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Review

An overview on Alzheimer's disease, diagnosis and treatment approach

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Abstract

Merely 40 million people suffers from dementia all-over the world which is a characteristic of Alzheimer's disease. There is no cure for Alzheimer's disease, but there are treatments which help manage symptoms and improve quality of life. The symptoms can vary from person to person, but they typically include Memory loss, Difficulties in learning new things, activities of daily living concentrating, Problems with language, Disorientation, Changes in mood and personality. The treatment for Alzheimer's disease is aimed at managing the symptoms and improving quality of life. There are two main types of medications used to treat Alzheimer's disease. It includes Cholinesterase inhibitors medications, help to improve memory and thinking skills by increasing the levels of acetylcholine in the brain and Memantine, which helps to improve cognitive function by blocking the effects of glutamate in the brain. Also, non-pharmacological therapy such as physical therapy, occupational therapy, speech therapy, support groups which provide emotional support and practical advice to people with Alzheimer's disease improves their prognosis of ailment. Early diagnosis and treatment of Alzheimer's disease can help to improve quality of life and manage symptoms.

Keywords: Biomarker, Amyloid, Amnestic, Memory, mild cognitive impairment, synaptic plasticity, and dementia.

INTRODUCTION

Alzheimer's disease, one of the greatest healthcare concerns of our century, is the most common cause of dementia. Estimates place the number of dementia patients at 40 million, between now and 2050, this number is expected to increase every 20 years.[(1)(2)]. Since dementia usually affects those over 60, the lengthening of life expectancy and the resulting rise in patients with the condition[(1)(3)], The need for effective treatments, particularly for people with Alzheimer's, has significantly increased research in this area. However, despite all the strenuous

scientific efforts, this sickness is now incurable[1][4][5]. According to the primary pathophysiology and neuropathology of the disorder, the basic histopathologic lesions of Alzheimer disease are believed to include extracellular amyloid plaques and intracellular Tau neurofibrillary tangles. Amyloid or senile plaques are mostly made up of extremely insoluble, proteolysis-resistant peptide fibrils that are produced by β-amyloid cleavage[1]. Intracellular neurofibrillary tangles (NFT) are made up of tau protein that has undergone significant hyperphosphorylation because of the pathology of Alzheimer's disease. Axon degeneration, dendritic spinal collapse, and microtubule disassembly are caused by the intracellular production of neurofibrillary tangles[6]. Alzheimer's patients will require full-time, round-the-clock assistance as they experience more severe cognitive changes, including a loss of ability to respond to the environment, confusion, restlessness, difficulty speaking and thinking, as well as difficulty controlling movements[6][7]. Despite all scientific evidence, there is no effective cure or preventative measure for Alzheimer's disease. The progression of Alzheimer's disease is slow, and it can linger for decades. The illness has three primary phases, each with its own difficulties and signs[8]. Both familial and sporadic occurrences of Alzheimer's disease can be attributed to inheritance of a particular gene. Apolipoprotein 4 (APOE4) and sporadic Alzheimer disease, which is the more prevalent kind, are related. Allele, with homozygotic conditions carrying a higher risk[8][9][10].

WHAT IS ALZHEIMER'S DISEASE?

Alzheimer's disease is a chronic degenerative neurological disorder with three primary types of symptoms. Memory loss, language problems, and executive dysfunction are all parts of the first group (cognitive dysfunction). The second group is made up of behavioral issues and psychiatric symptoms like agitation, hallucinations, delusions, and depression. These symptoms are usually referred to as non-cognitive symptoms[11][12]. Having trouble carrying out daily activities falls under the third category. Alzheimer's disease symptoms range from minor memory loss to very serious dementia. According to Clinical, pathological, and epidemiological studies are showing an increasing amount of cohabitation between vascular disease and Alzheimer's disease[11][13].

EPIDEMIOLOGY

Alzheimer's disease is a degenerative neurological ailment that significantly impairs memory, rational thought, and acceptable behavior. It is the most cause of dementia, a general term for a decline in cognitive function that makes it challenging to do daily tasks. The loss of connections between neurons and eventual cell death in Alzheimer's disease are caused by plaques and tangles, abnormal protein deposits that build up in the brain. This causes is the classic signs of the illness, such as behavioral and mood changes, memory loss, disorientation, difficulty speaking and comprehending people and communication problems. A typical early sign of Alzheimer's disease, which worsens over time and affects numerous cognitive functions, is mild memory loss[11].

RISK FACTORS

Age

The greatest risk factor for Alzheimer's disease is age, which is also one of the risk factors that cannot be modified. Most cases of Alzheimer's disease affect adults 65 years of age or older. Alzheimer's disease affects 5% of persons between the ages of 65 and 74. For those above 85, the risk increases to 50%[8][14]. Aging can impede the body's self-healing processes, including those in the brain, according to numerous studies. Additionally, numerous cardiovascular risk factors, such as high blood pressure, heart disease, and excessive cholesterol, become more prevalent as people age. In fact, Alzheimer disease prevalence rises dramatically with age[8].

Genetics

There is little indication that sporadic Alzheimer's disease follows a particular genetic inheritance pattern. Apolipoprotein E (ApoE) is a gene that has been linked to the emergence of Alzheimer's disease. The protein transports cholesterol in blood vessels is thought to be made by this gene. The ApoE4 gene variant has been found to raise the risk of contracting the illness more significantly. The ApoE2 variant, offers disease protection. Before 65 years of age, chromosomal mutations may be the cause of these cases. Familial Alzheimer's disease is an uncommon form of the illness that affects fewer than 10% of people with the condition. It has been determined that mutation in chromosomes 1, 14, 21 are the reason. If one chromosomal mutation is inherited, the likelihood of developing Alzheimer's disease is 50%[8][15]. Although it has been found that patients with late-onset disease have first degree relatives who are around twice more likely to get the disease over their lifetime, the pattern of transmission is rarely consistent with Mendelian heredity. Delusions and hallucinations are believed to occur at any time during course of a disease, despite not being common symptoms. Neurological symptoms such seizures, hypertonia, myoclonus, incontinence, and mutism may appear later in the course of the illness. Pneumonia, widespread hunger, and other common causes of death have all been well recorded[8].

EDUCATION

It has been discovered that the likelihood of developing Alzheimer's disease and educational attainment are associated. People with lower levels of education appear to be more at risk since they are unaware of the typical causes. While the precise origin of this correlation is unknown, it is hypothesized that a greater level of education leads to the formation of more synaptic connections in the brain. As the condition worsens, the brain develops a "synaptic reverse" that enables patients to compensate for the loss of neurons[8][14]. Alzheimer's disease is an irreversible, degenerative brain disorder that eventually makes it difficult to do even the most basic daily tasks and shrinks brain cells. It also gradually weakens thinking and memory skills. Most Alzheimer patients begin to have symptoms around their mid-60s. When healthy neurons completely stop working, they lose their ability to perform crucial functions, lose connections with other neurons, and eventually die as a result of the intricate brain changes that cause the disease to proceed. The brain's hippocampus, which is entirely involved in memory formation, seems to be the first part of the brain to suffer damage. As more neurons die and more parts of the brain are affected, the brain gradually starts to shrink. When Alzheimer's reaches its most advanced stage, considerable brain tissue loss and extensive damage have taken place. Alzheimer's disease is the most common cause of dementia among older persons. Dementia is the loss of basic and everyday abilities, such as thinking, remembering, reasoning, behavioral capacity, and linguistic ability, to the point where it interferes with a person's day-to-day activities and renders them powerless. The severity of dementia varies depending on the stage, from moderate when it first begins to affect a person's capacity to function to severe when Alzheimer's disease causes a person to be completely dependent on others for basic daily activities. It has been discovered that memory loss and other cognitive problems don't appear until ten years or more after brain damage has started. During this preclinical stage of Alzheimer's disease, people seem to be symptom-free, although damaging changes are taking place in the brain. The brain is covered in aberrant protein and lipid deposits called amyloid plaques[8].

ETIOLOGY

Although there is no known cause for the condition, it is obvious that the disease has an adverse effect on the brain, causing cell destruction and shrinking. Age, family history, apolipoprotein (ApoE4) status, head injury, depression, hypertension, diabetes, high cholesterol, atrial fibrillation, the presence of cerebral emboli, low levels of physical and mental activity, and others have all been linked to it in case-control studies. Some risk factors might be adaptable. Neurofibrillary tangles and neuritic (or senile) plaques are the two main histological symptoms of Alzheimer's disease; the former is characterized by the deposition of the insoluble protein amyloid, while the latter by the presence of phosphorylated tangles. The intensity of the clinical symptom of the dementia syndrome has been connected to both synaptic deposition and a measurement of neuronal death[11].

NEUROPATHOLOGY

The normal structure and function of the brain are significantly disrupted by Alzheimer’s disease, a neurodegenerative brain illness that progresses over time. The increasing loss of cortical neurons, particularly pyramidal cells, which mediate higher cognitive processes, is a key feature of Alzheimer’s disease at the cellular level[16][17][18]. There is strong evidence that Alzheimer’s disease interferes with brain circuit connections early in the disease process by causing synaptic disruption[16][19]. The medial temporal lobe, specifically the entorhinal cortex and hippocampus, is where Alzheimer’s disease related deterioration starts[16][20]. Memory and learning problems, which are typically seen with early clinical signs of Alzheimer’s disease, are caused by damage to various brain areas. Then, the parietal regions and temporal association cortex are affected by the degeneration. The frontal cortex and eventually majority of the remaining neocortex begin to degenerate as the disease worsens[16][21][22]. It is noteworthy that Alzheimer’s disease significantly impairs number of limbic system organelles, such as the thalamus, amygdala, cingulate gyrus, fornix, and key fiber tracts (fornix and cingulum) that connect them to the cerebral cortex. The extensive range of cognitive deficits and behavioral abnormalities that Alzheimer’s disease patients experience is closely corelated with this pervasive pattern of neurodegeneration, which affects both limbic and neurocritical regions[16][21]. Patients with Alzheimer’s disease exhibit diminished capacity to perform activities of daily living in addition to cognitive impairment across several domains such as memory, language, reasoning, executive, and cognitive function and frequently develop mental, emotional, and personality problems. It has been hypothesized that the deposition of aberrant proteins both inside and outside of neurons is responsible for the neuronal damage seen in Alzheimer’s disease. The plaques and tangles, or typical pathological lesions of Alzheimer’s disease. A characteristic pattern of dissemination through neuronal circuits that mediate memory is followed by the aberrant proteins when they are deposited in the cerebral cortex, and other mental processes[16][18]. Extracellular amyloid protein accumulations known as “senile plaques” are made up of insoluble amyloid-beta proteins that release soluble proteins after cleavage of a cell surface receptor. Alzheimer’s disease involves abnormal cleavage of Amyloid Precursor Protein (APP) that results in the precipitation of dense beta sheets and the formation of senile plaques. After clearing, amyloid aggregates it is thought that microglia and astrocytes initiate an inflammatory reaction, this inflammation most likely results in the degeneration of nearby neurons and their neurites (axon and dendrites)[16][23][18]. Neurofibrillary tangles (NFT) are intracellular clumps of

abnormally hyperphosphorylated tau, a protein that typically functions as a microtubule stabilizer and is involved in intracellular (axonal and vesicular) transport. Neurofibrillary tangles may obstruct the normal axonal transport of elements required for healthy neuronal survival and function, such as synaptic vesicles containing neurotransmitters, neurotrophic factors, and mitochondria, leads to the eventual death of neurons. There is strong evidence to suggest that amyloid production and deposition in the cerebral cortex are among the first pathogenic processes in Alzheimer's disease. Despite this, there is disagreement on the exact timing of the formation neurofibrillary tangles and the deposition of amyloid plaques during course of Alzheimer's disease development. In fact, a recent study contends that neurofibrillary tangles may first form in the brainstem rather than the medial temporal lobe and that it may do so before the earliest amyloid plaques in the brain[16][24].

AMYLOID CASCADE HYPOTHESIS

The primary disease is thought to be the formation of Aβ-42 amyloid plaques in the brain. The successive actions of β-secretase and γ-secretase result in the sequential synthesis of Aβ-42 from amyloid precursor protein (APP). Since Aβ-42 is insoluble, it gathers into plaques, which inflict oxidative harm and start inflammatory processes that eventually result in neuronal death. As a result of amyloid accumulation, tau proteins are hyperphosphorylated and form neurofibrillary tangles. There are two types of Alzheimer's disease: familial and sporadic versions. Early onset and mutations in the amyloid precursor protein (chromosome 21), presenillin-1 (chromosome 14), and presenillin-2 (chromosome 1) genes are related with familial variants. The presence of the ApoE4 allele is linked to both the sporadic and late-onset familial forms of Alzheimer's disease. The three alleles 2, 3, and 4 of the protein ApoE, which transports cholesterol, are implicated. 40–80% of Alzheimer's patients carry the apoE4 allele, compared to a typical distribution of 24–30% in the Caucasian population. It has been demonstrated that ApoE4 both increases amyloid formation and decreases its clearance[25].

TAU HYPOTHESIS

The level of amyloid deposits does not correspond with the severity of cognitive impairment, and the amyloid cascade theory is unable to adequately explain sporadic occurrences of Alzheimer's disease. This gives rise to the Tau hypothesis, which claims that the underlying disease is the deposition of tau and the development of neurofibrillary tangles, with the deposition of amyloid occurring secondarily. The protein tau, which is linked with microtubules, bind and stabilizes the microtubules used for intracellular transport. Tau's ability to link with microtubules is decreased by hyperphosphorylation, and tau's availability to do so is decreased by sequestration of hyperphosphorylated tau in neurofibrillary tangles (NFT). Microtubules break down as consequence, which reduces axonal transport cell death[25]**.**

MITOCHONDRIAL HYPOTHESIS

Alzheimer's disease is thought to start with diminished mitochondrial ability to manage free radicals[25][26].

PHASES OF ALZHEIMER DISEASE

Depending on the individual, each Alzheimer's disease will manifest itself slightly differently. Although there will be variations in emotional, behavioral, and cognitive changes, therapists and researchers largely accept the stage model, which outlines common traits[25][27].

The "forgetfulness phase" of the first phase is characterized by difficulties remembering recent events and a propensity to lose one's location[25,28]. Prior known names of people and locations may be difficult to recall, and overall disorientation and poor short-term memory may also remain[25][29].

The "confusional phase" is a term used to describe the Second Recognized Phase. Memory loss is accompanied by a declining attention span and a drop in general intellectual function. Disorientation when moving around, trouble finding words, and other speech modifications may be seen[29][25]. Complex jobs are generally executed awkwardly or inaccurately, and frequently the abilities that were learnt last come into play first. It doesn't take long for a person to lose interest in the news and surroundings, which may be quite upsetting to family and friends[25][30].

The Third Phase, sometimes known as the "dementia phase," is characterized by the person acting randomly and occasionally bizarrely without any apparent reason. As people in this stage continue to lose memory capacity, their ability to calculate (dyscalculia), and some components of their language, which are severely impaired and ultimately lost, regular supervision is required for their remaining intellectual and self-care capacities. For self-care activities including clothing, grooming, using the restroom, and feeding constant support is needed. Additionally, a physical wasting that will require assistance walking can be noted. Sometimes a period of one or two years in a nearly vegetative condition is followed by death. In those who are susceptible, environmental variables may play a part in precipitating Alzheimer's disease. Aluminium has been linked to Alzheimer's disease, according to research[25][31].

DIAGNOSIS OF ALZHEIMER'S DISEASE

A pathological analysis based on an autopsy is the gold standard for the diagnosis of Alzheimer's disease. The number and location of neurofibrillary tangles and amyloid plaques in the brain are used to stage the disease and determine the presence of definitive Alzheimer's disease. In clinical settings, the diagnosis of Alzheimer's disease is mostly made using the patient's medical history, physical, neurological examinations, and neuropsychological testing. Selected ancillary testing is also used to rule out other potential causes. In comparison to the pathological diagnosis, the clinical diagnosis of Alzheimer's disease has an accuracy of 70-90%, with higher accuracies being attained in specialized settings such as memory disorder[16][32]. A set of consensus criteria first established in 1984. Most recently updated in 2011 by the National Institute on Aging and Alzheimer's are the corner stone of the clinical diagnosis. The diagnosis of possible Alzheimer's disease dementia is advised when the patient's cognitive impairment follows an unusual clinical course or suspected of being brought on by etiologies other than Alzheimer's disease. On physical and neurological exams[16][33], Alzheimer's disease patient's typically have normal results. Only for exploratory purposes or as a supplement to the clinical criteria for Alzheimer's disease are laboratory and neuroimaging techniques utilized, notably to rule out structural brain lesions and find it reversible dementia causes. The American Academy of Neurology advises only the routine measurement of serum B12, thyroid stimulating hormone (TSH), free thyroxine (T4) levels as part of the workup for dementia to rule out cerebral hematomas, brain tumors, cerebrovascular lesions as well as normal pressure hydrocephalus, structural MRI or non-contrast computed tomography (CT) may be helpful[16][34].

DETECTION METHODS

A promising and rapidly developing field of study for diagnosing Alzheimer's disease is neuroimaging. Magnetic resonance imaging, positron emission tomography, and computed tomography scans—considered to be the initial screening for disease—are just a few of the brain imaging techniques that can be used to detect abnormalities in the brain. Each scan uses a different technique to identify particular structure and abnormalities in the brain and related organs. Although it is not currently a requirement for Alzheimer's disease testing, recent clinical studies have produced encouraging findings that could transform how doctors now identify the condition. The most common form of dementia, Alzheimer disease, presently has no effective treatments despite years of dedicated and successful research. It is becoming more and more obvious that in order to successfully treat the disease, it must be found as soon as possible, sometimes even before symptoms appear. Therefore, there is a huge need for accurate diagnostic techniques so that the disease can be properly treated and treatment to halt or prevent it can start as soon as feasible[8].

POSITRON EMISSION TOMOGRAPHY

Positron emission tomography (PET) creates a three-dimensional, colorful image of the human body using radiation signals. The patient receives an injection of a radiotracer, which is made up of a radioactive medication coupled to a naturally occurring molecule. Glucose is frequently used in research on Alzheimer's disease. The organs that use the specific chemical as an energy source receive the radiotracer. These positrons' energy is used by the positron emission tomography scan to convert the input into a picture that can be seen on the output screen. This image illustrates how the patient's body functions by showing how effectively the radiotracer is broken down. The positron energy's spectrum of colors and intensities corresponds to the level of brain activity. Changes in the brain's metabolism, blood flow, cellular communication pathways, and other internal processes can be detected with a Positron Emission Tomography scan. An article from 1996's Journal of Clinical Psychiatry described how to use a positron emission tomography scan to identify changes in glucose metabolism in an Alzheimer's patient's brain. It is demonstrated that the parietal, temporal, and posterior cortices have an atypically slow rate of glucose metabolism. A higher reduction in the rate was observed in patients whose illnesses were more serious and had spread to more areas of the brain. Positron emission tomography scans can identify issues with glucose metabolism years before symptoms start to show up clinically, as demonstrated by Small and his colleagues. In addition to diagnosis, positron emission tomography scans may also be used to evaluate the efficacy of Alzheimer's disease treatments[35][8].

COMPUTED TOMOGRAPHY

A computed tomography (CT) scan produces a series of cross-sectional images of the body. A computer is used to merge and blend the several scans into a single, comprehensive image. The computed tomography scan provides the physician with specifics regarding the tissue densities throughout the body and in various parts of the brain. For improved clarity, a contrast dye may be injected to aid in differentiating between tissues that are identical[8][36].

MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance imaging techniques, which were initially used in 1997, allow the body to be seen in two or three dimensions. A key component of the magnetic resonance system is the super conducting magnet,

which generates a powerful and stable magnetic field. A smaller gradient magnet generates a weaker magnetic field. It is feasible to scan numerous bodily parts thanks to these magnets. The human body is made up of billions of atoms. The hydrogen atom is nevertheless impacted by the magnetic field. Under the magnetic field of magnetic resonance imaging, the molecules are aligned with the direction of the field, whereas each hydrogen atom spins randomly around an axis. Half of the atoms point at the patient's head, while the other half points at their feet, to balance each other out. A few atoms out of every million do not cancel out. Then, the device emits a radio frequency pulse that is specific to hydrogen, which causes these protons to spin in a certain detection. When the spinning stops, the protons release energy, which the system interprets. Each form of tissue reacts differently to a contrast dye, and when the picture is created, each type of tissue appears as a unique shade of grey[(8)]. By comprehending how the system works, researchers can determine if an MRI can correctly identify the structural abnormalities and cellular death that are present in the brain of an Alzheimer's patient. Hippocampal atrophy is frequently present in Alzheimer's disease even before the development of the clinical indications. 56 participants in the Nun research, which was conducted in 2002, who had varying degrees of cognitive impairment contributed postmortem MRI pictures. Using MRI, the hippocampal volume was discovered, and its significance as a sign of the neuropathology connected to Alzheimer's disease was established[(8)(37)]. According to the research, scans may be used to identify older adults without dementia who have neuropathology indicative of Alzheimer's disease but have not yet shown signs of memory loss. By identifying the possibility that these individuals may develop Alzheimer's disease long before any symptoms appear, doctors may be able to provide medicine to slow the progression of the illness. A more recent study, conducted in 2009 by the radiology and neurology departments at the University of Pennsylvania, focused on the use of sodium magnetic resonance imaging in the diagnosis of Alzheimer's disease. This imaging technique uses the same fundamental concept as the one previously mentioned. However, sodium, which is cheap and can be detected naturally, is used in this procedure instead of hydrogen atoms. This ion was selected because sodium in the brain can identify tumors and monitor cell death[(8)(38)]. The participants consist of five elderly people in good health and five others who may have been diagnosed with Alzheimer's disease. When neuronal death occurs, the intracellular volume is smaller. As a result, there is more salt in the extracellular space, which causes Alzheimer's disease patients to have a higher MRI signal intensity. Even though this method has not yet been perfected, studies are being conducted to determine if the higher signal strength is caused by a change in ion concentration or a change in volume[(8)(35)].

ADVANCES IN BIOMARKER STUDIES

Monitoring treatment efficacy, enabling early Alzheimer disease identification in people, and supporting differential diagnosis are the three main uses of biomarkers in clinical practice[(39)(40)(41)(42)]. Although the three primary CSF biomarkers for Alzheimer's disease—the Aβ peptide, total tau protein (T-tau), and phosphorylated tau protein (P-tau)—have been studied for more than 20 years, the pathological hallmark of Alzheimer disease has only recently been discovered. This signature consists of elevated levels of T-tau and the serine residue of 181 P-tau (181 P-tau) together Aβ peptide ($A\beta_{1-42}$)[(39)(43)(44)(45)]. Cognitive improvement assessments are a typical objective in clinical trials. As was already indicated, these are not as trustworthy as biochemical or physiological markers. Pharmacodynamic endpoints, such as the Alzheimer disease hallmark or specific A concentrations in cerebrospinal fluid, can also be used to analyze medicines that inhibit A-producing enzymes. [(39)(46)]. On the other hand, measurements differ amongst clinical laboratories, and the lack of standardization makes it difficult to set trustworthy threshold levels [(40)(48)(49)]. Genetic anomalies associated with Alzheimer's disease result in neuropathological changes such as an increase in $A\beta_{1-42}$, brain amyloidosis, tauopathy, brain shrinkage, and a decrease in glucose metabolism[(39)(47)]. There is at least one proven biomarker for each of these major pathogenic traits. Using the A/T/N method, the primary biomarkers can be divided into three groups: those that indicate A metabolism and accumulation, those that indicate tau pathology, and those that indicate neurodegeneration or neuronal damage[(48)(39)]. These biomarkers have been verified and are often used. Levels of $A\beta_{1-42}$ in the cerebrospinal fluid and molecular amyloid imaging, such as Pittsburgh compound B ([^{11}C]-PIB) PET, florbetapir (^{18}F) PET, and flutemetabol (^{18}F) PET which demonstrate cerebral retention of Aβ, fall under the first group. Elevated 181P-tau levels in the cerebrospinal fluid and molecular tau imaging, including flortaucipir (^{18}F) PET, are included in the second group. The last group contains elevated T-tau in the cerebrospinal fluid and reduced fluorodeoxyglucose (FDG) uptake on PET topographic pattern including the temporoparietal cortex, mesial temporal, and parietal areas [(39)(49)(41)]. Cerebrospinal fluid and imaging biomarkers have recently made encouraging advancements; however, they are currently only widely available in research settings [(39)].

BIOMARKERS OF AMYLOID ACCUMULATION

Cerebrospinal fluid $A\beta_{1-42}$ and amyloid PET are two molecular indicators of Alzheimer disease that are related to amyloid. Low $A\beta_{1-42}$ suggests amyloid accumulation in the brain and has excellent agreement with amyloid PET. This pathogenic alteration is detected with a sensitivity of over 90% in prodromal and Alzheimer's disease [(39)(5)]. [^{11}C]-PIB is the amyloid imaging agent used most often. It distinguishes between people with Alzheimer's disease and those with normal cognition by binding to A aggregates with high affinity. For the

diagnosis of Alzheimer disease pathology, researchers discovered that the sensitivity of cerebrospinal fluid $A\beta_{1-42}$ levels and PiB-PET were equivalent[39][50].

BIOMARKERS OF tau PATHOLOGY AND NEURONAL DEGENERATION

P-tau levels are thought to signify the existence of tau pathology, including neurofibrillary tangles, while CSF T-tau levels are thought to reflect disease progression more accurately by reflecting neuronal damage or neurodegeneration. Other dementias do not have high P-tau levels[39][51][42]. A precedes tau disease, although NFT has a stronger correlation with cognitive decline than amyloid deposition does. Different patterns of tau deposition correspond with even the apoE4 status[39][50][52]. The need of creating tau-specific tracers or imaging investigations is further emphasized by the fact that assessments of tau deposition in certain locations are more directly connected to early degeneration, atrophy measures, and cognitive decline[39][53][54]. The creation of tau tracers began approximately two decades ago, with flortaucipir [^{18}F] being the most researched, however accuracy and reliability of the technology are still being investigated[39][55][56]. For the diagnosis and follow-up of Alzheimer's disease, well-established imaging modalities include magnetic resonance imaging and fluorodeoxyglucose-positron emission tomography, which monitors glucose. Fluorodeoxyglucose-positron emission tomography detects synaptic dysfunction and monitors glucose absorption in neurons and glial cells. A temporoparietal and posterior cingulate hypometabolism is the characteristic pattern of altered fluorodeoxyglucose-positron emission tomography in Alzheimer's disease[39][4]. Later in the course of the disease, changes in magnetic resonance imaging are observed. It is thought that over time, cerebral atrophy spreads from the mesial temporal lobe to the parietal, occipital, and frontal lobes, with changes in hippocampus volume and entorhinal cortex thickness. People with moderate cognitive impairment exhibit the greatest rates of atrophy[39][50].

TREATMENT

Drug therapy

There are two categories of drugs. Anticholinesterase inhibitors and N-methyl D-aspartate antagonists are used to treat Alzheimer's disease. These medications function in two distinct ways.

CHOLINESTERASE INHIBITORS

A person with Alzheimer's disease has reduced amounts of the neurotransmitter acetylcholine in their brain. Acetylcholine is used to transmit signals between nerve cells. In order to cure memory problems, cholinesterase inhibitors work by increasing the availability of acetylcholine during synaptic neurotransmission. Galantamine, donepezil, and rivastigmine are the three cholinesterase inhibitors now being used as the first line of therapy for mild to severe Alzheimer's disease[57][8]. Galantamine inhibits both acetylcholine and butyrylcholinesterase, in contrast to donepezil and rivastigmine, which are both selective inhibitors. No improvement in everyday activities and behavior was found in a meta-analysis that included 13 randomized, double-blind studies that were conducted to assess the efficacy and safety of cholinesterase inhibitors. Additionally, there was no discernible difference between donepezil and rivastigmine in terms of how they affected behavior, everyday activities, and cognitive processes. All three medications showed essentially the same advantages[8][58]. Despite the fact, cholinesterase inhibitors have been shown to have effects that last for a significant amount of time, it is recognized that they cannot stop the course of illness. According to a randomized double-blind experiment, people receiving donepezil for a prolonged period of time did not experience any positive side effects for up to two years[59][8]. Increased cholinesterase inhibitor dosages may also have some additional advantages. In a randomized, double-blind, parallel group, 48-week study to assess the efficacy and safety of a higher dose of rivastigmine patch, patients receiving higher doses experienced a significant decrease in activity of daily living decline and an improvement in assessment scale cognitive subscale scores[8][38]. Cholinesterase inhibitors cause side effects, which are often restricted to gastrointestinal symptoms such diarrhea, nausea, and vomiting[8][10]. Guidelines for the usage of these medications have been released by the NICE (National Institute for Health and Care Excellence). Drugs are evaluated by NICE, which determines whether they offer a good enough return on investment to be included in NHS care[8].

N-METHYL D-ASPARTATE RECEPTOR ANTAGONIST

Alzheimer’s disease that is mild to severe can be effectively treated with the non-competitive N-methyl D-aspartate receptor antagonist memantine. The reduction of glutamate-induced excito-toxicity is achieved modulating N-methyl D-aspartate receptors. A 28-week, double-blind, parallel group study that demonstrated its advantages revealed that the medication markedly decreased patient deterioration. The majority of pharmacological side effects were mild and thought to be unrelated to the drug. Patients' behavior improved as a result an improvement in cognitive performance, which led to fewer agitated patients and less requests for care assistance. A meta-analysis of six studies involving the treatment with memantine also showed improvement of the behavioral and psychological symptoms associated with dementia[60][8]. Memantine is advised for use as part of National health service care for those with severe Alzheimer’s disease, according to national institute for health

care and excellence guidance. For those with intermediate Alzheimer's disease who are unable to take cholinesterase inhibitor medications due to adverse effects, national institute for health care and excellence also suggests memantine[8].

ANTIDEPRESSANT AND ANTIPSYCHOTICS

A frequent occurrence in Alzheimer's disease and a significant source of stress for care is behavioral and psychological symptoms of dementia. To some extent, cholinesterase inhibitors and memantine can help regulate these symptoms, but as patient conditions worsen, their ability to do so decreases. Especially in the early and late stages of the illness, depression is particularly prevalent. Tricyclic drugs, combination serotonergic and nor-adrenergic inhibitors, selective serotonin reuptake inhibitors such as citalopram, fluoxetine, paroxetine, sertraline, trazodone and other antidepressant may be used to counter this [8,61]. Risperidone, olanzapine, quetiapine which are used to treat agitation and psychosis, respectively. However, the use of such medications appears to be debatable because individuals who received antipsychotic medication showed significantly lower cognitive function than those who received a placebo[8,62].

DISEASE MODIFYING TREATMENT

While symptomatic therapies have been effective, the most important thing is to discover a cure. Interest in anti-amyloid therapeutics is driven by the amyloid hypothesis, which suggests that Aβ generation and deposition from overexpressed amyloid precursor proteins cleavage are the underlying substrate of Alzheimer's disease. These treatments reduce the formation of Aβ, enhance its clearance, and stop it from congregating to form amyloid plaques[63][8][64]. Immunotherapy has also attracted attention since it aims to eliminate Aβ peptides, which may have an influence on cognitive decline either directly or indirectly[65][8]. Overall Aβ production and deposition would be decreased by inhibiting β- and γ-secretases while concurrently potentiating γ-secretases activity. According to scientists, the majority of cases of Alzheimer's disease are brought on by an influence of hereditary, dietary, and environmental factors that have an ongoing negative impact on the brain over time and ultimately result in damaged brain cells. Less than 5% of the time, precise genetic alterations that almost assure a person would tend to get the illness are the cause of Alzheimer's. Although the exact origins of Alzheimer's disease are still unknown, it is obvious that the disease has an adverse effect on the brain, causing cell destruction and shrinking. Brain cells are severely harmed and killed by Alzheimer's disease. The number of cells and connections between surviving cells are significantly lower in an Alzheimer's disease-affected brain than in a healthy brain. Alzheimer's disease causes a considerable shrinking of the brain and consequent memory loss as more and more brain cells begin to die[8].

FUTURE TREATMENT

Targeting the neurofibrillary tangles (composed of p-tau) and senile plaques (Aβ), which are the illness's etiological pathologies, is a key component of research into potential treatments for Alzheimer's disease. The optimal way to delay or stop neurological deterioration, as well as how soon treatment should be started, are still up for dispute[66][67][68]. Another strategy tries to strengthen inter-neuronal connections and transcortical networks in order to improve cognitive performance[69][67]. We know from past research that the best strategy to delay or stop the course of Alzheimer disease is early identification of people at-risk age group and subsequent therapy in the preclinical period[67][70]. Results are anticipated early in the next decade from clinical studies that are now recruiting asymptomatic people with a genetic predisposition or biomarker suggesting a higher probability of acquiring Alzheimer's dementia. In 2016, the EU/US/Clinical Trials in Alzheimer Disease Task Force reviewed a number of these trials in an effort to determine the most efficient methods for enlisting and retaining patients, building infrastructure, and assessing patients, including the use of biomarkers and objective testing for clinical outcomes [67][70]. Some of the ongoing issues identified include timelines for recruiting and recruitment failures, difficulty predicting success based on the available research for specific drugs, and overall costs for such sizable clinical trials. A better indicator of successful clinical trials can be developed with more collaboration between researchers, corporate and governmental financing, and screening of people at-risk groups[67].

ANTI-AMYLOID

According to the amyloid cascade hypothesis, toxic plaques are the earliest indicator of the disease, and there is evidence of Aβ up to 20 years before symptoms arise[49][67]. Researchers learned in 2013 that this abnormal amyloid plaque phosphorylates tau protein, which then spreads almost infectiously to neighboring neurons via microtubule transport, ultimately leading to neuronal death[67][71]. Monoclonal antibodies (passive immunotherapy) are one class of drugs created utilizing this research. This type of treatment is injecting an antibody that, by focusing on aberrant Aβ, aids in removing it from the brain. In order to eliminate these plaques from the brains of individuals with Alzheimer disease, two of these monoclonal antibodies were first created in 2014[67][72][73]. Researchers came to the conclusion that neither drug improved cognitive scores in people with mild to moderate illness (MMSE 16–26), and that they may only be beneficial when used in the early stages of mild

dementia and mild cognitive impairment. But a recent study on the impact of this class of drugs in patients with minimal to no symptoms (MMSE 20–26) but positive amyloid positron emission tomography imaging results also failed to demonstrate a significant difference in cognitive outcomes between the study group and asymptomatic controls(67)(74). Studies using medications in this class are still being conducted with the aim of enhancing or maintaining cognition in people with mild cognitive impairment brought on by Alzheimer's disease. Inhibiting the enzymes that create the Aβ peptide from its precursor, amyloid precursor protein (APP), is another method for reducing the amount of Aβ plaque in the brain. Target-site APP cleaving enzyme 1 (BACE1), which is assumed to be necessary for the generation of Aβ peptides, is the subject of several medicines now under investigation[(67)(75)]. The new drug verubecestat recently produced a more than 40-fold decrease in Aβ levels in the brains of rats and primates, and it has demonstrated a favorable safety profile in early investigations, despite prior research with BACE1 inhibitors failing to produce substantial results in human subjects[(67)(76)]. In the early research, a different medication is now being examined for its impact on memory and cognitive function in elderly individuals with positive biomarkers or a family history of Alzheimer's disease. In 2014, it was demonstrated by researchers that monoclonal antibody treatment combined with a BACE1 inhibitor greatly decreased the quantity of Aβ in mice that produced amyloid[(67)(77)]. Although no studies are currently being conducted, using this strategy to eradicate A will ultimately result in success in the treatment of Alzheimer disease[(67)(78)].

ANTI-TAU

Drugs to lessen the load of this protein are also being developed, as it appears that p-tau is the downstream pathology and is most likely the direct source of the symptoms in Alzheimer's disease[(67)(79)]. In animal models, several different tau vaccines have exhibited both safety and efficacy[(67)(80)]. In recent research, an anti-tau medication showed an excellent safety profile and even induced a favorable immunological response in people[(67)(81)]. The treatments and research areas that are now being considered are explained by the findings of additional early phase therapeutic studies that target the tau protein that are still pending publication[(67)(82)].

CONCLUSION

Alzheimer disease is a neurogenerative disorder which is a most challenging disease in present era which is expected to double every 20 years. It is a cognitive dysfunction, including memory loss, language problems, and executive dysfunction, significantly impairing an individual's quality of life. Age is the primary risk factor, while genetics, education level, and environmental factors also play roles in its development. Promising research is underway, focusing on targeting the neurofibrillary tangles and senile plaques at the core of the disease's pathology. Early detection through brain imaging procedures and the use of medications like anticholinesterase inhibitors and N-methyl-D aspartate antagonists offer hope for improved management of Alzheimer's disease, but continued research and innovation are essential to address this growing global health crisis.

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