GG was higher in MDD patients group with odds ratio of 18 compared with AHC group (95% CI 3.34-34.73) $P<0.05$ $\chi^2= 3.6$. While, the frequency of *interleukin-1beta* allele G was higher in Alzheimer patients group with odds ratio of 11.6 compared with AHC group (95% CI 4.4 - 22.4) $P<0.05$ $\chi^2= 5$, the frequency of *interleukin-1beta* allele G was higher in schizophrenia patients group with odds ratio of 28.3 compared with AHC group (95% CI 9.41 – 56.28) $P<0.05$ $\chi^2= 5.9$, the frequency of *interleukin-1beta* allele G was higher in major depression patients group with odds ratio of 9.28 compared with AHC group (95% CI 3.6 – 23.76) $P<0.05$ $\chi^2= 4.6$. As noted in figures (4.2),(4.3),(4.4),(4.5) and(4.6).

Table (4.10):Distribution of allele frequencies for polymorphism of *interleukin-1β* gene (rs16944) with psychological stress patients and AHC groups.

Genotypes	Frequency n (%)				AHC *vs.* Alzheimer Patients		AHC *vs.* Schizophrenia patients		AHC *vs.* Major depression Patients	
	AHC group N=30 N (%)	Alzheimer Patients N=20 N (%)	Schizophrenia patients N=20 N (%)	Major depression Patients N=20 N (%)	*OR (95% CI)*	χ2/ P value	*OR (95% CI)*	χ2/ P value	*OR (95% CI)*	χ2/ P value
AA	24(80)	0(0)	0(0)	3(15)	1.00(Ref.)	--	1.00(Ref.)	--	1.00(Ref.)	--
GA	2(6.67)	12(60)	6(30)	8(40)	--	--	--	--	32 (2.93-64.35)	3.4/ 0.0005
GG	4(13.33)	8(40)	14(70)	9(45)	--	--	--	--	18 (3.34-34.73)	3.6/ 0.0008
Alleles										
A	50(83.3)	12(30)	6(15)	14(35)	1.00(Ref.)	--	1.00(Ref.)	--	1.00(Ref.)	--
G	10(16.7)	28(70)	34(85)	26(65)	11.6 (4.4-22.4)	5/ P<0.0001	28.3 (9.41-56.28)	5.9/ P<0.0001	9.28 (3.6-23.76)	4.6/ P<0.0001

p-value ≤ 0.05 was significant



Figure(4.1):Distribution of allele frequencies for polymorphism of *interleukin-1β* gene (rs16944) with psychological stress patients and AHC groups showed that the allele frequency in AHC group was AA, Alzheimer group was GA, Schizophrenia group was GG and major depression group was GG. PCR product was subjected to electrophoresis on 1% agarose gel, 30 minutes at 60 volts and PCR done according to one specific allele PCR.

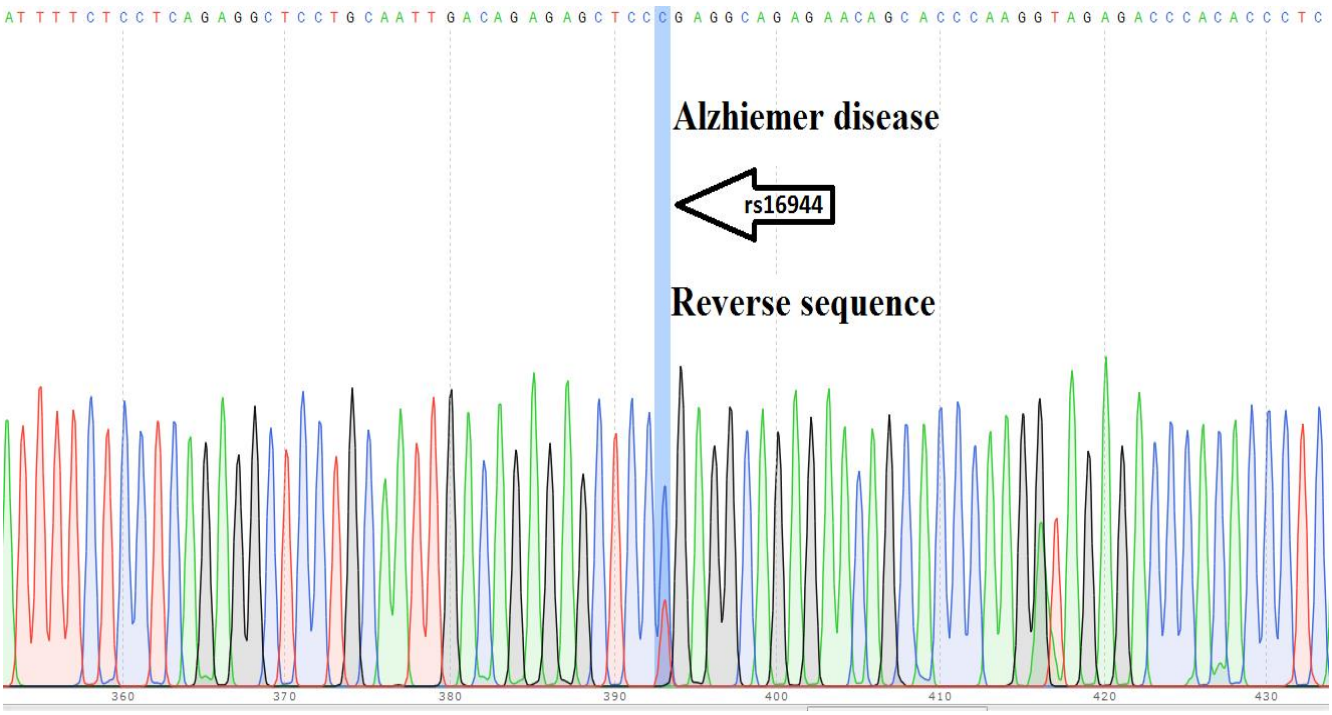


Figure (4.2): Snap Gene viewer sequencer showed the allele sequence of *IL-1β* gene (rs16944) polymorphism showed that the allele reverse sequence in Alzheimer disease was C (mutation allele)

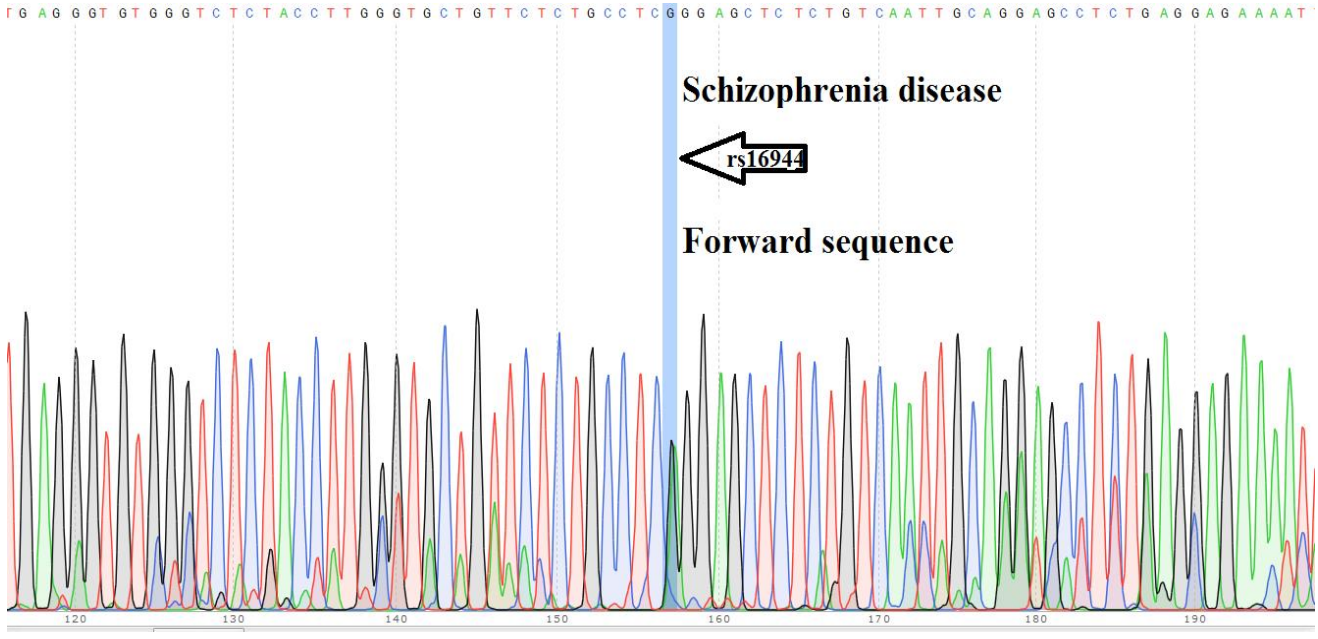


Figure (4.3): Snap Gene viewer sequencer showed the allele sequence of *IL-1β* gene (rs16944) polymorphism showed that the allele forward sequence in Schizophrenia disease was G (mutation allele)

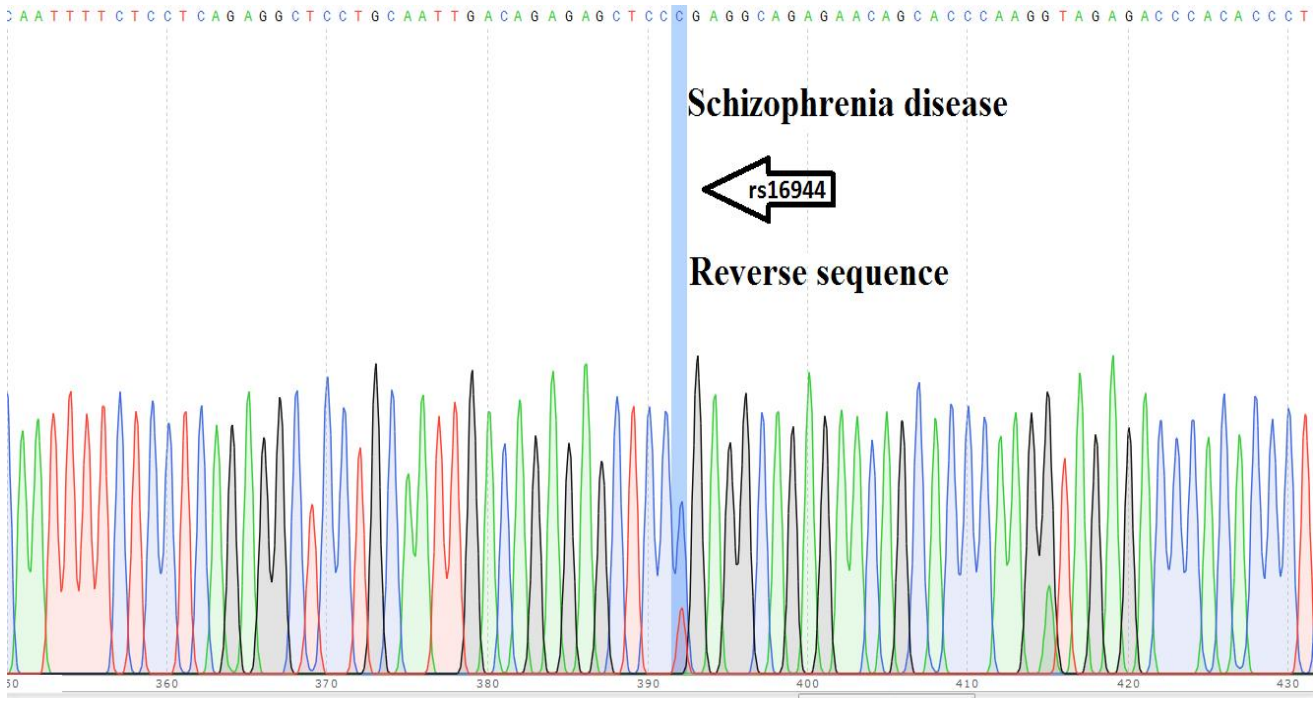


Figure (4.4): Snap Gene viewer sequencer showed the allele sequence of *IL-1β* gene (rs16944) polymorphism showed that the allele reverse sequence in Schizophrenia disease was C (mutation allele)

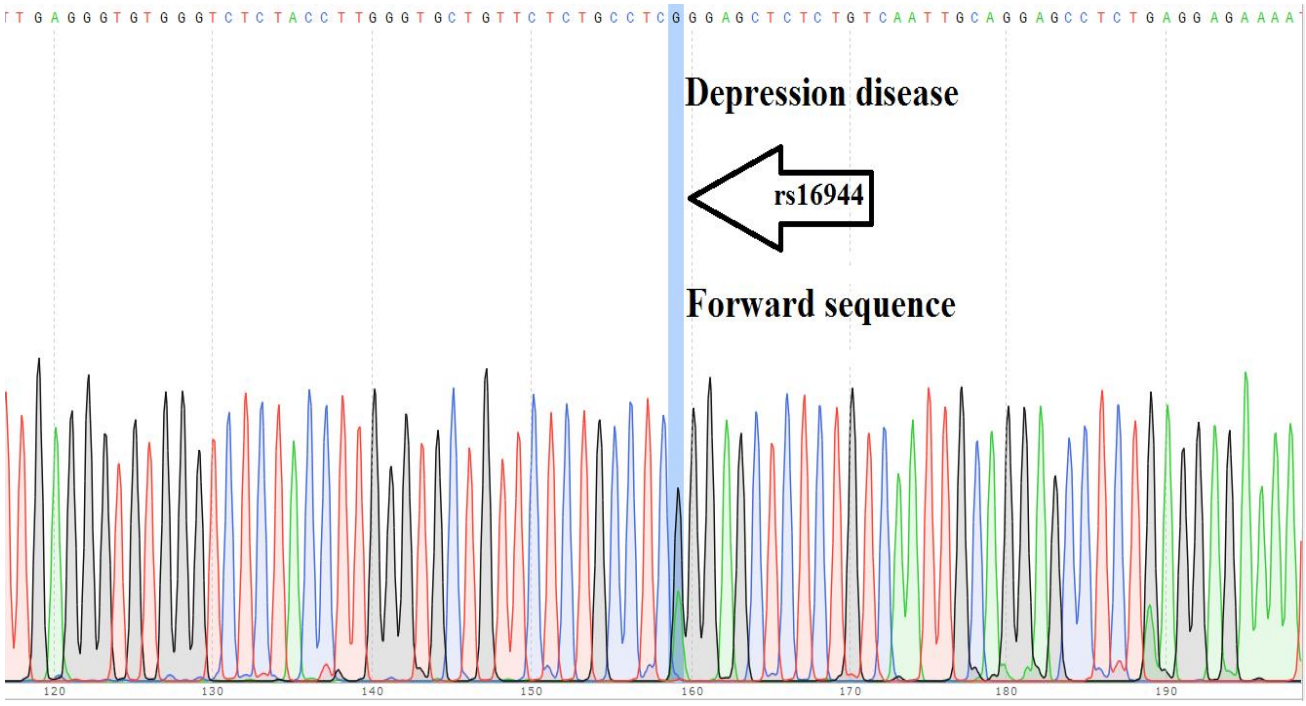


Figure (4.5): Snap Gene viewer sequencer showed the allele sequence of *IL-1β* gene (rs16944) polymorphism showed that the allele forward sequence in depression disease was G (mutation allele)

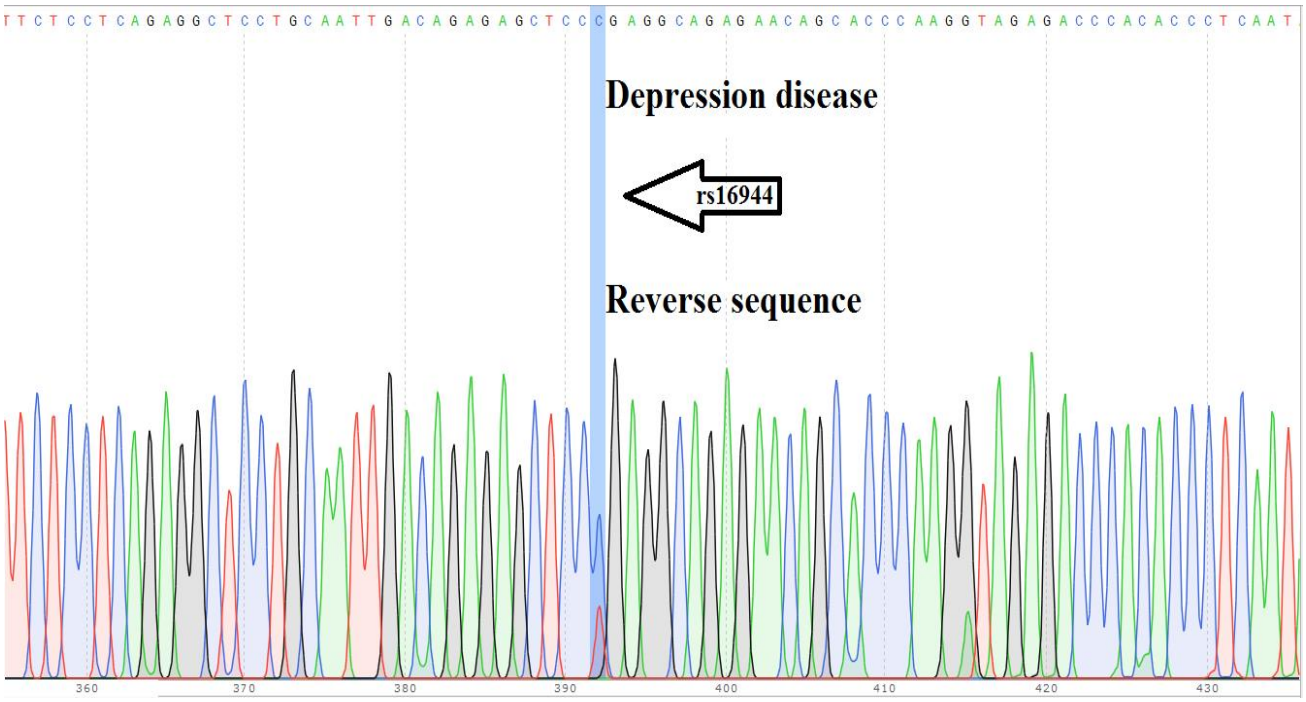


Figure (4.6): Snap Gene viewer sequencer showed the allele sequence of *IL-1β* gene (rs16944) polymorphism showed that the allele reverse sequence in depression disease was C (mutation allele)

4.5.2: Distribution and Association of *Serotonin Receptor (5- HT1A)* Genotype in Psychological Stress Patients and AHC Groups

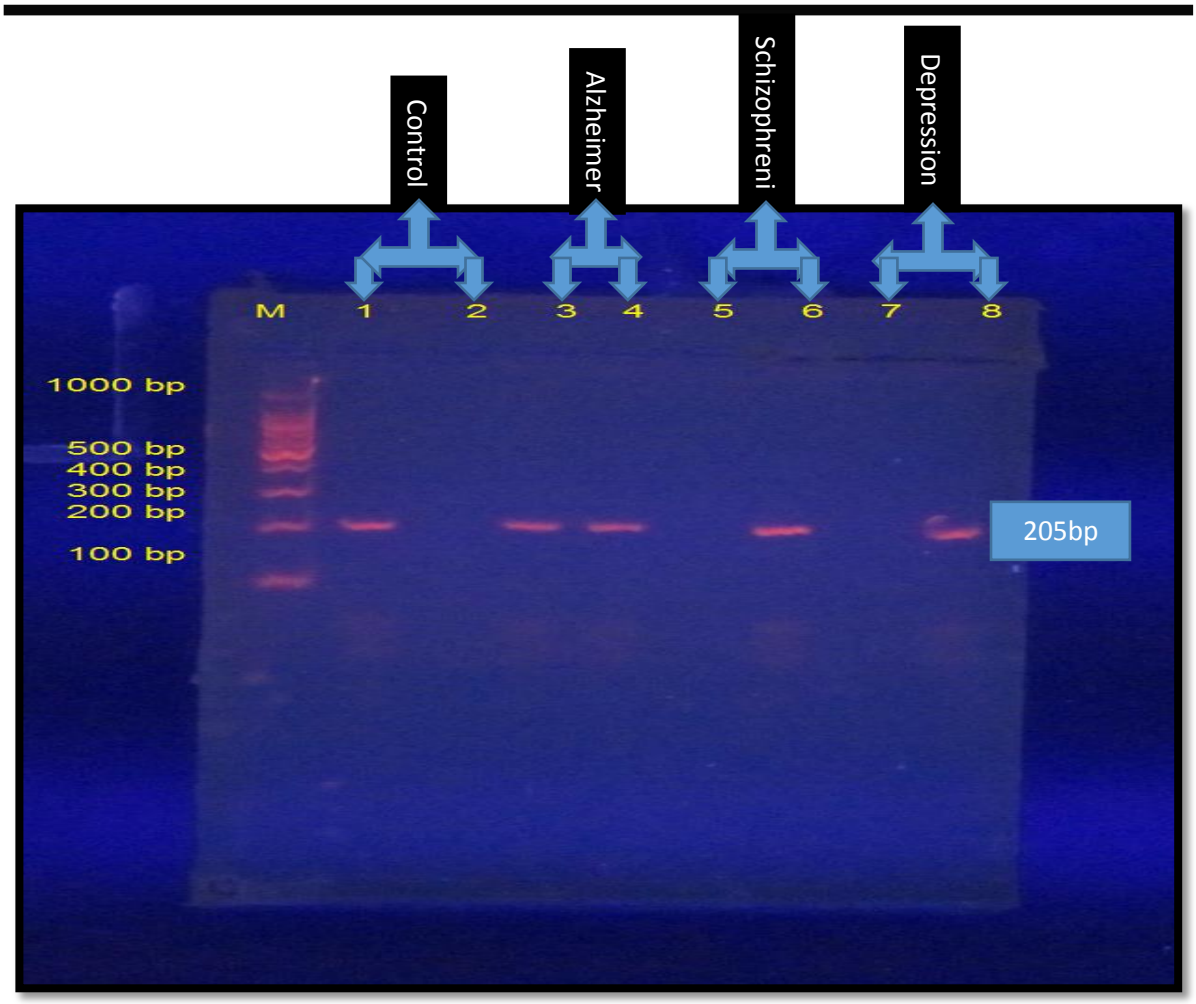
Table (4.11) and figure (4.7) showed that the AHC group revealed that the highest percent (76.67%) in *5-HT1A* genotype GG compared with patients groups , also the Alzheimer and Schizophrenia patients group was the highest percent (50%) in *5-HT1A* genotype GC compared with other groups ,but major depression patients groups are formed the highest percent which reached to (50%) in *5-HT1A* genotype CC compared with other groups. The data , also showed the AHC group was the lowers percent (6.67%) in *5-HT1A* genotype GC in comparison with other groups , while, the patients groups revealed the lowers percent in *5-HT1A* genotype GG compared with AHC group. Also, the results of present study revealed that AHC group was the highest percent in *5-HT1A* allele G compared with other groups , and Alzheimer , Schizophrenia and major depression patients groups are revealed the highest percent in *5-HT1A* allele C

compared with AHC group. Whereas, the patients groups were showed the lowers percent in *5-HT1A* allele G in comparison with AHC group.In contrast, The frequency of *5-HT1A* genotype GC was higher in MDD patients group with odds ratio of 17.2 compared with AHC group (95% CI 2.52-34.7) P<0.05 χ^2= 2.9, but the frequency of *5-HT1A* genotype CC was higher in MDD patients group with odds ratio of 11.5 compared with AHC group (95% C2.5-22.05) P<0.05 χ^2= 3.1. While, the frequency of *5-HT1A* allele G was higher in Alzheimer patients group with odds ratio of 9.33 compared with AHC group (95% CI3.6-23.5) P<0.05 χ^2= 4.7, the frequency of *5-HT1A* allele G was higher in schizophrenia patients group with odds ratio of 9.33 compared with AHC group (95% CI 3.6-23.5) P<0.05 χ^2= 4.7, the frequency of *5-HT1A* allele G was higher in major depression patients group with odds ratio of 7.42 compared with AHC group (95% CI 2.9-18.39) P<0.05 χ^2= 4.3 . As noted in figures (4.8),(4.9),(4.10),(4.11) and(4.12).

Table (4.11) :Distribution of *serotonin receptor (5- HT1A)* (rs6296) gene polymorphism with psychological stress patients and AHC groups.

Genotypes	Frequency n (%)				AHC *vs.* Alzheimer Patients		AHC *vs.* Schizophrenia patients		AHC *vs.* Major depression Patients	
	AHC group N=30 N (%)	Alzheimer Patients N=20 N (%)	Schizophrenia patients N=20 N (%)	Major depression Patients N=20 N (%)	*OR (95% CI)*	$\chi 2$/ P value	*OR (95% CI)*	$\chi 2$/ P value	*OR (95% CI)*	$\chi 2$/ P value
GG	23(76.67)	1(5)	1(5)	4(20)	1.00(Ref.)	--	1.00(Ref.)	--	1.00(Ref.)	--
GC	2(6.67)	10(50)	10(50)	6(30)	--	--	--	--	17.2 (2.52-34.7)	2.9/ 0.003
CC	5(16.67)	9(45)	9(45)	10(50)	--	--	--	--	11.5 (2.5-22.05)	3.1/ 0.001
Alleles										
G	48(80)	12(30)	12(30)	14(35)	1.00(Ref.)	--	1.00(Ref.)	--	1.00(Ref.)	--
C	12(20)	28(70)	28(70)	26(65)	9.33 (3.6-23.5)	4.7/ P < 0.0001	9.33 (3.6-23.5)	4.7/ P < 0.0001	7.42 (2.9-18.39)	4.3/ P < 0.0001

p-value ≤ 0.05 was significant



Figure(4.7):Distribution of *serotonin receptor (5-HT1A)* gene (rs6296) polymorphism with psychological stress patients and AHC groups revealed that the allele frequency was GG in AHC group, GC in Alzheimer group, CC in Schizophrenia group and CC in major depression group. PCR product was subjected to electrophoresis on 1% agarose gel, 30 minutes at 60 volts and PCR done according to one specific allele PCR.

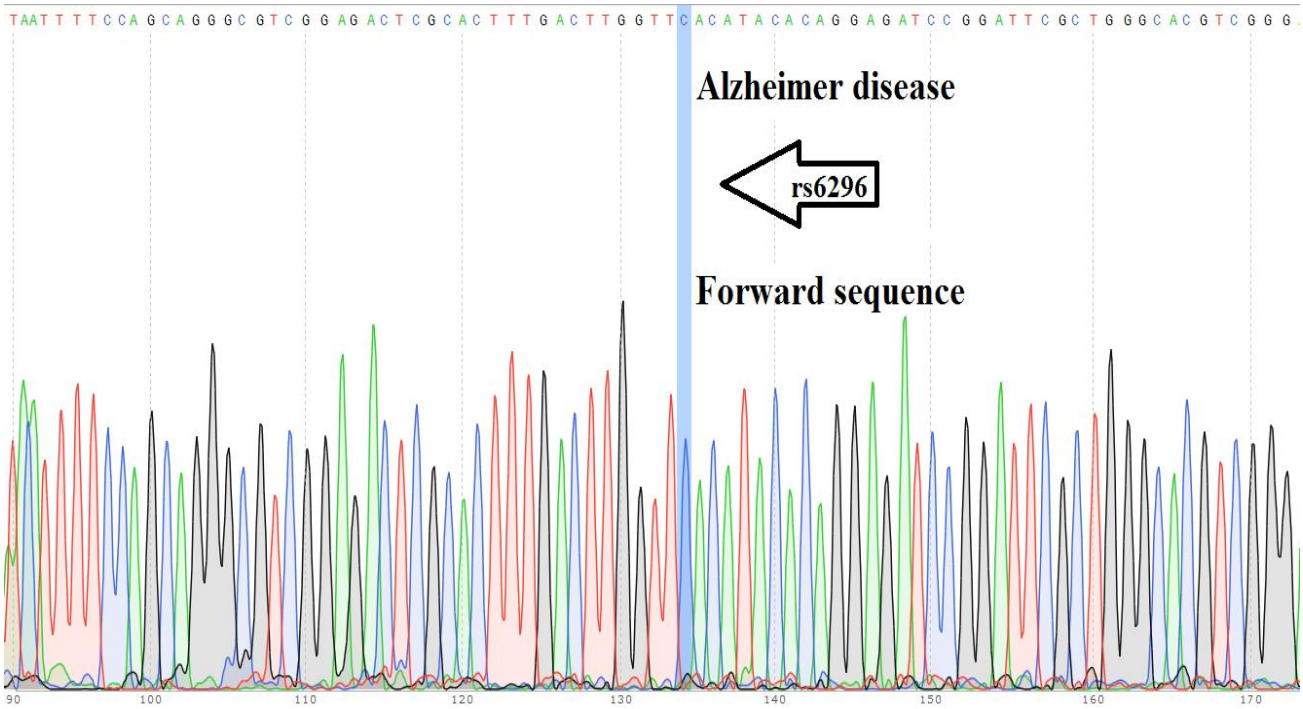


Figure (4.8): Snap Gene viewer sequencer showed the allele sequence of *serotonin receptor* gene (rs6296) polymorphism showed that the allele forward sequence in Alzheimer disease was C (mutation allele)

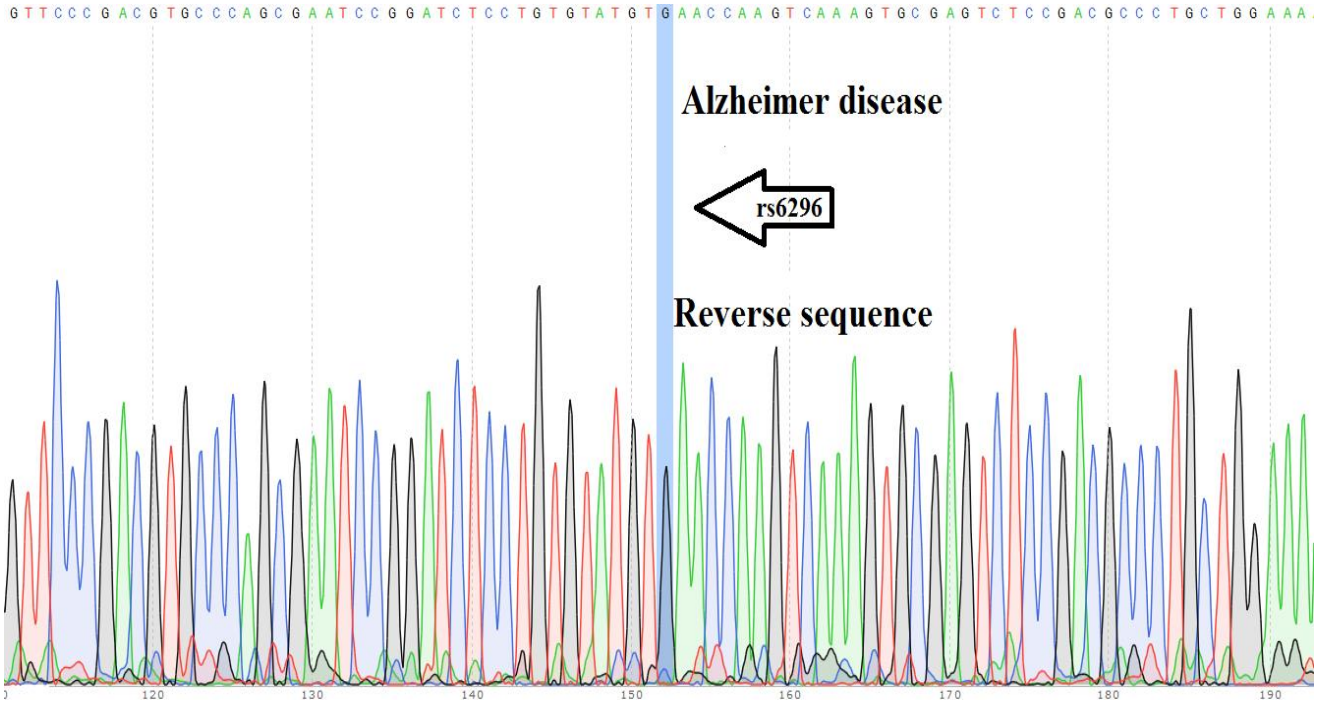


Figure (4.9): Snap Gene viewer sequencer showed the allele sequence of *serotonin receptor* gene (rs6296) polymorphism showed that the allele reverse sequence in Alzheimer disease was G (mutation allele)

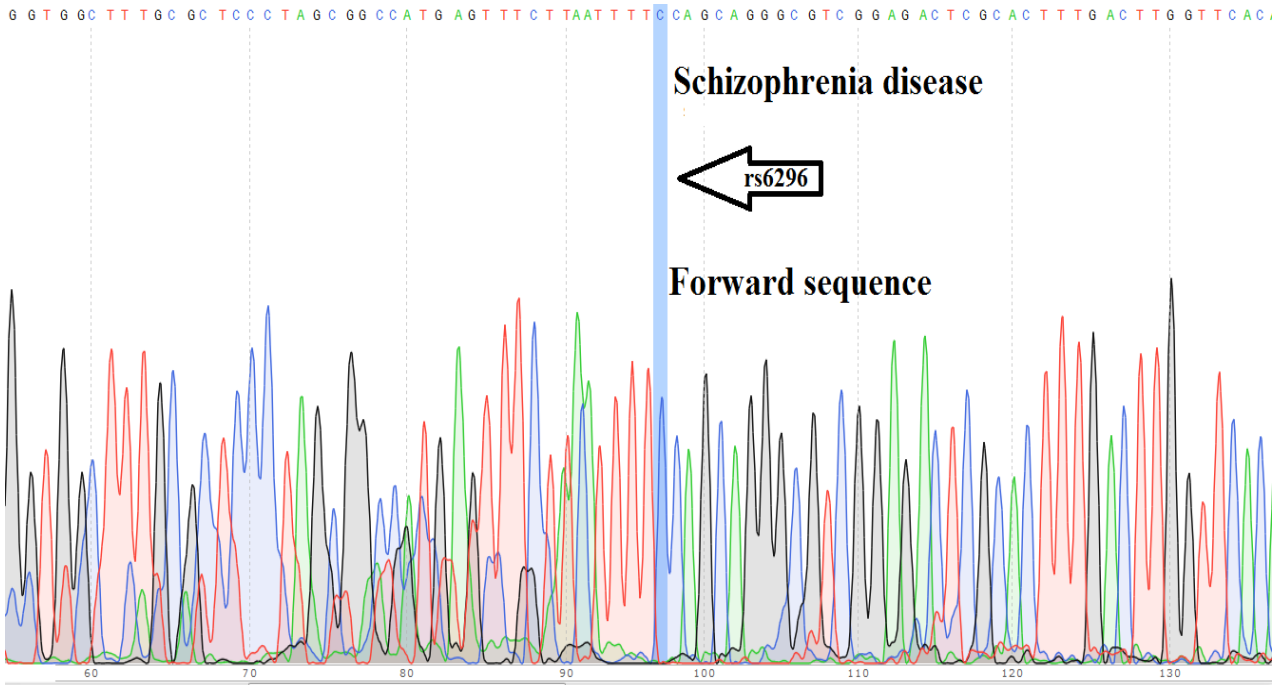


Figure (4.10): Snap Gene viewer sequencer showed the allele sequence of *serotonin receptor* gene (rs6296) polymorphism showed that the allele forward sequence in Schizophrenia disease was C (mutation allele)

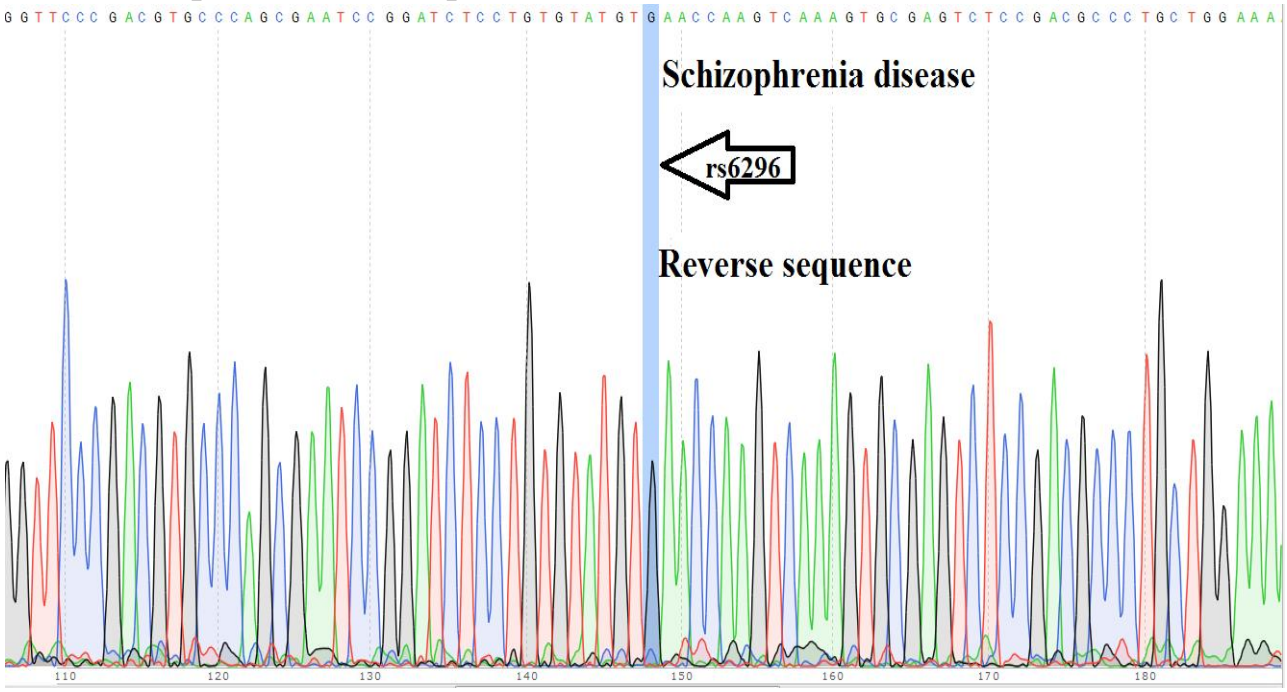


Figure (4.11): Snap Gene viewer sequencer showed the allele sequence of *serotonin receptor* gene (rs6296) polymorphism showed that the allele reverse sequence in Schizophrenia disease was G (mutation allele)

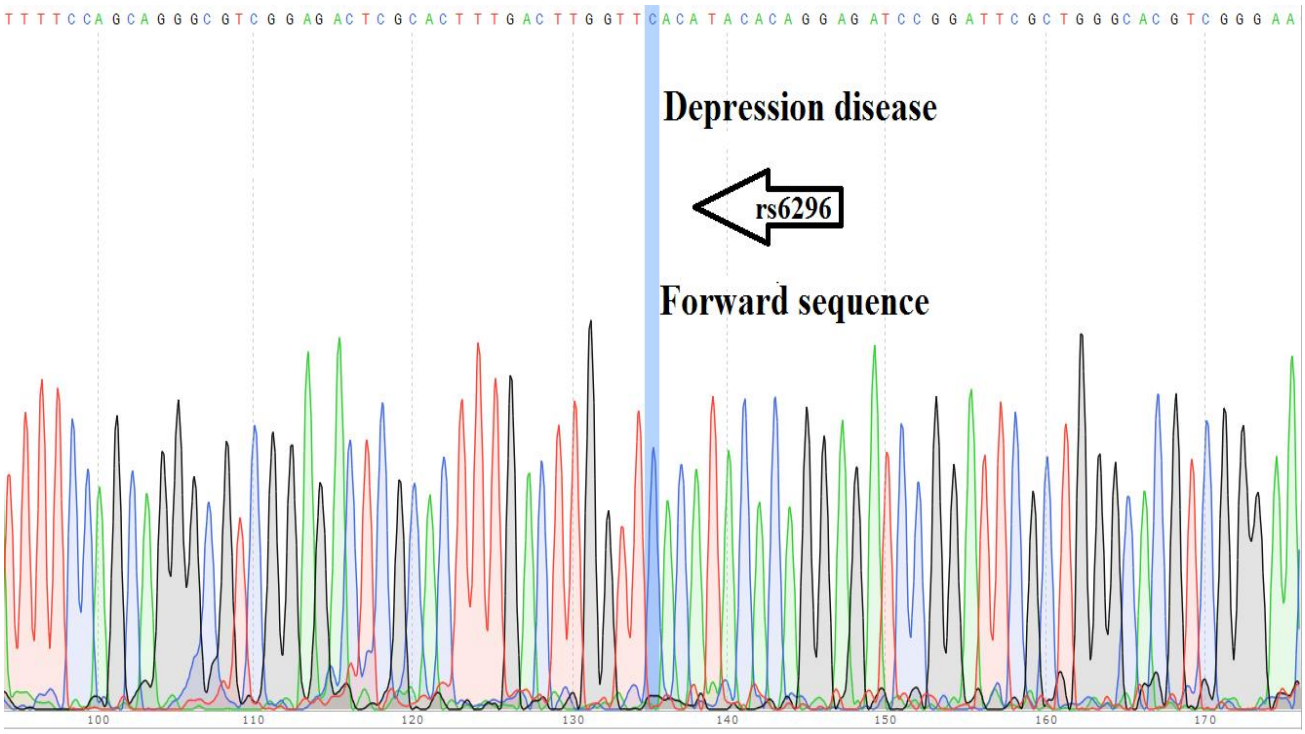


Figure (4.12): Snap Gene viewer sequencer showed the allele sequence of *serotonin receptor* gene (rs6296) polymorphism showed that the allele forward sequence in depression disease was C (mutation allele)

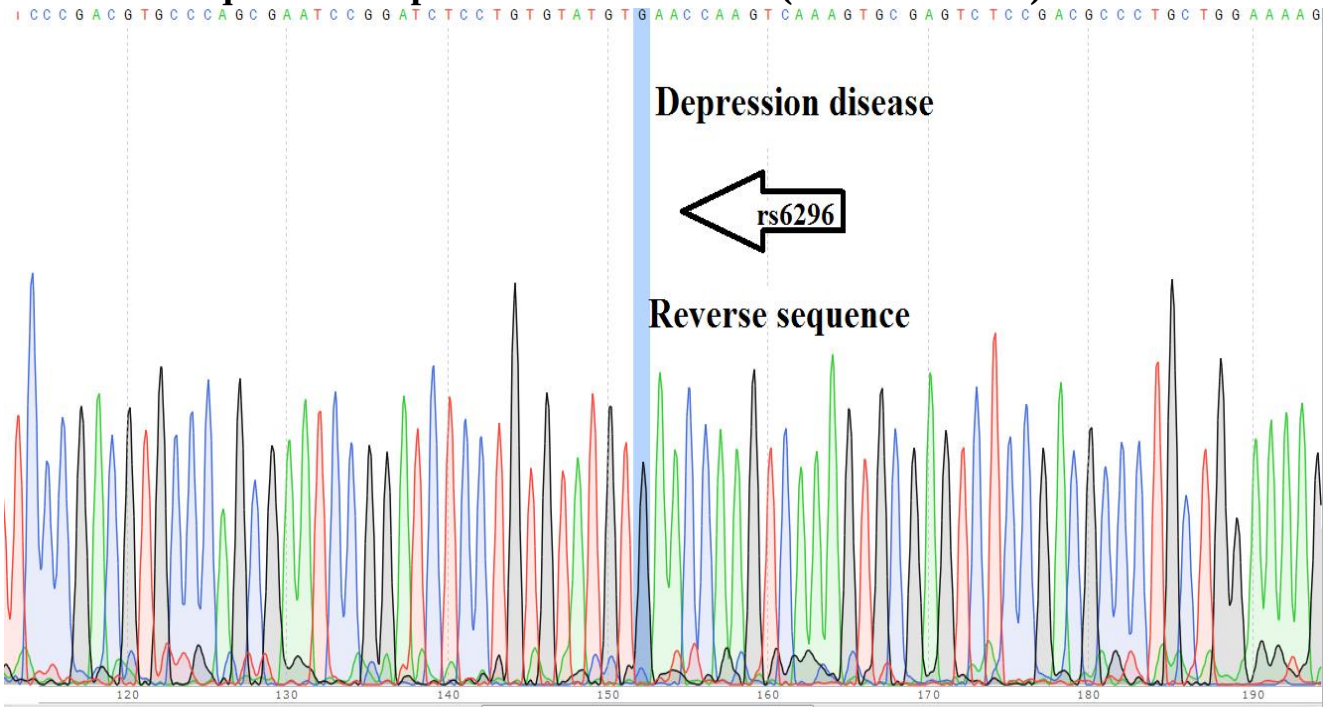


Figure (4.13): Snap Gene viewer sequencer showed the allele sequence of *serotonin receptor* gene (rs6296) polymorphism showed that the allele reverse sequence in depression disease was G (mutation allele)

4.6:Association for Polymorphism of *Interleukin-1β* Gene with IL-1β Levels in Patients With Psychological Stress and AHC Group(Means ± SE)

Table(4.12) revealed that a non-significant change($p \geq 0.05$) between genotypes(GA, GG and AA) of *IL-1β* gene and IL-1β levels in AHC group, while there was a non-significant changes($p \geq 0.05$) in Alzheimer patients group between genotypes(GA, GG) of *IL-1β* gene and IL-1β levels and Alzheimer patients don't have genotype (AA) of *IL-1β* gene in their chromosome. The schizophrenia patients group revealed a significant increase($p \leq 0.05$) between genotype(GA) of *IL-1β* gene and IL-1β levels in comparison with genotype(GG) of *IL-1β* gene and schizophrenia patients don't have genotype (AA) of *IL-1β* gene in their chromosome, while, the major depression patients group revealed non-significant change($p \geq 0.05$) between genotypes(GA, GG and AA) of *IL-1β* gene and IL-1β levels. On the other hand, there are significant difference between *IL-1β* genotype(GA) and IL-1β levels in Alzheimer, schizophrenia and Major depression patients compared with AHC group. Also noted that there are significant difference between *IL-1β* genotype (GG) and IL-1β levels in Alzheimer, schizophrenia and Major depression patients compared with AHC group. While there are significant difference between *IL-1β* genotype (AA) and IL-1β levels in Major depression patients compared with AHC group and Alzheimer, schizophrenia patients don't have genotype(AA) in their chromosomes.

Table(4.12): Association for polymorphism of *interleukin-1β* gene with IL-1β level in patients with psychological stress and AHC groups (Means ± SE)

IL-1β Genotype	IL-1β level (pg/ml)				
	AHC group	Alzheimer patients group	schizophrenia patients group	Major depression Patients group	p-value
GA	^{Aa}9.51±1.56	^{Ab}34.88±5.21	^{Ab}37.10±6.96	^{Aab}24.78±1.84	0.02
GG	^{Aa}8.15±1.83	^{Ab}34.04±3.68	^{Bb}29.00±2.99	^{Ab}24.66±1.60	0.04
AA	^{Aa}10.29±0.89	0	0	^{Ab}20.50±0.27	0.04
p-value	0.76	0.28	0.02	0.38	

Note : A different letter designates a significant change at ($p \leq 0.05$)
Capital letter represent difference between *IL-1β* genotypes and IL-1β levels in same group
Small letter represent difference between *IL-1β* genotypes and IL-1β levels in different groups

4.7:Association of *Serotonin Receptor(5-HT1A)* Gene Polymorphism with Serotonin Levels in Psychological Stress Patients and AHC Groups (Means ± SE)

The data of current study shown that there are non-significant change ($p \leq 0.05$) between genotypes (GC,CC and GG) of *serotonin receptor(5-HT1A)* gene and serotonin levels in AHC group, while, there was non-significant change ($p \geq 0.05$) between genotypes (GC, CC and GG) of *serotonin receptor(5-HT1A)* gene and serotonin levels in Alzheimer patients group. Whereas, there was non-significant difference ($p \leq 0.05$) between genotypes (GC, CC and GG) of *serotonin receptor(5-HT1A)* gene and serotonin levels in schizophrenia patients group. Furthermore, the major depression patients group revealed a non-significant change($p \geq 0.05$) between genotypes (GC,CC and GG) of *serotonin receptor(5-HT1A)* gene alleles and serotonin levels. On the other hand, there are significant difference between *5-HT1A* genotype(GC) and serotonin levels in Alzheimer, schizophrenia and Major depression patients compared with AHC group. While noted that there are non-significant difference between *5-HT1A*

genotype (CC) and serotonin levels in Alzheimer, schizophrenia and Major depression patients compared with AHC group. While there are significant difference between *5-HT1A* genotype (GG) and serotonin levels in Alzheimer, schizophrenia and Major depression patients compared with AHC group, as illustrated in table (4.13).

Table(4.13):Association of *Serotonin receptor(5-HT1A)* gene polymorphism with serotonin levels in psychological stress patients and AHC groups (Means ± SE).

5-HT1A **Genotype**	**serotonin level (pg/ml)**				
	AHC group	**Alzheimer patients group**	**schizophrenia patients group**	**Major depression Patients group**	**p-value**
GC	**^{Aa}50.92±13.52**	**^{Ab}26.90±3.96**	**^{Ab}26.59±3.02**	**^{Ab}22.28±2.36**	**0.03**
CC	**^{Aa}31.55±7.84**	**^{Aa}23.65±4.20**	**^{Aa}21.23±1.59**	**^{Aa}21.33±2.92**	**0.05**
GG	**^{Aa}50.51±3.72**	**^{Ab}22.91±0.00**	**^{Ab}14.76±0.00**	**^{Ab}26.92±2.39**	**0.04**
p-value	**0.25**	**0.95**	**0.39**	**0.48**	

Note : A significant difference is denoted by different letters at (p≤0. 05).
Capital letter represent difference between *5-HT1A* genotypes and serotonin levels in same group
Small letter represent difference between *5-HT1A* genotypes and serotonin levels in different groups

4.8:Microbial Infections

4.8.1:Viral Infections

4.8.1.1:Association of Psychological Stress Diseases and Herpes Simplex Virus(HSV-1) Infection

Table (4.14) showed that all samples of AHC group was negative(100%) to HSV-1 test , while HSV-1 test was positive in Alzheimer , Schizophrenia and major depression patients groups which reached to (50%), (50%) and (60%) respectively.

Table (4.14): Percentage of herpes simplex virus(HSV-1) in psychological stress patients groups and AHC control.

Groups	No.	HSV-1				Total	
		Positive		Negative			
		No.	%	No.	%	No.	%
AHC group	30	0	0	30	100	30	100%
Alzheimer patients	20	10	50	10	50	20	100%
Schizophrenia patients	20	10	50	10	50	20	100%
Major depression patients	20	12	60	8	40	20	100%
Total	90	32	35.56	58	64.44	90	100%

4.8.1.2:Association of HSV-1Infection with Study Parameters (IL-1β, Serotonin, Dopamine and GAD 65) in Psychological Stress Patients and AHC Group

Table(4.15) showed that there wasn't association between HSV-1 infection(positive and negative) and IL-1β, serotonin, dopamine and GAD 65 levels in AHC group, while there was a significant change ($p \leq 0.05$) in Alzheimer patients group between HSV-1 infection(positive and negative) and IL-1β levels, but there are non-significant change($p \geq 0.05$) between HSV-1 infection(positive and negative) and serotonin, dopamine and GAD 65 levels. The schizophrenia patients group revealed non-significant difference($p \geq 0.05$) between HSV-1 infection(positive and negative) and IL-1β, serotonin, dopamine and GAD 65 levels. In contrast, the major depression patients group revealed significant difference($p \leq 0.05$) between HSV-1 infection(positive and negative) and IL-1β level, while there was non-significant change($p \geq 0.05$) between HSV-1 infection(positive and negative) and serotonin, dopamine and GAD 65 levels.

Table(4.15):Association of HSV-1infection with IL-1β, Serotonin, dopamine and GAD65 parameters in psychological stress patients and AHC groups(Means ± SE).

Groups	HSV-1	IL-1β	Serotonin	Dopamine	GAD 65
AHC group	positive	0	0	0	0
	negative	10.04±0.75	128.60±8.89	217.38±9.73	19.91±1.41
Alzheimer patients group	positive	A 43.57±4.89	A 24.71±7.66	A 148.39±6.75	A 57.28±5.99
	negative	B 28.87±3.19	A 15.99±9.96	A 142.19±9.22	A 43.49±4.64
Schizophrenia patients group	positive	A 31.43±3.37	A 24.87±5.51	A 155.78±6.92	A 45.28±4.27
	negative	A 24.16±2.54	A 28.54±4.02	A 149.87±9.21	A 46.49±4.34
Major depression Patients group	positive	A 26.33±1.33	A 23.47±3.31	A 143.95±8.97	A 39.59±2.75
	negative	B 22.13±0.53	A 22.42±2.21	A 136.33±8.71	A 38.29±1.67

Note : At (p≤0. 05), different letters signify a significant difference.

4.8.2:Bacterial Infections

4.8.2.1:Association of Psychological Stress Patients(Alzheimer, Schizophrenia and Depression Diseases) and AHC Groups with Bacterial Infection

The results in table (4.16) illustrated that the AHC group show a negative test for *H. pylori*, while, Alzheimer, Schizophrenia and Major depression patients groups revealed positive results for *H. pylori* which reached to (35%), (25%) and (40%) respectively.

Table(4.16):Association of psychological stress patients (Alzheimer, Schizophrenia and depression diseases) and AHC groups with bacterial infections

Groups	Test result	*H. pylori*
		N(%)
AHC group	positive	0(0)
	negative	30(100)
Alzheimer Patients group	positive	7(35)
	negative	13(65)
Schizophrenia Patients group	positive	5(25)
	negative	15(75)
Major depression patients group	positive	8(40)
	negative	12(60)

CHAPTER FIVE

DISCUSSION

5:Discussion

5.1: Demographic Characteristics

5.1.1:Age

The current results showed that Alzheimer patients are formed of the largest percent (95%) in age >60 year and formed of the smallest percent (0%) in age <30 year compared with AHC group and these results were in coordinated with the study of Al Ganzawi (2013) who revealed the fact AD is an older-age disease is highlighted, with age 65 years being a risk factor for both morbidities. After the age of 65, research has revealed that the age-specific prevalence of AD nearly doubles every five years. In developed countries, 1 in 10 older people (over the age of 65) suffer from dementia to some extent, while more than one third of very old people (over the age of 85) may exhibit dementia-related symptoms and signs (Corrada *et al.,* 2008). Less occurrences of AD, which made up 4-6% of all cases, however, occur at younger ages.

The age characteristic of patients who have schizophrenia are formed of the largest percent (60%) in age 30-60 year and formed of the smallest percent (10%) in age >60 compared with AHC group and these results were in coordinated with previous studies (Dheeb,2016) who revealed that the highest frequency of schizophrenic patients among 30- 49 years old (50%), followed by the age group of < 30 years old (31.7%) , and the less frequency in the age 50 and more (18.3%). Hafner (2015) showed that schizophrenia is a disorder of all ages. These results are comparable to a research in which persons aged 18 to 64 years old made an average of 382,000 emergency department visits due to schizophrenia (Albert and McCaig ,2015). In addition, other studies documented an age range 12-59 years (Hafner *et al*., 2013). Major depression patients are formed of the largest percent (50%) in age 30-60 year and are

formed of the smallest percent (10%) in age >60 year in comparison with AHC group and these results were in coordinated with the results of Hassan (2018) that showed 50% of participants with age 20-44 and ≥65 had depression , that this high prevalence is similar to Korean study (Seon *et al.,* 2014) that revealed 57% for age18-44years and Indian study (Arifuddin *et al.*,2018) that were 52.8% for age 20-29 years.

5.1.2:Duration of Disease

Regarding the duration of the disease, Alzheimer patients are constituted of the largest percent (75%) during the duration of disease 5-20 year and are formed of the smallest percent (0%) during duration of disease >20 year compared with Major depression patients and these results were in coordinated with previous studies (Al Ganzawi,2013) that showed AD responded oppositely to duration of disease. In the case of AD, most cases (76.7%) had a duration of disease 6-15 years. According to research, AD typically lasts for 8 to 10 years, but the course can last anywhere from 1 to 25 years. For unexplained reasons, some AD patients exhibit a gradual decline in function, while others exhibit protracted plateaus without significant worsening (Roberson and Mucke, 2006). Furthermore, Schizophrenia patients group are formed of the largest percent (60%) during duration of disease 5-20 year and are formed of the smallest percent (5%) during duration of disease >20 year compared with Major depression patients and these results were in consistent with previous studies (Dheeb,2016) who showed that 35% of patient samples had their disease less than 5years, with the majority 41.6% of patients the disease duration was 5-15 years, while those disease duration more than 15 years represent a minority 23.3%. Other study stated that the majority of patients have duration of illness of 4.25- 5.5 years (Bharti *et al.*, 2013). Furthermore , the study of Samuel *et al.*,(2015) revealed that about

95% of selected patients sample their duration of illness 10-13 year with mean of 11.5 year ±11.1 . This disparity from current results may be explained by missed documentation of new cases of schizophrenia and long standing cases incompliance, all of which might be due to the lack of community awareness for the need of intensive follow up, in addition the rise of remedy tradition and religious advisers in the management of such psychiatric condition forcing the patient away from medical care (Katherine *et al.*, 2009).

Major depression patients are formed of the largest percent (80%) during duration of disease <5 year and are formed of the smallest percent (0%) during duration of disease >20 year compared with Alzheimer patients and Schizophrenia patients and this disease formed of the smallest percent (0%) during duration of disease >20 year and these results were in coordinated with the study of Hassan(2018) showed that (63.3%) of participants had 1month duration of symptoms, while in Saudi study (Fahad *et al.*, 2014) 51.7% of subjects had suffer from complaints for 6-30 years.

5.1.3:Sex

Sex characteristic revealed that Alzheimer patients are formed of the largest percent (60%) in female and are formed of the smallest percent (40%) in male compared with AHC group and these results were in consistent with the study of Al Ganzawi(2013) showed a high frequency of females than males 66.7 vs. 33.3% in AD , and the distribution was significantly changed ($P \leq 0.05$) in AD patients. These results suggests that females are at higher risk to progress AD than males. In line with these findings, the majority of studies point to a female preponderance in AD, with the chance of developing any type of dementia being about double as high in females as in males and up to three times greater in women(Povova *et al*., 2012). Such a discrepancy can

be described by the possibility that metabolic changes brought on by sex hormones may affect AD etiology, Because estrogen has been shown to protect the brain, its removal after menopause may be to blame for the deficiencies in brain metabolism that result in AD. The responses of the male and female brains to testosterone and estradiol are very different even though both sexes have receptors for each hormone (Anstey *et al.*, 2008).

Schizophrenia patients are formed of the largest percent (55%) in male and are formed of the smallest percent (45%) in female but the difference was statistically not significant from AHC groups and these results were in coordinated with previous studies (Dheeb,2016) showed that only slight predominance of male over female patients(46 M, 76.7% Vs. 16 F, 23.3%) with male: female ratio 2.87, but the difference was statistically not significant from both control groups . These results are consistent with a study conducted on data extracted from 1112 studies, revealed no sex difference with male to female ratio (1:11) and the P = 0.41 (Sukanta *et al.*, 2005). Ipsit *et al., (*2010) reported a significant predominance of female over male in older age group (late onset schizophrenia) P= 0.001, and this finding may be explained by the protective effect of estrogen (Riecher and De Geyter ,2007).

Regarding the sex, Major depression patients are formed of the largest percent (60%) in female and are formed of the smallest percent is(40%) in male compared with AHC group and these results were in coordinated with the study of Hassan (2018) showed that 47.1% of males had depression that is similar to Indian study (47.2%), (Arifuddin *et al.*,2018) , but regarding the females 40.7% and 52.9% were results for present study and Indian (Arifuddin *et al.*,2018) study respectively, that are inconsistent.

5.1.4:Education

Alzheimer patients are formed of the largest percent (60%) in illiterate persons and are formed of the smallest percent (40%) in educated persons compared with AHC group and these results were in coordinated with previous studies showed that most of AD patients were illiterate (86.7%) (Al Ganzawi,2013) and the change was highly significant ($P \leq 0.001$). These findings unmistakably indicate that illiterate is a significant danger determinant for AD. The majority of studies—though not all—have revealed that persons with less education appear to have a larger risk of AD than those with more education(Su *et al*., 2008). Additionally, it has been demonstrated that those with poor socioeconomic position and only an elementary school education had a threefold higher chance of developing AD than those with high socioeconomic status and more education (Blass and Rabins, 2008). This has led some researchers to hypothesize that a higher level of education offers a "cognitive reserve" that helps people to more effectively account for changes in the brain that could cause AD or other dementias(Su *et al*., 2001).

Schizophrenia patients are formed of the largest percent (65%) in educated persons and are formed of the smallest percent (35%) in illiterate persons compared with Alzheimer patients and these results were in coordinated with the study of Filiz *et al.,* (2019)showed that educated persons formed largest percent (93%) in schizophrenia. Major depression patients group are formed of the largest percent (80%) in educated persons and are formed of the smallest percent (10%) in illiterate persons and these results were consistent with other studies(*Khadega et al.,* 2016) that appeared largest percent is 98% in educated persons in major depression disorders compared with AHC group. Other study showed that the educational level shows significant differences between the two sexes, nearly third of the females

either illiterate(34.9 %) or primary (29.1 %), and nearly third of the males were primary level (30.9 %) (Hassan, 2018), in addition , other study showed that secondary school level (56.5%) had high percentage, where was similar to Pakistan study (57.0%) (Amin and Gerry,2007) .

5.1.5:Smoking Status

Alzheimer patients are formed of the largest percent (80%) in non-smoker persons compared with AHC group and these results weren't in coordinated with the study of Al Ganzawi(2013)showed that smoker and non-smoker AD patients were observed with a similar frequency (50%), but the change was not significant. The present results are not in favor of that using tobacco increases the risk of developing AD, although other investigations have suggested that cigarette smoking is either protective or can increase the risk to develop AD (Peters *et al*.,2008), therefore , this result may be because the small number of study samples or because the women ratio was higher than men, so the most women not smoking.

Schizophrenia patients are formed of the largest percent (65%) in smoker persons and are formed of the smallest percent (35%) in non- smoker persons compared with AHC group and these results were in coordinated with the study of Ding and Hu (2021) suggested that smoking is still very common among those with schizophrenia. While , other studies revealed that smoking rises the probability of having schizophrenia, Further investigation is therefore required to ascertain whether smoking is, in fact, the cause of this relationship, smokers with schizophrenia are more likely than non-smokers to have more severe positive symptoms and worse cognitive function, but their extrapyramidal side effects are less severe. According to another study, those with schizophrenia often pass away 28 years sooner than those without a history of mental illness, with the majority of the risk coming from diseases

directly linked to cigarette use (Olfson *et al.*, 2015). Another study examined 174,277 schizophrenia patients who were admitted to hospitals in California between 1990 and 2005 and found that almost 53% of all fatalities since first admission were caused by a condition that was causally related to cigarette use (Callaghan *et al.*, 2014). Major depression patients are formed of the largest percent (70%) in smoker persons and are formed of the smallest percent (30%) in non-smoker persons compared with AHC groups and these results were in coordinated with previous studies (Fluharty *et al.*, 2017) state that there is a link between mental disease and smoking. According to the self-medication theory, people smoke to treat their symptoms, which implies that depression and anxiety may cause people to start smoking (Boden *et al.*, 2010 and Taylor and McNeill, 2014). A total of 14 studies observed the link between pre-smoking depression and subsequent smoking initiation, and 71 % of these studies found evidence to support this link (Fuemmeler *et al.*, 2013)**.**

5.1.6:Marital Status

Alzheimer patients are formed of the largest percent (100%) in married persons and are formed of the smallest percent (0%) in single and these results were in consistent with the study of Noelle, *et al.*,(2017) which revealed that there was a substantial main effect for married status as well as a significant relations effect between mobility and marital status. Married people with dementia had longer (LOS) than those with dementia who were not married. Residents who are single and have mobility issues are more likely to be discharged. Schizophrenia patients are formed of the equivalent percent is 45% in single and married persons and are formed of the smallest percent (0%) in widowed persons compared with AHC group and these results weren't in coordinated with the study of Defaru *et al.*, (2017) found that

around one-third of those with schizophrenia were single (n= 120, 34.2%), while more than half of those with schizophrenia were married (n= 193, 55%). In a prior study, marital status and quality of life were found to be significantly correlated (Fanta *et al.,* 2017). Major depression patients are formed of the largest percent (65%) in married persons and are formed of the smallest percent (0%) in divorced persons compared with AHC group and these results were in coordinated with study of *Khadega et al.,* (2016) showed that major depression disorder is increased in married persons (61.2%)compared with AHC group. Other study showed that most of them were married (70.1 %) undergoing from major depression disorder (Hassan, 2018), while the prevalence of depression were high in widow participants (66.7%) was more prevalent (Arifuddin *et al.*,2018).

5.7:Immunological Parameters

5.7.1: Interleukin-1β (IL-1β)

The present results shown a significant rise ($p \leq 0.05$) in IL-1β levels in Alzheimer patients in comparison with AHC group and these results were in consistent with the study of Forlenza *et al.,* (2009). Only highlights are presented below because an outstanding overview outlining the changing viewpoint on the role of IL-1β in AD has already been published elsewhere (Shaftel *et al.,* 2008). Overall, there has been evidence linking alterations in CNS for IL-1β levels to the beginning and spread of neuroinflammatory changes in AD (Mrak and Griffin, 2005). Other findings, suggest that the situation is more complicated, in which chronic overexpression of IL-1β did in fact result in a significant neuroinflammatory response within the hippocampus (Matousek *et al.,* 2012).

The present results revealed significant rise ($p \leq 0.05$) in IL-1β level in schizophrenia patients in comparison with AHC group and these results were in similar with the study of Al-Asmari and Khan (2014) appeared that TNF-α ,IL-6 and IL-1β levels were shown to have significantly raised, and inflammation caused by dysregulated cytokines and altered antioxidant systems may be a major contributor in the etiology of schizophrenia. Some pro-inflammatory indicators, such as, TNF-α,CRP, IL-6and IL-1β appear to be raised across illnesses, according to a frequent observation. 44 inflammatory biomarkers have been investigated in eight psychiatric diseases, including major depressive disorder, schizophrenia, sleeping problems ,autistic spectrum disorder, posttraumatic stress disorder, suicide, bipolar disorder and obsessive-compulsive disorder. 44 inflammatory biomarkers were analyzed for repeatability and specificity in a recent systematic analysis of 43 meta-analyses(Yuan *et al.,* 2019).

According to four cytokine markers (IL-1β, IL-2, CXCL8 and IL-18) analyzed by other studies, schizophrenia's decreased Broca's area volume is linked to the disease's elevated inflammatory subtypes (Fillman *et al.,*2016). Kindler *et al.,* (2020) identified associations between altered kynurenine (l-tryptophan metabolite) metabolism and dorsolateral prefrontal brain sizes in high inflammatory subgroups also defined by CXCL8, IL-1β, IL-2 and IL-18, but not in low inflammatory subgroups.This is an illustration of how inflammatory burden in living individuals may put patients at risk for neurotransmitter dysregulation. Another study found that plasma levels of IL-1β,IFN-γ and IL-2 were higher in schizophrenia sufferers compared to controls, and that these levels were positively connected with psychotic symptoms as assessed by the scale for the assessment of positive signs in participants (Lesh *et al.,* 2018). The severity of both negative and positive

signs as well as the overall psychopathological presentation are correlated with peripheral IL-1β levels(Momtazmanesh *et al.*, 2019).

The present results shown significant rise ($p \leq 0.05$) in IL-1β level in major depression patients (table ,4.1) compared AHC group and their data were in accordance with prior researches (van den Biggelaar *et al.*, 2007) that indicated a greater increase in depression symptoms was preceded by a higher production capability of the pro-inflammatory cytokine IL-1β. Additionally, compared to those without depression, Depression in T2DM patients was associated with noticeably higher serum IL-1β levels(Prabhat *et al.*, 2019), in addition T2DM and depression patients had greater levels of IL-1β and IL-6, according to a study of Habibi *et al.*, (2017). Depression may have an inflammatory component to its pathogenesis, according to the study, which found increases in the concentration of inflammatory biomarkers (Laake *et al.*, 2014).

Numerous studies have suggested that alterations in the levels of specific biological markers, such as chemokines and proinflammatory cytokines, may be a factor in MDD(Cassano *et al.*, 2017). Some investigations discovered that the serum levels of IL-1β, IL-6, MDA, cortisol, IL-15,CRP,IL-10,IL-18 and TNF-α were greater in MDD patients, however other studies found no differences(Nishuty *et al.*, 2019). Certain investigations showed a connection between these indicators and depression severity(Farooq *et al.*, 2017) , whereas some claimed there was a bad correlation between them (Einvik *et al.*, 2012).Other studies suggest that increased cytokine levels are one of the main risk factors for increasing depression, and that there is a connection between depression and psychological stress(Kim *et al.*,2015). Numerous earlier research results provide support for the current study's conclusions. According to studies, people with MDD had noticeably greater levels of TNF-

α, IL-1β and IL-10 than healthy (Zou *et al.,* 2018), furthermore it was found that serious depressed individuals had greater serum IL-1β levels than healthy(Mota *et al.,* 2013) , furthermore , people with MDD had greater plasma levels of IL-1β than healthy (Miklowitz *et al.,* 2016). When compared to the healthy group, the baseline blood levels of IL-6 and IL-1β were considerably greater in the MDD group(Zhang *et al.,* 2018).

5.7.2: Glutamic Acid Decarboxylase 65(GAD 65)

Data discovered that a significant rise ($p \leq 0.05$) in GAD65 levels in Alzheimer patients in comparison with AHC group and these results coordinated with the study of Dracheva *et al.*, (2004) displayed that GABAergic system in AD were inconclusive and reported either no change or reduction of GAD enzyme activity, contrasting with an increase in GAD mRNA expression and either increase, no change, or reduction of GABA levels and GABAT activity. In (AD), the GABAergic system has long been considered relatively spared and only affected late in the disease process (Gsell *et al.,* 2004).However,GAD65 immunohistochemistry with the antibody yielded adequate staining in all cases. Even though it is considered that in AD, the GABAergic system is mostly unaffected, there are reports of selective loss of subclasses of GABAergic interneurons containing the calcium binding proteins (Koliatsos *et al.,* 2006). It was an inhibitory role of GABA in inflammation has been suggested (Bhat *et al.,* 2010).

A GABAergic deficit may worsen this process because the immune system has been implicated in several neurodegenerative illnesses as being detrimental. However, it was found that, in a sizable cohort of 22,472 probable paraneoplastic and autoimmune encephalitis patients, psychotic individuals have a twofold increased risk of producing GAD65 autoantibodies in comparison with healthy (Kunchok *et al.,* 2021). GAD65Ab has been

associated to a number of neurological conditions, such as stiff person syndrome, autoimmune encephalitis and epilepsy, which can all involve cognitive dysfunction as an early symptom (Tohid, 2016).

The current results revealed that a significant rise ($p \leq 0.05$) in GAD65 in schizophrenia patients in comparison with AHC group and these results coordinated with the study of Najjar *et al.,* (2012) revealed that brain inflammation linked with high serum anti-GADAb titers can be a cause of schizophrenia. However , other studies in psychiatric disorders found either an elevation of both GAD65 and 67 mRNA schizophrenia (Dracheva *et al.,* 2004). Reduced levels of GAD and GABAergic terminals as well as reduced mRNA encoding GAD67 have been found in postmortem schizophrenia brains since 1977(Guidotti *et al.,* 2005).

Glutamic acid decarboxylase 65 (GAD65) autoantibodies have not yet been connected to catatonia, but they are known to exist in schizophrenia. These antibodies are identified in 4.6 percent of patients with schizophrenia and 2.7 percent of healthy individuals, with no detectable differences(Hansen *et al.,* 2013). However, it was shown that the risk of developing GAD65 autoantibodies is twice as high in psychotic patients as it is in controls (Hansen *et al.,* 2013). It is therefore hypothesized that GAD65 antibodies, which disrupt GABAergic neural signaling, may have an impact on the disease activity in schizophrenia patients. Additionally, catatonia may result from increased neuronal activity in premotor areas(Walther *et al.,* 2019).

The present results revealed that a significant rise ($p \leq 0.05$) in GAD65 in major depression patients in comparison with AHC group and these results coordinated with the research Bielau *et al.,* (2007) that claimed that bipolar illness and severe depressive disorder increased the density of GAD65 and GAD67 immunostained neurons. Other study showed that A 24-year-old lady

with Major Depressive Disorder (MDD) who had decreased psychomotor activity showed very high serum GAD65 autoantibody titers. Meanwhile, longitudinal analysis showed a four-fold rise in anti-GAD65 serum antibody titers, which was connected to an exacerbation of psychomotor symptomatology. These findings raise the hypothesis that the psychomotor damage in this depression patient may be brought on by CNS autoimmune(Chinga *et al.,* 2010).

A female MDD patients with substantial psychomotor disruption who was part of a cohort of psychiatric patients who were autoantibody-screened revealed high levels of anti-GAD65 in both CSF and serum. These autoantibodies grew with time and were connected to the progression of the patient's psychomotor slowness. Anti-GAD65 autoantibodies in other neurological conditions with movement problems, such as School Psychological Services (SPS), Batten Disease, and cerebellar ataxia, are consistent with the presence of these autoantibodies in the CSF and blood patient's (Chattopadhyay *et al.,* 2005).

GABA is another neurotransmitter synthesis from GAD 65 that plays major role in depressive and anxiety behaviors , The GABAergic processes also elicit an inhibitory action on the discharge of many other neurochemicals that facilitate anxious activities. GABA neurotransmitter decrease firing of the brain cells, thus further lowering the anxious messages transported from the cortex, but when a person is under severe stress or anxiety, the brain uses up all current GABAs and depression and anxiety grow in the person(Harrison and May, 2009).

5.8:Physiological Parameters

5.8.1:Serotonin (5-HT)

Data revealed a significant decrease ($p \leq 0.05$) in serotonin hormone in AD patients compared with AHC group and these results were in consistent with the study of Kalbitzer (2009) that showed serotonin levels in AD patients' brains are lower, which can cause aging, learning difficulties and numbness. Selective serotonin reuptake inhibitors (SSRIs), which increase serotonin levels in the central nervous system, are among the several antidepressants that act to raise levels of serotonin in neural connections, Therefore, it can be argued that depression and in more severe cases, anxiety are caused by a reduction in serotonin in the brain, Alzheimer's and cardiovascular disease (Salmon, 2007).

There is a sharp increase in immune response proteins that are crucial in AD and heart disorders under stressful conditions and decrease serotonin concentrations. Because Alzheimer's disease, heart disease and other illnesses that cause the immune system to respond more aggressively afflict the majority of angry and depressed persons whose decrease in serotonin concentrations. In this manner, antidepressant medications that increase serotonin also decrease the likelihood of AD and cardiovascular disorders (Eliecer *et al.,* 2003). In a new study, the inhibitory neurotransmitter serotonin and its precursor tryptophan were evaluated.AD ITG reduced ($p<0.05$)(Stuart *et al.,* 2018).

The essential amino acid tryptophan is converted into serotonin via the combination of aromatic amino acid decarboxylase (AAAD) and tryptophan monooxygenase (TM) . As previously mentioned, research has demonstrated that Alzheimer patients have higher levels of the protein alpha-synuclein in their brains, inhibits the activity of AAAD(Tehranian *et al.,* 2006). It's

intriguing that serotonin is linked to AD because certain studies have revealed the ability of antidepressants like Trazodone, a serotonin blocker, to preserve neuronal integrity(Halliday *et al.*, 2017).

5-HIAA and Serotonin concentrations in the brain were discovered to be lower in Alzheimer patients (kepe *et al.*, 2006), in which serotonin synthesis appears to be declining in AD patients based on the lower levels of serotonin found in their platelets, CSF, and brains (Markkula *et al.*, 2019). The pathogenesis of Alzheimer disease has been related to changes in the serotonergic and kynuramine pathways of tryptophan metabolism , in which Ruddick *et al.*, (2006), demonstrating that increased tryptophan breakdown via the kynuramine pathway may contribute to the low plasma tryptophan levels in AD, in addition to, mild to moderate AD patients or healthy volunteers who were depleted of tryptophan experienced alterations in cognitive function. The lower platelet serotonin concentration seen in AD patients in the late stages of the disease may be caused by decreased serotonin active transport via platelet membrane(Muck-Selerd *et al.*, 2009).

This result is consistent with the discovery that extremely ill AD patients have a lower maximum number (Vmax) of serotonin transporters than mildly ill AD patients and healthy controls. Changes in blood or urine have not before been documented and are described here for the first time, in spite of findings showing reduced levels of serotonin in CSF fluid and post-mortem brains in AD(Snowden, 2019).

The current results shown a significant decrease ($p \leq 0.05$) in serotonin hormone in Schizophrenia patients in comparison with AHC group and These data agreed with earlier research(Boris *et al.*, 2009) indicating that at least a subset of schizophrenia patients has a pathogenic role for the serotonin system. One percent of people worldwide suffer from schizophrenia, a

complicated and multifaceted mental disorder, and the "dopaminergic hypothesis" of schizophrenia is based on changes to the dopaminergic system and its receptors. Since this argument cannot explain the complex disease symptoms and effectiveness of atypical antipsychotics, which have a lower presence for D2 receptors than5-HT2A receptors, other neurotransmitter systems, such the serotonergic system, may be at fault in schizophrenia(Abi-Darghama *et al.*,1997). Additionally, numerous physiological and behavioral activities that are disrupted in schizophrenia are regulated by the serotonergic system(Lucki,1998). According to the serotonin hypothesis of schizophrenia, schizophrenic patients' brains showed altered serotonergic activity, with decreased serotonin neurotransmission in cortical regions and increased serotonin neurotransmission in the putamen, acumens, and pallid us. The frontal cortex's decreased or unaltered 5-HT2 receptor density, 5-HT1A receptor density, and 5-HT6 receptor binding (Wongahc and Vantolhhm, 2003) were also found in schizophrenic patients.

There are a significant decrease ($p \leq 0.05$) in serotonin hormone levels in major depression patients in comparison with AHC group and these results were coordinated to the study of Vahid-Ansari *et al.*, (2019) demonstrated that depression may be brought on by impairments in 5-HT innervation related to growth, ongoing stress, or brain damage. Reduced serotonin (5-hydroxytryptamine, 5-HT) neurons and their projections as well as higher levels of 5-HT autoinhibition have all been linked to MDD in pre-clinical and clinical trials, as well as reduced responses to antidepressants (Prakash *et al.*, 2020). Depression was thought to be caused by low serotonin and/or noradrenaline levels as well as abnormalities in the dopaminergic, noradrenergic, and central nervous systems. Additionally, elevated brain serotonin turnover rate was reported in patients with depression who were not

taking any medication, especially in those who had the short form (s allele) of the serotonin transporter gene(Barton *et al*., 2012). It was unclear, though, whether the increased brain serotonin turnover is due to decreased brain serotonin transporter availability, increased vesicular leakage and subsequent intraneuronal metabolism, or higher neuronal activity. Serotonin-related mood disorders like depression are complex, meaning they can have a variety of causes. Low serotonin levels can affect mood, sleep, digestion, and other functions but are not sufficient to cause depression on their own (Cowen and Browning, 2015).

The body is producing serotonin, but it may not be being used properly if you have low serotonin levels for another cause. This may occur if your brain is lacking in serotonin receptors or if the ones that are present aren't functioning properly(Carhart-Harris and Nutt, 2017). Increasing serotonin levels in the brain appears to improve communication between brain cells, which lifts mood and lessens symptoms of depression. Although serotonin's role in depression is more complex than an imbalance, it is thought to play a key role. Depression is known to be associated with chemical imbalances in the brain. This is why clinical depression and other mood disorders are treated with prescription antidepressants(Wnuk, 2019). The monoamine-serotonin theory for depression was put forth in the 1960s and contends that a lack of monoamines in the brain, notably 5-HT, causes depression to start(Albert *et al.,* 2012).

5.8.2:**Dopamine(DA)**

The current results shown a significant decrease ($p \leq 0.05$) in dopamine hormone in AD patients in compassion with AHC group and these results were in consistent with the study of Stuart *et al.*,(2018) that showed Alzheimer's disease-related brain degeneration may cause dopamine depletion.

The catecholamine neurotransmitter dopamine functions in the brain primarily through four pathways: the tuberoinfundibular, , mesocortical, nigrostatial and mesolimbic pathways(Neuhaus *et al.,* 2013). These pathways help with motor and cognitive function as well as mood regulation, Alzheimer's patients who have this system damaged may have depression, cognitive loss, and poor motor control (Dailly *et al.,* 2004). Tyrosine, an essential amino acid, is transformed into L-DOPA in the first stage by the enzyme tyrosine hydroxylase (TH), and L-DOPA is then converted to dopamine by the enzyme aromatic amino acid decarboxylase (AAAD) in the second stage. Tyrosine does not cross the blood-brain barrier during this process. The asymptomatic individuals showed the highest dopamine drop in the Manual Grasp Force (MGF). The MGF route shows an increase in the levels of tyrosine and L-DOPA, the precursors of dopamine, followed by a decrease in dopamine levels, indicating a decrease in the levels or activity of both TH and AAAD. The protein alpha-synuclein has been shown to play important pathogenic roles in a number of neurological disorders, including as Lewy bodies dementia, Parkinson's and Alzheimer's, inhibits the action of both TH and AAAD(Tehranian *et al.,* 2006) . Additionally, Some studies have shown that in the absence of Lowy body illness, soluble intra-neuronal alpha-synuclein abundance is up to two times more abundant in the brains of AD patients (Larson *et al.,* 2012).

The current results shown a significant decrease ($p \leq 0.05$) in dopamine hormone in schizophrenia patients compared with AHC group and these results were in consistent with the study of Kahn *et al.,* (2008) that showed that Self-reported symptom reduction across all dopamine-targeting antipsychotic medications was almost 60% in 498 persons with schizophrenia, demonstrating a relationship between dopamine antagonism and improved

schizophrenic symptoms. It suggests that excessive dopamine sensitivity in people with schizophrenia causes positive symptoms and the disease. Dopamine is an inhibitory and excitatory neurotransmitter that functions by being released from a neuron into a synapse (gap between neurons), where it is then taken up by the post-synaptic neuron by one of five primary receptors on the surface of the neuron: D1, D2, D3, D4, and D5(Eisenstein *et al.,* 2017).

The particular dopamine receptors linked to schizophrenia are called D2 receptors because they are linked to medications that cause symptoms. In fact, the dopamine hypothesis was first proposed in response to the discovery that amphetamines, which are dopamine agonists drugs that make the receptor act as though there is an increase in neurotransmitter, cause positive schizophrenic symptoms in drug users who are not suffering from the disorder. This data illustrates how a dopamine neurotransmitter system malfunction might influence the system and cause the symptoms associated with schizophrenia by increasing the body's sensitivity to dopamine. There are much more D2 receptors in the brains of schizophrenia patients than in brains of healthy controls, indicating a connection between the receptors (and hence dopamine) and the disease. Several investigations have indicated that schizophrenic individuals have fewer D2 receptors in additional brain regions, including the thalamus and anterior cingulate cortex, as well as lower D2 neurotransmitter binding in specific extrastriatal regions including the thalamus (Toda and Abi-Dargham, 2007). There is evidence that dopamine activity in schizophrenia is disturbed, and the majority of antipsychotic medications used to treat illness are dopamine antagonists, which lower dopamine levels(Moncrieff,2008).

The present results shown a significant reduction ($p \leq 0.05$) in dopamine hormone in major depression patients in comparison with AHC group and

these results were in coordinated with the data of Schneier *et al.,* (2009) that showed there are abnormalities in the sufferers' dopaminergic system. Depressed persons exhibit symptoms such as depression, decreased personality, weariness, loss of interest in daily activities and social interactions, and impaired focus. One CNS mediator, dopamine, functions as a dopaminergic mesolimbic route. Dopamine acts on the brain through two groups of dopamine receptors, D1 and D2, with D1 and D5 receptors in the D1 receptor and D2, D3, and D4 receptors in the D2 receptor. Impairment of the dopaminergic mesolimbic route plays an important role in the formation of depression and mediation of drug rewards (Nasehi *et al.,* 2010).

Furthermore, as compared to healthy participants, PET imaging investigations on depressed patients with anhedonia revealed considerably lower DA transporter (DAT) binding (Sarchiapone *et al.,* 2006), furthermore , other study showed that altering the dopamine-related processes (Scholl *et al.,* 2010). hence reducing the immobility behavior during the forced swim test(FST) and having the antidepressant effects of drugs that enhance dopamine.

Dopamine-lowering medications can lead to agitation and depression (Dunlop and Nemeroff,2007), Given that studies have indicated that a number of factors, including changes in neurotransmitters like dopamine, play a role in diabetes-induced depression and that perceptual disorders, particularly depression, appear to become one of the most significant issues connected with diabetes in the future, Additionally, it has been demonstrated that dopamine receptors and mRNA are upregulated in cases of depression and diabetes mellitus, which suggests a reduction in dopamine transmission (Gupta *et al.*, 2014). An additional neuromediator involved in depression is dopamine, which is expressed in brain regions that control movement,

emotion, and feelings. Dopamine, which acts as a brain stabilizer, is crucial in regulating how information is sent from the brain to various regions of the body (Solati *et al.,* 2017b). The intracellular cascades that activate the proteins linked to the differentiation and development of nerve cells are noted to be reduced in depressed people as a result of the reduction of brain-derived neurotropic factor (BDNF), and the absence of differentiation and development of these cells results in mental problems, including depression (Lee *et al.,* 2007).

5.9:Correlation Coefficient Between Study Parameters (IL-1β, Serotonin, Dopamine and GAD-65) in Patients and AHC Group

There are positive significant correlation ($P \leq 0.05$) between IL-1β and serotonin levels and these results was coordinated with the results of Pantouli *et al.,* (2005) that demonstrated Pro-inflammatory cytokines including IL-1β and TNF-α activate p38 MAPK in peripheral systems, these cytokines may acutely boost serotonin activity through p38 MAPK activation, and may provide a crucial link to physiologically relevant systems known to regulate SERT in *vivo*. Whereas, there was a negative correlation (non-significant) between the levels of IL-1β and dopamine and these results were similar with the study of Bergmann and Sautner (2002) showed that Endotoxaemia poses a challenge to the immune system by causing immune cells to produce large amounts of inflammatory cytokines (e.g., IL-6, IL-1β and TNF-α), which act to stimulate the systemic-adrenomedullary sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal axis, inflammatory conditions also cause dopamine synthesis to be induced quickly. Whereas , there was a positive correlation(non-significant) between IL-1β and GAD-65 levels and these results coordinated with previous studies **(**Pagni *et al.,* 2014**)** showed that ,a pro-inflammatory cytokine made by T-cells or macrophages, IL-1 β

may be a therapeutic target in diabetes since it can be blocked and paired with islet antigen-specific methods using plasmids that express GAD of 65 KDa (GAD65). But, there is a positive correlation between serotonin and GAD-65 levels and these results coordinated with the results of Melik and Fanardzhyan(2004) that showed The cerebellum's Lugaro cells, a specific family of inhibitory interneurons present only in cerebellar cortex, have been implicated in 5-HT-GABA interactions in areas related to motor regulation.

5.9.1:Correlation Coefficient Between Study Parameters (IL-1β , Serotonin, Dopamine and GAD-65) in Alzheimer Patients

The results of present study revealed that there were a positive correlation(non-significant) between IL-1β and serotonin levels and these results with was consistent with the previous studies (Metaxas *et al.,* 2019) demonstrated that higher levels of IL-1β preceded the declines in neocortical SERT density and activity in AD. IL-1β can increase SERT activity in the mouse midbrain and striatum by lowering the apparent Michaelis constant (Km) of the transporter for 5-HT in AD (Zhu *et al.,* 2010).Whereas, there was a negative correlation(non-significant) between IL-1β and dopamine levels and these results consistent with the study of Stojakovic *et al.,* (2017) that revealed Determine the role of the IL-1β pathway on dopaminergic neurodegeneration and motor skills during aging. IL-1β, a pro-inflammatory cytokine synthesized and released by activated microglia, can cause dopaminergic neurodegeneration that results in AD and PD. It is unknown whether IL-1β can act directly or by amplifying the detrimental effects of other brain insults. Meantime , there was a positive correlation between serotonin and dopamine levels , in which CeyzÃriat *et al.,* (2020) showed that Dopaminergic (DA) and serotoninergic (5HT) system impairment is present in 50% of AD patients, also, there was a positive correlation between serotonin

and GAD-65 levels and these results coordinated with the study of Aaldijk and Vermeiren(2022) showed that A few human intervention trials suggest the role of serotonergic modifications in reducing AD brain neuropathology in addition to its clinical symptoms, these alterations can be brought about by selective serotonin reuptake inhibitors or serotonin receptor (ant)agonists and de la Torre (2000)showed that dysfunction of GABAergic system possibly contributes to the impaired cerebral perfusion thought may contribute to the AD pathology.

5.9.2:Correlation Coefficient Between Study Parameters (IL-1β, Serotonin, Dopamine and GAD-65) in Schizophrenia Patients Group

positive correlation between IL-1β and serotonin levels .Sacramento *et al.,* (2018) showed that Pro-inflammatory cytokine levels that are too high in the CNS are linked to decreased serotonin (5-HT) production, a neurotransmitter with a variety of immune-boosting effects. In addition a positive correlation between IL-1β and dopamine levels and these results consistent with the study of Rudolf *et al.,* (2002) that showed that IL-1β can cause the conversion of rat mesencephalic progenitor cells into a dopaminergic phenotype, and it has been suggested that schizophrenia is caused by a malfunction of the brain's dopaminergic and glutamatergic circuits. Whereas, there was a negative correlation between IL-1β and GAD-65 levels and this was confirmed by the study of Najjar *et al.,* (2012) demonstrated that anti-GADAbs can be linked to a psychotic illness that satisfies the diagnostic criteria for schizophrenia in the text version of the Diagnostic and Statistical Manual of Mental Disorders. In contrast, there was a positive association between serotonin and dopamine levels and these results coordinated with previous studies (Muck-Seler *et al.,* 2009) demonstrated that schizophrenic patients with a largely chronic time course, paranoid symptoms,

positive symptoms, and those born in the winter had higher platelet serotonin concentrations. Additional research demonstrates that schizophrenia patients' distinctive amounts of D2 receptors behave differently from neurotypical patients, demonstrating how these variable receptor numbers act to generate a different effect on the brain. Numerous imaging investigations have indicated that untreated chronic and freshly onset schizophrenia patients exhibit an increase in D2 receptors of about 12% in certain brain regions—striatal regions—compared to healthy controls (Toda & Abi-Dargham, 2007). There was a negative correlation between serotonin and GAD-65 levels which is confirmed by the study of Marchiori *et al.,* (2001) that The intrathecal synthesis of anti-GADAbs and, in certain cases, CSF oligoclonal bands have been utilized to support the pathogenic involvement of anti-GADAbs in neurological disease. Meantime , the data reveled that there was a positive correlation between dopamine and GAD-65 levels and these results coordinated with previous studies(Blanc *et al.,* 2009) demonstrated that immunosuppressive therapy's therapeutic value in treating anti-GADAb encephalitis, and a link between neurological symptoms and high anti-GADAb titers further supports a pathogenic role.

5.9.3:Correlation Coefficient Between Study Parameters (IL-1β, Serotonin, Dopamine and GAD-65) in Major Depression Patients

There was negative correlation between IL-1β and serotonin levels and these results coordinated with the study of Nestler *et al.,* (2001) showed that Major depressive people had higher serum levels of the pro-inflammatory cytokines IL-6, IL-1β and TNF-α and 5-HT is a neurotransmitter that regulates a variety of behaviors, including those linked to aggression, mood, sleep and hunger. Also , there was a negative correlation between IL-1β and dopamine levels and these results was augmented by the study of Sherdell *et al.,* (2012)

suggested that The transformation of the perception of enjoying a reward into a sought incentive requires DA, which is consistent with disturbances of the motivation to seek out enjoyable experiences documented in people with MDD, DA is also required for the attribution of incentive salience to motivating cues. Whereas, there is a positive correlation between IL-1β and GAD-65 levels. These results coordinated with previous studies (Hsieh *et al.*, 2010) showed that elevated serum levels of IL-1β have a significant role in the release of the hormones corticotropin-releasing hormone (CRH) from the hypothalamus, adrenocorticotropic hormone (ACTH), and adrenal steroid synthesis, all of which indirectly contribute to depression. In contrast, the data shown a negative association between serotonin and dopamine levels and these results coordinated with recent studies showed that 5-HT rewiring is induced during recovery and can be accelerated by SSRI therapy or activation of 5-HT neurons, the 5-HT system is capable of rebuilding lost projections, particularly after injury or prolonged stress (Zahrai *et al.*, 2020). There is a positive correlation between dopamine and GAD-65 levels and these results consistent with the study of Tremblay *et al.*, (2002) that showed a lower DA turnover. These results are consistent with the degree of amphetamine-induced rewarding effects that MDD patients have reported. It has been established that the degree of euphoria experienced following amphetamine injection correlates with the severity of MDD.

5.10:Molecular Study

5.10.1: *IL-1β* Gene Polymorphism

The results of current study showed that Alzheimer patients group revealed the highest percent (60%) in *IL-1β* genotype GA compared with AHC group and these results was confirmed by the study of Licastro *et al.*,

(2004) demonstrated that human *IL-1β* gene polymorphisms linked to higher IL-1β production have been shown to raise the relative risk for AD and encourage earlier disease onset, Additionally, it has been suggested that the *IL-1β* gene may influence the age at which the disease develops by altering brain immune responses, which may in turn contribute to the pathophysiology of the illness. In fact, *IL-1β* gene polymorphisms have been linked to a higher incidence of the condition in people with likely medical AD and neuro-pathological diagnoses of the condition (Nicoll *et al.*, 2000). One of the *IL-1β* gene's polymorphism regions, situated at position 511 in the promoter region, has been shown to alter IL-1β plasma levels in AD patients and has been linked to a higher risk of developing late-onset AD (Licastro *et al.*, 2000).

Both the age at which AD patients first experienced symptoms and the quantity of IL-1β produced by (lipopolysaccharide) LPS-activated peripheral mononuclear cells from healthy controls are impacted by the other polymorphism, which is located at position +3953 on exon 5 of the *IL-1β* gene (Sciacca *et al.*, 2003). The major component of neurofibrillary tangles, TAU protein, has been found to be phosphorylated by IL-1β, which is generated by activated microglia (Li *et al.*, 2003). The previous studies showed that the *IL-1β* gene is linked to a higher chance of acquiring clinical AD (Grimaldi *et al.*, 2000), Position 511 in the promoter of the *IL-1β* gene is one of the gene's polymorphism areas, which has been linked to a higher risk of developing late-onset AD and shown to alter IL-1β plasma levels in AD patients, has been connected to an increased risk of the disease (Sciacca *et al.*, 2003). The IL-1β functional polymorphism *IL-1β* -511 T allele has been linked to elevated risk of AD, but it is yet unknown how this association is caused (Wang *et al.*, 2005). The effects of the *IL-1β* C-511 T polymorphism on the levels of

amyloid beta in cerebral spinal fluid and amyloid beta immune reactivity in the brains of AD patients show that this polymorphism plays a significant role in regulating the pathogenesis of AD (Ehl *et al.,* 2003).

The results of current study showed that Schizophrenia patients groups revealed the highest percent (70%) in *IL-1β* genotype GG compared with AHC groups and these results coordinated with previous studies (Xu and He, 2010). The greatest study to date investigating the association between *IL-1β* gene polymorphisms and schizophrenia showed that the G allele of rs16944 and the G allele carrier status of rs1143634 were strongly related with a risk of schizophrenia in Caucasian people, but not in Asian groups. The findings offer the first concrete proof that schizophrenia and the G allele of rs1143633 are related. The investigation into a population of Americans by (Shirts *et al.,* 2006) was the only study examining the relationship between rs1143633 and schizophrenia and it showed no discernible change in allele incidences between controls and patients.

Despite the fact that Japanese people's 9 SNPs of the *IL-1β* gene complex were also looked at by Watanabe *et al.,* (2007), however none of the SNPs they observed were in significant linkage disequilibrium with rs1143633 or rs16944 (all r2 0.1 based on Hap Map Japanese and Han Chinese population data, release). In a larger study, there is still a chance that the allele frequency of rs16944 will differ considerably between controls and Japanese female schizophrenia patients. There have been numerous genome-wide association studies (GWAS) to look for SNPs linked to schizophrenia(Yamada *et al.,* 2011). These studies and recent findings point to a hereditary component to immunological changes in schizophrenia. There has been a noticeable shift in schizophrenia in the direction of the T helper type 2 (Th2) system (Schwarz *et*

al., 2001). Additionally, a considerable rise in the levels of circulating IL-1β mRNA expression has been seen in individuals with schizophrenia, In order to activate T-helper cell activity in the direction of Th2 cells, prostaglandin E2 is a necessary component, and IL-1β increases its production (Liu *et al.,* 2010).

The results of current study showed that Major depression patients groups revealed the highest percent (45%) in IL-1β genotype GG compared with AHC groups . These results was confirmed by the study of Tartter *et al.,* (2015) that revealed, Although the effect size was minor, people with the GG genotype of the *IL-1β* rs16944 SNP had higher levels of depressive symptoms; this result was particularly prominent in people who had encountered hardship as children. These results are consistent with past studies that GG carriers exhibit earlier onset of depression, more severe depressive symptoms, and poorer antidepressant responsiveness, in addition, people with the GG genotype also showed more depressed symptoms after repeated instances of interpersonal stress.

The current findings thus confirm this earlier study's finding that individuals with the GG genotype had a higher relationship between childhood abuse and depressive symptoms. However, it has also been shown that those with the GG genotype showed reduced depression levels after experiencing trauma as children (Kovacs *et al.*, 2016a). Pro-inflammatory cytokine genetic variations that can change gene transcription and thus affect inflammatory proteins, such as IL-1β, have been linked to a variety of medical and psychiatric disorders, including serious depression (Khazim *et al.,* 2018). A single nucleotide polymorphism (SNP), rs16944, found in the gene's promoter region can affect how much IL-1β protein is secreted(Hall *et al.,* 2004). However, conflicting information is now available regarding whether the GG

genotype (Iacoviello *et al.*, 2005) or elevated IL-1β levels are linked to the A/A genotype. There have also been some contradictory findings, such as an increased risk of depression in minor allele A carriers who had schizophrenia spectrum disorders, Alzheimer's disease, or who experienced trauma as a child (Kovacs *et al.*, 2016a).

5.10.2:*Serotonin Receptor(5-HT1A)* Gene Polymorphism

Alzheimer patients group was the highest percent (50%) in *5-HT1A* genotype GC compared with AHC groups and these results coordinated with the study of Dongping *et al.*, (2014) showed that Gene C for 5-HT1A (-1019) G polymorphism and the (-1019)G allele may both be risk factors for AD. Serotonin and 5-HIAA concentrations in the brain decreased, and presynaptic somatodendritic 5-HT1A autoreceptors and postsynaptic 5-HT1A heteroreceptors were lost in AD patients (Kepe *et al.*, 2006).

Schizophrenia patients groups showed the highest percent which reached to (75%) in *5-HT1A* genotype CC compared with AHC groups and these results was confirmed by the results of Ikeda *et al.*, (2008) showed that Increased 5-HTR1A density in raphe presynaptic neurons is correlated with the G/C genotype, whereas, According to a Chinese study, people with schizophrenia who took risperidone had a higher chance of improving their negative symptoms if they had the CC genotype -1019C/G. rs6295, C-1019G, A *5-HT1A* receptor gene promoter variation has been connected to treatment effects on schizophrenia's negative symptoms(Reynolds *et al.*, 2006). In line with this Serotonin neurotransmission was discovered to be altered in the brains of schizophrenia patients, with reduced serotonin neurotransmission in cortical regions and elevated serotonin neurotransmission in the pallidus, putamen and accumbens. Patients with schizophrenia also had unchanged 5-

HT6 receptor binding, decreased 5-HT1A receptor density, and unchanged 5-HT2 receptor density in the frontal brain (Wongahc and vantolhhm, 2003).

The major depression patients groups showed the highest percent which reached to (50%) in *5-HT1A* genotype CC compared with AHC groups and these results augmented by Donaldson *et al.,* (2016) study shown lower responsiveness to antidepressant treatment and an association between the SNP's CC genotype and changed levels of *5-HT1A* receptor expression. A polymorphism in the *5-HT1A* regulatory region (rs6295; G-1019C) has also been connected to higher risks for depression in gene association studies. The development of MDD or anxiety linked to serotonin receptor classes (Yohn *et al.,* 2017), such as 5-HT1A has numerous connections to the pathophysiology of depression and anxiety (Kaufman *et al.,* 2016).

The cortico-limbic regions of the suicidally depressed victims displayed diminished 5-HT1A ligand binding or receptor gene expression both with and without treatment (Lopez-Figueroa *et al.,* 2004). One of these, designated C-1019G (rs6295), is a helpful polymorphism that exists in the gene's promoter region. It has been the subject of the most extensive research and affects the majority of people worldwide. This polymorphism has been demonstrated to control gene expression (Lemonde *et al.,* 2003). Genetic research has found a correlation between the C-1019G C allele and increased presynaptic *5-HT1A* receptor expression and lower postsynaptic *5-HT1A* receptor expression. These opposing effects may be brought on by Both presynaptic and postsynaptic *5-HT1A* receptors co-localize with Deformed Epidermal Auto-Regulatory Factor-1 (Deaf-1 or NUDR) and Hes5 (Szewczykb *et al.,* 2009).

5.11:Association of *IL-1β* Gene and *Serotonin Receptor(5-HT1A)* Gene Polymorphisms with Study Parameters (IL-1β and Serotonin Levels) in Psychological Stress Patients and AHC Groups

5.11.1:Association of *IL-1β* Gene Polymorphism with IL-1β Levels in Patients and AHC Groups

There are non-significant change($p \geq 0.05$) between *IL-1β* gene alleles (GA, GG and AA) and IL-1β levels in AHC group and these results appeared that *IL-1β* gene alleles showed that AHC group are the highest percent (80%) in *IL-1β* genotype AA in comparison with patients groups.

Also , the current results revealed that there was a non-significant changes($p \geq 0.05$) in Alzheimer patients group between *IL-1β* gene alleles(GA, GG) and IL-1β levels and Alzheimer patients don't have *IL-1β* gene alleles (AA)in their chromosome and these results appeared that there was significant rise($p \leq 0.05$) in IL-1β levels and highest percent (60%) in *IL-1β* genotype GA in Alzheimer patients compared with AHC group. These results was coordinated with the study of Scarabino *et al.*, (2020) revealed that there are a correlation between IL-1β levels and *IL-1β* gene polymorphism. The G allele was shown to be related with rise in IL-1 β levels in AD patients, while the A allele was found to be related with the lowest levels of IL-1β. Neuroinflammation and cytokine release across the blood-brain barrier may be to blame for the rise in inflammatory mediators like IL-1β in the peripheral blood of AD patients. There was a potential relationships between *IL-1β* genotypes and serum IL-1β levels because the *IL-1β* rs16944 SNP is situated in the promoter region of the *IL-1β* gene. According to the current findings and prior studies (Su *et al.*, 2019) , the G allele was related to higher levels of IL-1β , particularly in the AD group, whereas the A allele was related to lower levels of IL-1β.

The schizophrenia patients group revealed a significant increase ($p \leq 0.05$) between *IL-1β* gene alleles(GA) and IL-1β levels in comparison with *IL-1β* gene allele (GG), in which schizophrenia patients don't have *IL-1β* gene alleles (AA) in their chromosome and these results appeared that there was significant rise ($p \leq 0.05$) in IL-1β levels and Schizophrenia patients revealed the highest percent (70%) in *IL-1β* genotype GG compared with AHC group, also these results was confirmed by the results of Marta *et al.*, (2021) that demonstrated a correlation between IL-1β levels and *IL-1β* gene polymorphism. Serum IL-1β levels in patients with paranoid schizophrenia were statistically greater than those in the AHC group. The main causes of functional impairment and shorter life expectancy in schizophrenia patients are metabolic and cognitive abnormalities, which may have related biological underpinnings.IL-1β, a crucial mediator of the inflammatory response, is one of these and is of particular importance. *IL-1β* polymorphism has been linked to cognitive and metabolic changes in the general population as well as neuropsychiatric diseases. Monocytes, which resemble microglia in their phagocytic functions and the expression of cell surface markers, release IL-1β in peripheral organs.

In fact, people with schizophrenia frequently have monocyte activation (Uranova *et al.*, 2017). The major depression patients group revealed non-significant difference($p \geq 0.05$) between *IL-1β* gene alleles (GA, GG and AA) and IL-1β levels and these results appeared that there was significant increase($p \leq 0.05$) in IL-1β levels , furthermore, in Major depression patients groups revealed the highest percent (45%) in *IL-1β* genotype GG compared with AHC group and these results inconsistent with the study of Yu *et al.*,

(2003) that revealed neither IL-1β levels nor the *IL-1β* gene SNP (rs16944) were related in depression patients in comparison with healthy.

5.11.2:Association of *Serotonin Receptor(5-HT1A)* Gene Polymorphism with Serotonin Level in Patients and AHC Groups

The data of current study shown that there are non-significant change ($p \leq 0.05$) between genotypes (GC,CC and GG) of *serotonin receptor(5-HT1A)* gene and serotonin levels in AHC group and these results appeared that there was a significant rise($p \leq 0.05$) in serotonin levels and revealed the highest percent (76.67%) in *5-HT1A* genotype GG in AHC group compared with patients.

There was non-significant change ($p \geq 0.05$) between serotonin receptor(*5-HT1A*) gene alleles(GC, CC and GG) and serotonin levels in Alzheimer patients group compared with AHC group and these results appeared that there are significant reduction ($p \leq 0.05$) in serotonin , also the Alzheimer patients group was the highest percent (50%) in *5-HT1A* genotype GC compared with AHC groups , as well as these results in consistent with previous studies (Dongping *et al.*, 2014) showed that *5-HT1A* gene C (-1019)G polymorphism and the (-1019)G allele may both be risk factors for AD. Serotonin and 5-HIAA concentrations in the brain decreased, and postsynaptic 5-HT1A heteroreceptors and presynaptic somatodendritic 5 HT1A autoreceptors were lost in AD patients (Kepe *et al.*, 2006).

There was non-significant difference ($p \leq 0.05$) between genotypes (GC, CC and GG) of *serotonin receptor(5-HT1A)* gene and serotonin levels in schizophrenia patients group and these results revealed that a significant reduction ($p \leq 0.05$) in serotonin levels , also Schizophrenia patients groups showed the highest percent which reached to (65%) in *5-HT1A* genotype CC compared with AHC group and these results coordinated with the results of

Wongahc *et al.*,(2003) that showed there was association between *5-HT1A* gene and decrease in serotonin levels according to the putamen, accumbens, and pallidus all had enhanced serotonin neurotransmission, while cortical serotonin neurotransmission was decreased in schizophrenia patients, according to the serotonin theory of schizophrenia. Also, schizophrenia patients were shown to have intact 5-HT6 receptor binding, decreased or unaffected 5-HT1A receptor density, and decreased density of 5-HT2 receptors in the frontal brain.

The MDD patients group appeared a non-significant change($p \geq 0.05$) between *serotonin receptor(5-HT1A)* gene alleles (GC, CC and GG) and serotonin levels compared with AHC group, and these results appeared that a significant reduction ($p \leq 0.05$) in serotonin levels, also major depression patients groups showed the highest percent which reached to(50%) in *5-HT1A* genotype CC compared with AHC groups and these results in consistent with the study of Donaldson *et al.*, (2016) revealed that the CC genotype at this single nucleotide polymorphism (SNP) is linked to higher levels of *5-HT1A* receptor expression and a reduced response to antidepressant medication. A polymorphism in the *5-HT1A* regulatory region (rs6295; G-1019C) has also been connected to higher risks for depression in gene association studies.

5.12:Microbial Infections

5.12.1:Viral Infections

5.12.1.1: Herpes Simplex Virus(HSV-1)

The present results showed that Alzheimer patients 50% of infection was HSV-1 test positive and HSV-1 test negative compared with AHC group and these results in coordinated with previous studies (De Chiara *et al.*, 2019) that showed a relationship between persistent HSV-1 Infection and AD. HSV-1 can avoid immune clearance by maintaining a chronic infection within

neurons, leading to lifelong infection. Recent research links chronic HSV-1 infection to the emergence of AD. HSV-1 is expected to mostly reside in the peripheral nervous system (PNS) and only sometimes infect the central nervous system (CNS). One of two scenarios could describe how peripheral HSV-1 infection could result in CNS neurodegenerative disorders. The first hypothesis postulates that age-related changes in blood-brain barrier permeability and persistent peripheral inflammation may promote the invasion of inflammatory mediators and immune cells into the brain (CNS), leading to abnormal neurodegeneration and neuroinflammation. While , Another hypothesis is that synaptically linked neurons outside of the peripheral ganglia may allow HSV-1 to infiltrate the central nervous system (CNS) and perpetuate latent subclinical infection, causing specific parts of the brain afflicted by AD to experience localized neurodegeneration and neuroinflammation (Popescu *et al.*, 2009 and Weiskopf *et al.*, 2009).

In the peripheral ganglia, localized immune cell infiltration may progress over time (Popescu *et al.*, 2009). Additionally, HSV-1 has been found in the brains of both AD patients and elderly individuals in good health, indicating that HSV-1 infection of the central nervous system is not the first risk element for the progress of Alzheimer disease(Wozniak *et al.*, 2005). Increased HSV-1 brain penetration with advancing age may be a factor in the progress pathogenesis of Alzheimer disease in these areas. In the brains of AD patients, amyloid plaques have been revealed to contain HSV-1 DNA, lending weight to this theory(Wozniak *et al.*, 2009). A thorough evaluation of the putative molecular mechanisms by which HSV-1 infection may play role in pathogenesis of Alzheimer disease was conducted(Harris and Harris, 2018). In vitro and in vivo studies of HSV-1 infection have shown overexpression and

deposition of amyloid beta; these effects have been related to neuronal dysfunction, neurotoxicity, hyperphosphorylation of tau, and amyloid beta deposition in neurons(Harris and Harris, 2018). Amyloid beta protein builds up in adult hippocampus neural stem cells as a result of HSV-1 infection, causing both *in vitro* and *in vivo* reductions in proliferation and differentiation (Li Puma *et al.*, 2019).

In present study schizophrenia patients are formed 50% in positive and negative HSV-1 test compared with AHC group and these results were confirmed by the results of Houenou *et al.*, (2014) This study demonstrated a potential impact of virus infection on initial neural development, showing neurotropism to areas linked to negative and psychotic disorders in schizophrenia patients and the brain areas also be related to microbiological positive, negative agents, and that show up with numerous deficiencies in schizophrenia, such as CMV and HSV-1 are believed to be linked neurological problems. Other studies that examined the link between cortex efficiency and volumetric research results in patients with HSV-1 seropositive schizophrenia found a significant correlation between mental function variables and volumetric variations in the parahippocampus, spindle - shaped gyrus, anterior cingulate gyrus, and frontal cortex (Prasad *et al.*, 2013).

The volumetric shrinkage of brain tissue may be caused by viral reactivation, and in schizophrenia patients, this neuronal loss may result in a decline in cognitive function(Prasad *et al.*, 2011). Chronic inflammatory reactions brought on by these medicines and the anti-inflammatory development that follows them may also contribute to the pathophysiology of latent viruses in schizophrenia patients. In schizophrenia, there have been

clear links shown between the HLA polymorphism and the genetic components of the disorder (Stefansson *et al.,* 2009). One of the etiological hypotheses for this sickness is that it develops after contracting a viral infection or as a result of an autoimmune response directed against central nervous system tissue(Adarsh *et al.,* 2018). Indirect evidence for this idea is provided at this time by the consequences of infections including HSV 1-2, influenza, CMV, Epstein-Barr virus (EBV), and Borna disease virus (BDV), Also emphasized is the correlation between the geographical distribution of schizophrenia prevalence, the time of delivery, and exposure to viral epidemics during pregnancy(Zhang *et al.,* 2014).

In present study major depression patients are formed 60% in HSV-1 test positive, while, HSV-1 test negative are formed 40% compared with AHC group and these results were in consistent with the study of Jing *et al.,* (2020) that shown Herpes simplex virus type 1 (HSV-1) infection has been linked to depression. Previous investigations showed that viruses that might infiltrate nerves and cause depression(Serafini *et al.,* 2015), In addition, another study used observational data and a GWEIS (Genome-Wide by Environment Interaction Studies) to investigate the link between HSV-1 and depression. HSV-1 and the risk of depression were found to be significantly correlated in the UK Biobank cohort, GWEIS detected many gene-HSV-1 connections for depression and hypothesized that the risk of depression was controlled by HSV-1 and various genes connected to immunological or nerve development(Jing *et al.,* 2020).

The relationship between HSV exposure and depression, however, is controversial. For example, HSV-1 was not linked to a higher risk of depression after adjusting for potential confounders such alcohol usage,

sex, race, age, the proportion of people living in poverty and smoking status(Gale *et al.*, 2018). However, after gender classification, seropositivity and serointensity of HSV-1 may be linked to the occurrence of depression (Markkula *et al.,* 2019), another investigation revealed that depression significantly enhanced the HSV 1/host interaction susceptibility genes (Carter, 2013). Additionally, a study's findings suggested that having high HSV-1 antibodies or being seropositive for the virus was linked to an increased risk of developing depression (Curanovic and Enquist, 2009), suggesting that these impacts on axons and nerves could help depression develop(Dean *and Keshavan,* 2017). It was demonstrated that illnesses like HSV, human HIV, and even hepatitis C virus might penetrate the central nervous system, trigger neuroinflammatory pathways, and then cause depression(Miller and Raison, 2016), Additionally, a different study found that exposure to infectious diseases such hepatitis C, influenza, varicella-zoster, and herpes viruses is one of the factors linked to serious depression (Gale *et al.,* 2017). Infection with herpes simplex virus-1,Epstein-Barr virus, Varicella zoster virus, Chlamydophila trachomatis and the Borna disease virus were all statistically associated with depression(wang *et al.*, 2015).

5.13:Association of HSV-1Infection with IL-1β, Serotonin, Dopamine and GAD 65 in Psychological Stress Patients and AHC Group

There wasn’t association between HSV-1 infection(positive and negative) and IL-1β, serotonin, dopamine and GAD 65 levels in AHC group and these results coordinated with the previous study of Lokensgard *et al.,* (2001) demonstrated that human microglial cells infected with HSV-1 release cytokines and pro-inflammatory chemicals, including IL-1β. Due to the direct effects of HSV-1 on neurons and the inflammatory response of the host to infection, reactive oxygen and reactive nitrogen species are created in larger

amounts, which may cause oxidative damage(Valyi-Nagy and Dermody, 2005). While there was a significant change ($p \leq 0.05$) in Alzheimer patients group between HSV-1 infection(positive and negative) and IL-1β levels and these results consistent with the study of Wyss-Coray and Rogers (2012) showed that in the brains of AD patients, increased levels of pro-inflammatory cytokines are frequently observed. HSV-1 and oxidative stress interact to speed up the neurological processes that lead to AD. Experimentally produced oxidative stress was observed to greatly increase the buildup of intracellular Aβ and block Aβ production in human neuroblastoma cells that were infected with HSV-1 (Santana *et al.*, 2013).

The schizophrenia patients group revealed non-significant change ($p \geq 0.05$) between HSV-1 infection(positive and negative) and IL-1β, serotonin, dopamine and GAD 65 levels and these results was augmented by the study of Masiá *et al.*, (2014) demonstrated that co-infection with human herpes virus 8 (HHV-8) was linked to chronic inflammation and immunological activation in HIV-infected individuals and promoted hepatocellular damage that is linked to elevation of certain inflammatory cytokines. While, the major depression patients group showed significant difference ($p \leq 0.05$) between HSV-1 infection(positive and negative) and IL-1 β level and these results was consistent with previous studies (Gnann and Whitley, 2017). It's significant to note that both in vitro and in vivo, various cell types that HSV-1 infects in the CNS can produce pro-inflammatory responses, while there are non-significant difference($p \geq 0.05$) between HSV-1 infection(positive and negative) and serotonin, dopamine and GAD 65 levels in Alzheimer and major depression patients compared with AHC group , and these results was similar to the results of Battaglia *et al.*, (2012) demonstrated that HSV infection increased the expression of the essential serotonin

synthesis enzymes DOPA decarboxylase (DDC), TPH-1and TPH-2 as well as the serotonin transporter, SERT Ocular illnesses. Concurrently, serotonin production and intracellular absorption were both increased in HSV-infected cells. It has been demonstrated that increased serotonin production and absorption affect HSV replication. Exogenous serotonin supplementation boosted HSV-1 yield, whereas pharmacological suppression of TPH-1/2 and SERT decreased viral yield. The elderly are the group most afflicted by PD, and it is hypothesized that having HSV1 in DNA is connected with getting older. Blood-brain barrier compromise is more likely to occur as people age, making it possible for HSV-1 to penetrate the central nervous system, also Hiemstra *et al.,* (2001) demonstrated that viral infections like HSV-1 have been associated with the development of the neuroendocrine autoimmune diseases stiff-man syndrome and type 1 diabetes, which share glutamic acid decarboxylase (GAD65) as a major autoantigen.

5.14:Bacterial Infections

5.14.1:*Helicobacter pylori(H. pylori)* Infection

The current results illustrated that Alzheimer patients groups revealed a positive results for *H. pylori* reached to (35%) compared with AHC groups and these results was consistent with study of Tan and Goh (2012) that showed Alzheimer disease (AD), cardiovascular ischemia, parkinson's disease and atherosclerosis are among the non-gastric disorders that are related to *H. pylori* infection. Two genetic association studies on individuals of European ancestry both found a connection between AD and *H. pylori* infection in the case of Alzheimer disease(Kountouras, 2009).

AD symptoms were present in two of patients who had *H. pylori* infections, and these observation inspired the current investigation, which sought to identify any potential biological relationships between *H. pylori*

infection and AD. The *H. pylori* metabolite D-proline is the most prevalent of the 20 metabolites linked to AD(Xu and Wang, 2016). Because there is solid proof that the human microbiome interacts with the CNS via immunological, neuronal and endocrine pathways, *H. pylori* from the stomach affects the brain(Cryan and Dinan, 2012). There is proof that *H. pylori* disrupts gut metabolites and the brain-blood barrier directly interact with enteric neurons to get to the brain(Main and Minter, 2017). Several upper digestive illnesses, such as peptic ulcers, are brought on by the heterogeneous bacterial species *H. pylori*, which has degenerative characteristics with AD. Extra-digestive diseases and *H. pylori* have been linked, such as atherosclerosis, hypertension, and stroke, were linked to an raised risk of AD due to blood-brain barrier dysfunction(Sawayama *et al.*, 2005).

It's significant to note that a number of proposed mechanisms have recently been discovered for the probable causative relationship between AD and *H. pylori*: (1) vitamin B-12 and Float malabsorption leading to elevated neurotoxicity and serum homocysteine levels; (2) apoptosis through T cell-mediated immune response; (3) increased eicosanoids , platelet activation , cytokines and acute phase proteins (D'Elios *et al.*, 2005) and (4) the possibility that *H. pylori* infection will pass the blood-brain barrier and cause the buildup of amyloid(Kountouras *et al.*, 2012). The association between *H. pylori* infection or eradication and a number of cognitive consequences, including AD, has been studied in the past. Although earlier modest case-control studies found a link between *H. pylori* seropositivity and the development of AD and/or mild cognitive impairment(Kountouras *et al.*, 2009).

The results illustrated that Schizophrenia patients groups revealed positive results for *H. pylori* reached to (25%) compared with AHC groups and these results was consistent with study of Papamichael *et al.*, (2009) that

indicated schizophrenia and *H. pylori* are associated with higher endocrine problems. *H. pylori*-related peptic ulcer incidence has decreased , although people with schizophrenia may be at higher risk for developing one(Bytzer and Teglbjærg, 2001). Chronic immunological response and inflammation are brought on by *H. pylori* infection, which also results in the release of many pro-inflammatory mediators. Patients with *H. pylori* infections caused by cagA-positive strains in particular show elevated production of several pro-inflammatory molecules, such as IL-1β, IL-6, and TNF-α (Robinson *et al.,* 2007). Moreover, it has been shown that chronic *H. pylori* infection may cause elevated serum C-reactive protein (CRP) (Manolakis *et al.,* 2007), and CRP concentrations have been shown to be raised in schizophrenic patients (Fan *et al.,* 2007).Other study identified at least four distinct mechanisms (dopaminergic dysfunction, inflammation, PUFA alterations, and hyperhomocysteinemia) where by *H. pylori* infection occurring in early childhood could represent a risk factor for schizophrenia in genetically predisposed individuals (Yilmaz *et al.,* 2008).

The results illustrated that Major depression patients groups revealed positive results for *H. pylori* reached to (40%) compared with AHC groups and these results coordinated with previous studies (Takeoka *et al.,* 2017) showed that Verifying the risk of mood disorders in people with *H. pylori*-associated atrophic gastritis (AG), researchers discovered that women with HP-associated AG who are older than 50 years old are more likely to experience psychological distress or melancholy mood. A much greater chance of developing peptic ulcer disease (PUD) was linked to psychological issues like extreme stress, depression, suicidal thoughts, and psychological counseling (Lee *et al.,* 2017).

According to the study of Levenstein *et al.,* (2015), psychological stress increases the risk of developing peptic ulcers. Several earlier research have proposed potential pathogenic processes for the onset of PUD caused by mental health issues. First, through the autonomic nervous system, specifically the brain gut axis, the GI system and brain are strongly related (Gazouli *et al.,* 2016).When people are stressed or depressed, their neurologic function may be altered, which could cause an increase in pepsin and stomach acid release and mucosal damage(Di Mario and Goni, 2014). Second, psychological issues may affect the hypothalamic-pituitary-adrenal axis, which in turn affects cortisol secretion(Brown *et al.,* 2004). The cortisol level is typically increased under stressful circumstances, which may cause an increase in gastric acid secretion levels (Di Mario and Goni, 2014).

The natural inflammatory response in the GI tract may be hampered by the elevated cortisol and stomach acid levels. Third, moderate dyspepsia brought on by gastritis or duodenitis may not receive the attention it needs, making depressed people more likely to develop PUD. Fourth, those with mental health issues are more likely to smoke and drink. Smoking encourages the generation of free radicals and causes vasoconstrictors to disrupt the blood flow to the mucous membranes. By triggering the production of vasoactive and inflammatory chemicals, alcohol also compromises the mucosal barrier. But after controlling for the effects of alcohol and smoking, our findings showed that psychological issues were linked to the emergence of PUD. (Graham, 2014).

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1.Psychological stress diseases increased pro inflammatory cytokines (IL-1β and GAD-65).

2.Serotonin and dopamine were induced by psychological stress diseases.

3.There was association between genotypes (GA, GG) for *IL-1β* (rs16944) and genotypes (GC, CC) for (*5-HT1A*) **(**rs6296) gene polymorphisms with psychological stress diseases.

4.Microbial infection (HSV-1and *H. pylori*) was associated with psychological stress diseases, because the stress leads to minimize the activity and efficiency of immune response against foreign antigens.

Recommendations

1.Checking of some biomarkers that considered indicator for psychological stress diseases such as IL-8 and TNF-α.

2.Study the relationship between psychological stress diseases and autoimmune diseases.

3.Study another SNPs and genes related with psychological stress diseases.

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APPENDIXES

Appendix

Appendix(1):Materials supplied for IL-1β, GAD 65, Serotonin, Dopamine and HSV-1 ELISA Kits .

Name	96 determinations	48 determinations
Microelisa strip plate	12*8strips	12*4strips
Standard	0.3ml*6tubes	0.3ml*6tubes
Sample Diluent	6.0ml	3.0ml
HRP-Conjugate reagent	10.0ml	5.0ml
20X Wash solution	25ml	15ml
Chromogen Solution A	6.0ml	3.0ml
Chromogen Solution B	6.0ml	3.0ml
Stop Solution	6.0ml	3.0ml
Closure plate membrane	2	2
User manual	1	1
Sealed bags	1	1

Appendix(2): Kit components for DNA Extraction From Blood

Solution and Materials	Size
Spin column	100 ea
Lysis buffer	30 ml
Precipitation	20 ml
Binding buffer	25 ml
Washing buffer 1	30 ml (Add ethanol 22.5 ml)
Washing buffer 2	12 ml (Add ethanol 48 ml)
Elution	25 ml
Proteinase K (20 mg/ml)	1.2 ml X 2 tubes

Appendix(3): Primers of IL-1β (rs16944G/A)

IL-1β (rs16944G/A)	sequences	TM	Product size
anti-sense primer	5-TGT TCC TAC ACT CCA GGC ACT GTT C-3	60.4	446bp
Sense primer G	5-CTT GGG TGC TGT TCT CTG CCT CG-3	62.1	
Sense primer A	5-CTT GGG TGC TGT TCT CTG CCT CA-3	61.4	
anti-sense primer	5-TGT TCC TAC ACT CCA GGC ACT GTT C-3	60.4	607 bp
Sense primer sequencing	5-TGG GAC AAA GTG GAA GAC ACA CAG-3	59.1	

Appendix(4):Primers of Serotonin receptor (5-HT1A) (rs6296G/C)

(5-HT1A) (rs6296G/C)	sequences	TM	Product size
anti-sense primer	5-TGT TCC TAC ACT CCA GGC ACT GTT C-3	60.4	205bp
Sense primer G	5-GGA GAC TCG CAC TTT GAC TTG GTT G-3	59 .9	
Sense primer C	5-GGA GAC TCG CAC TTT GAC TTG GTT C-3	60.4	
anti-sense primer	5-TGT TCC TAC ACT CCA GGC ACT GTT C-3	60.4	342 bp
Sense primer sequencing	5- TTG CAG ATA GGC ATC ACT AGG GAG-3	58.1	

Appendix(5):IL-1β gene (rs16944) G Allele PCR reaction Mix

PCR Master mix	Volume
Common reverse primer (10 pmol)	1 µl
G-allele forward primer (10 pmol)	1 µl
DNA template	4 µl
Distal water	4 µl
master mix	10 µl
Total volume	20 µl

Appendix(6):IL-1β gene (rs16944) A Allele PCR reaction Mix

PCR Master mix	Volume
Common reverse primer (10 pmol)	1 µl
A-allele forward primer (10 pmol)	1 µl
DNA template	4 µl
Distal water	4 µl
master mix	10 µl
Total volume	20 µl

Appendix(7):5-HT1A gene (rs6296)G Allele PCR reaction Mix

PCR Master mix	Volume
Common reverse primer (10 pmol)	1 µl
G-allele forward primer (10 pmol)	1 µl
DNA template	4 µl
Distal water	4 µl
master mix	10 µl
Total volume	20 µl

Appendix(8): 5-HT1A gene (rs6296) C Allele PCR component reaction Mix

PCR Master mix	Volume
Common reverse primer (10 pmol)	1 µl
C-allele forward primer (10 pmol)	1 µl
DNA template	4 µl
Distal water	4 µl
master mix	10 µl
Total volume	20 µl

Appendix(9):program used for IL-1β (rs16944) amplification.

PCR step	Temp.	Time	Repeat
Initial denaturation	95 ^{o}C	5 min.	1
Denaturation	95^{o}C	30sec.	35 cycle
Annealing	61^{o}C	35 sec.	
Extension	72^{o}C	1min.	
Final extension	72^{o}C	5 min	1
Hold	4 ^{o}C	forever	-

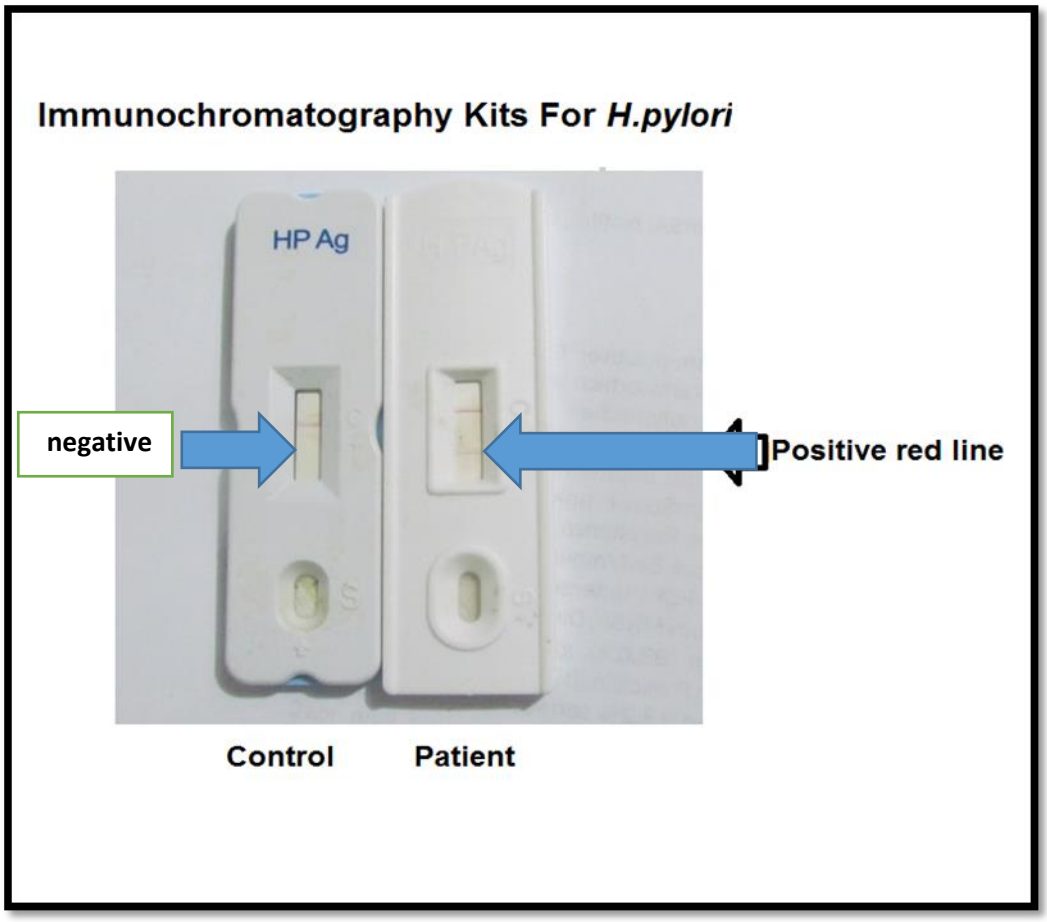
Appendix(10):program used for serotonin receptor (rs6296) amplification

PCR step	Temp.	Time	Repeat
Initial denaturation	95^{o}C	5 min.	1
Denaturation	95^{o}C	30sec.	35 cycle
Annealing	60^{o}C	35sec.	
Extension	72^{o}C	1min.	
Final extension	72^{o}C	5 min	1
Hold	4 ^{o}C	forever	-

Appendix

Appendix(11): bio information programs and websites for sequencing and PCR in molecular diagnosis

No.	Programs	Websites
1	NCBI	/https://www.ncbi.nlm.nih.gov
2	SnapGene Viewer	https://www.snapgene.com/snapgene-viewer
3	Interleukin-1β gene (rs16944) polymorphism	https://www.ncbi.nlm.nih.gov/snp/?term=rs16944
4	Serotonin receptor (5-HT1A) gene (rs6296) polymorphism	https://www.ncbi.nlm.nih.gov/snp/?term=rs6296



Appendix(12):Immunochromatography kit For *H.Pylori*.

الخلاصة

هنالك العديد من الامراض النفسية المرتبطة بالإجهاد مثل مرض الزهايمر الذي يعد اضطراب عصبي تحطيمي ، حيث تبين في عام 2020 وجود حوالي 50 مليون من الاشخاص حول العالم يتعرضون لهذا المرض، بينما مرض الفصام هو مرض عقلي يؤثر تقريبا على 1% من سكان العالم ، أما مرض الاكتئاب الرئيسي فهو مرض شائع يرتبط تقريبا بحوالي 7% من الاشخاص البالغين الذين يتعرضون لحالة الاكتئاب الحاد كل سنة.

أجريت الدراسة الحالية في مستشفى الامام الحسن المجتبى ومدينة الامام الحسين الطبية في مدينة كربلاء خلال الفترة من شهر شباط (2022) الى شهر ايلول (2022) ، ولقد تضمنت الدراسة 90 فردا تراوحت اعمارهم بين (19 -92) سنة قسمت الى اربع مجاميع : المجموعة الاولى تضم 30فردا من مجموعة السيطرة الأصحاء ظاهريا وثلاث مجاميع من المرضى تضم 60 من مرضى الاجهاد النفسي موزعة على 20 مريض لكل من أمراض الزهايمر، الفصام و الاكتئاب . وتم في هذه الدراسة جمع عينات الدم والخروج من المرضى والاشخاص الأصحاء ظاهريا.

اظهرت الخصائص الديوموغرافية للدراسة بان توزيع العمر في مرضى الزهايمر والفصام و الاكتئاب كانت (اكبر من 60 سنة و30-60 سنة و30-60 سنة) بنسبة (95% و60% و50%) على التوالي مقارنة مع مجموعة الافراد الاصحاء. مرضى الزهايمر والفصام و الاكتئاب توزعوا بواسطة فترة المرض كانت (5-20 سنة و 5-20 سنة واقل من 5 سنوات) بنسبة (75% و60% و80%) على التوالي. توزيع مرضى الزهايمر والفصام و الاكتئاب اعتمادا على الجنس كانت (الاناث والاناث والذكور) بنسبة (60% و60% و55%) على التوالي مقارنة مع مجموعة الافراد الاصحاء. حالة التدخين اظهرت بان مرضى الزهايمر والفصام و الاكتئاب كانت (غير مدخنين ومدخنين ومدخنين) بنسبة (80% و65% و70%) على التوالي مقارنة مع مجموعة الافراد الاصحاء. اعتمادا على النتائج بينت بان مرضى الزهايمر والفصام و الاكتئاب كانت (متزوجين ومتزوجين وغير متزوجين ومتزوجين) بنسبة (100% و45% و65%) على التوالي مقارنة مع مجموعة الافراد الاصحاء.

اظهرت نتائج المعايير المناعية زيادة معنوية ($p\leq0.05$) في مستويات الانترلوكين واحد بيتا والاجسام المضادة لحامض الكلوتاميك منقوص الكاربوكسليز في كل مجاميع المرضى مقارنة مع مجموعة السيطرة، بالإضافة الى ذلك بينت نتائج المعايير الفسيولوجية بان هناك انخفاض معنوي

($p\leq0.05$)في مستويات الهورمونين السيروتونين والدوبامين في مجاميع المرضى مقارنة مع مجموعة السيطرة.

اوضحت نتائج الارتباط بين معايير الدراسة (الانترلوكين واحد بيتا ، السيروتونين ، الدوبامين والاجسام المضادة لحامض الكلوتاميك منقوص الكاربوكسيل65) بان هناك ارتباط معنوي ايجابي ($P \leq 0.05$) بين مستويات الانترلوكين واحد بيتا والسيروتونبن في مجموعة السيطرة.

اظهرت الدراسة الجزيئية لجين الانترلوكين واحد بيتا بان مرضى الزهايمر 60% منهم يحملون الطراز الوراثي GA مقارنة مع مجموعة السيطرة ، بينما كانت نسبة مرضى الفصام والاكتئاب (70 %) و(45%) على التوالي في الطراز الوراثي GG مقارنة مع مجموعة السيطرة . اظهرت نتائج جين مستقبل السيروتونين بان مرضى الزهايمر والفصام بنسبة 50% منهم يحملون الطراز الوراثي GC مقارنة مع المجاميع الاخرى، بينما كانت النسبة 50% في مرضى الاكتئاب ذات طراز وراثي CC مقارنة مع المجاميع الاخرى. بينت علاقة جين الانترلوكين واحد بيتا مع مستوى الانترلوكين واحد بيتا في مرضى الاجهاد النفسي ومجموعة السيطرة وجود زيادة معنوية ($p\leq0.05$) في الطراز الوراثي GA لمرضى الفصام مقارنة مع الطراز الوراثي (GG) لجين الانترلوكين واحد بيتا ومرضى الفصام الذين لا يمتلكون الطراز الوراثي (AA) في كروموسوماتهم . أما بالنسبة الى علاقة جين مستقبل السيروتونين مع مستوى السيروتونين في مرضى الاجهاد النفسي ومجموعة السيطرة فقد اظهرت النتائج بان هناك انخفاض معنوي ($p\leq0.05$) في الطرز الوراثية (GC, CC) لجين مستقبل السيروتونين و مستوى السيروتونين مقارنة مع الطراز الوراثي (GG) لجين مستقبل السيروتونين في مجموعة السيطرة، بالإضافة الى ذلك هناك زيادة معنوية ($p\leq0.05$) في الطرز الوراثية (GC, CC) لجين مستقبل السيروتونين و مستوى السيروتونين مقارنة مع الطراز الوراثي (GG) لجين مستقبل السيروتونين في مرضى الفصام.

أن نسبة الاصابة بفيروس الهيربس من النوع الاول كانت(50%) و(50%) في فحص فايروس الهربس النوع الاول الايجابي و فحص فايروس الهربس النوع الاول السلبي لمرضى الزهايمر والفصام على التوالي، بينما كانت النسب لمرضى الاكتئاب (60%)و(40%) في فحص فايروس الهربس النوع الاول الايجابي و فحص فيروس الهربس النوع الاول السلبي على التوالي. كما وجد اختلاف معنوي ($p\leq0.05$) في مرضى الزهايمر والاكتئاب بين الاصابة(الايجابية والسلبية) بفايروس الهيربس من النوع الاول ومستويات الانترلوكين واحد بيتا.

اشارت نسب الاصابات البكتيرية لمرضى الزهايمر والفصام والاكتئاب (35%)، (25%) ، (40%) على التوالي في الاختبار الايجابي لبكتريا اللولبية البوابية *Helicobacter pylori* مقارنة مع مجموعة السيطرة.

نستنتج بان امراض الاجهاد النفسي ادت الى زيادة السايتوكينات قبل الالتهابية (الانترلوكين واحد بيتا والاجسام المضادة لحامض الكلوتاميك) وادت الى حث المعايير الفسيولوجية (السيروتونين والدوبامين). كذلك هناك علاقة بين الطرز الوراثية (GA, GG) لجين الانترلوكين واحد بيتا والطرز الوراثية (GC, CC) لجين مستقبل السيروتونين مع امراض الاجهاد النفسي. كذلك الاصابات الميكروبية ارتبطت مع مرضى الاجاد النفسي لان الاجهاد يودي الى تثبيط فعالية وكفاءة الاستجابة المناعية ضد الانتجينات الغريبة .واخيرا هناك علاقة بين امراض الاجهاد النفسي ومعظم الخصائص الديموغرافية مثل العمر وفترة المرض والجنس والتعليم

جمهورية العراق

وزارة التعليم العالي والبحث العلمي

جامعة بابل

كلية العلوم

قسم علوم الحياة

دراسة المعايير المناعية الوراثية والفسيولوجية بين المرضى ببعض امراض الاجهاد النفسي

أطروحة مقدمة

الى مجلس كلية العلوم / جامعة بابل وهي جزء من متطلبات نيل درجة الدكتوراه فلسفة في العلوم/علوم الحياة/ الحيوان

من قبل

قاسم حمادي عبد فاضل

بكالوريوس/كلية العلوم /علوم الحياة
جامعة كربلاء
(2013)
ماجستير/ كلية العلوم /علوم الحياة
جامعة كربلاء
(2016)

بإشراف

أ. د. علاء جواد حسن

كلية العلوم

جامعة بابل

1444هـ 2023 م