Pathology of Alzheimer's Disease and Its Therapeutic Approaches: A Review

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Abstract
Dementia is a broad term that refers to a decrease in cognitive abilities severe enough to cause problems with daily activities. Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for at least two-thirds of dementia cases in persons 65 and older. Alzheimer's disease is a neurological illness that causes gradual decline in behavioral and cognitive abilities such as memory, understanding, language, attention, reasoning, and judgment. Alzheimer's disease symptoms vary depending on the stage of the disease. Alzheimer's disease is categorized into three stages based on the degree of cognitive impairment. The review article focuses on the JAK2/STAT3 signaling pathway's position in the hippocampus and its relevance in Alzheimer's disease. Key proteins that activate the system include p-JAK2-Tyr1007 and p-STAT3-Tyr705, both of which have been reported to be increased in Alzheimer's disease models. The study also examines the significance of glial cells like astrocytes in Alzheimer's disease development. The JAK2/STAT3 pathway has a behavioral influence in animal models of Alzheimer's disease in reactive astrocytes but has no effect on tau and amyloid pathology. The clinical stages of Alzheimer's disease can be divided into four categories: (1) pre-clinical or pre-symptomatic, (2) prodromal AD, (3) mild AD dementia, and (4) moderate to severe AD dementia. AD has been considered a multifactorial disease associated with several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors (heavy metals, trace metals, and others). The underlying cause of pathological changes in Alzheimer's disease (Aβ, NFTs, and synaptic loss) is still unknown. Several hypotheses were proposed as a cause for AD but two of them are believed to be the main cause: some believe that an impairment in the cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloid β-protein production and processing is the main initiating factor. Alzheimer's disease cases are currently predicted to be over 24 million globally, with the total number of dementia patients expected to more than 4 times by 2050.

Several physiological mechanisms in Alzheimer's disease damage Ach-producing cells, reducing cholinergic transmission through the brain. Acetylcholinesterase inhibitors (AChEIs), which are classed as reversible, irreversible, and pseudo-reversible, work by preventing cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, resulting in increased ACh levels in the synaptic cleft. The present Alzheimer's disease treatment is only symptomatic. The only four FDA-approved treatments for Alzheimer's disease are AChE inhibitors (donepezil, galantamine, and rivastigmine) and NMDA antagonists (memantine). Anti-amyloid treatment is a type of Alzheimer's disease drug that targets the protein fragments that aggregate in the brain and form plaques, which is a defining feature of the illness. In conclusion, while promising medications are now being tested, more study is needed to better understand the pathophysiology of Alzheimer's disease and, as a result, to identify novel biomarkers and targets that will allow the creation of really disease-modifying therapies.

Keywords: Alzheimer's disease, risk factors, tau protein, disease-modifying therapy, neurodegeneration, -amyloid peptide, heat shock proteins.

Introduction

Dementia is a broad term that refers to a decrease in cognitive abilities severe enough to cause problems with daily activities. Alzheimer's disease (AD) is the most prevalent form of dementia, accounting for at least two-thirds of dementia cases in persons 65 and older. Alzheimer's disease is a neurological illness that causes gradual decline in behavioral and cognitive abilities such as memory, understanding, language, attention, reasoning, and judgment. In the United States, it is the sixth biggest cause of death. Early onset (before the age of 65) is rare and occurs in less than 10% of Alzheimer's disease patients. There is no cure for Alzheimer's disease, although there are therapies that may mitigate certain symptoms (1).

Alzheimer's disease symptoms vary depending on the stage of the disease. Alzheimer's disease is categorized into three stages based on the degree of cognitive impairment: preclinical or presymptomatic, mild, and dementia-stage. Preclinical

Alzheimer's disease (AD) was divided into four clinical stages: Preclinical AD, prodromal AD, mild AD dementia, and moderate to severe AD dementia (2).

Multiple States Model

In the multi-state model, the arrows represent the fitted advancement and reversal rates between phases. For readability, moderate to severe Alzheimer's disease dementia is condensed to mild Alzheimer's disease dementia.

The earliest and most common presenting symptom is episodic short-term memory loss with relative sparing of long-term memory, which may be evoked in the majority of patients even if it is not the presenting symptom. Impaired short-term memory is followed by impaired problem-solving, judgment, executive functioning, lack of motivation, and disorganization, resulting in difficulties with multitasking and abstract thinking. Executive functioning impairment ranges from modest to serious in the early stages (3).

This is followed by a language dysfunction and a consequent decline of visuospatial abilities. In the mid to late stages, neuropsychiatric symptoms such as detachment, social isolation, anxiety, agitation, psychosis, and restlessness are also common. Late in the disease, difficulty executing learned motor tasks (dyspraxia), olfactory dysfunction, sleep difficulties, and extrapyramidal motor indications such as dystonia, akathisia, and parkinsonian symptoms appear. Following this come basic reflexes, urinary tract problems, and utter reliance on caretakers (4).

Precision medicine techniques and approaches have enhanced our understanding of the pathophysiological alterations involved in the development and progression of Alzheimer's disease dementia during the last decade and can guide the creation of focused therapies. However, gender and sex have yet to be included into precision medical techniques. The removal of these criteria has slowed progress in the identification and treatment of Alzheimer's disease. Such advancements are critical to reducing health-care consumption and the high expenses associated with Alzheimer's disease care (5).

Long Acting Injectables (LAIs) were initially produced and used to treat schizophrenia, prostate cancer, and as hormone replacement therapy, but research for the treatment of human immunodeficiency virus (HIV), Alzheimer's disease, and Parkinson's disease is undergoing. LAIs have been found in randomized controlled studies to be superior and more effective than oral medicine. Because of the bypass of first pass metabolism, LAIs improve bioavailability and minimize medication interaction. They also reduce renal and liver damage. Because reversal of therapy is not feasible with depot formulations, oral induction is usually advised prior to LAI administration to avoid undesirable effects. Because of the reduced pill load and lower dose frequency, LAIs have improved patient compliance and treatment adherence (6).
Alzheimer's disease (AD) is the most widespread form of dementia, affecting an estimated 24 to 35 million individuals worldwide. It is an extremely serious condition marked by impaired cognitive. Because of an aging population, the incidence is anticipated to rise to 1 in 85 individuals by 2050. People with Alzheimer's disease generally live for 3 to 9 years following diagnosis. As Alzheimer's disease develops, individuals and their loved ones are frequently forced to seek full-time care. With the expected rise in Alzheimer's disease incidence, it is critical to obtain early detection, effective therapies, and a better knowledge of the underlying etiology (7).

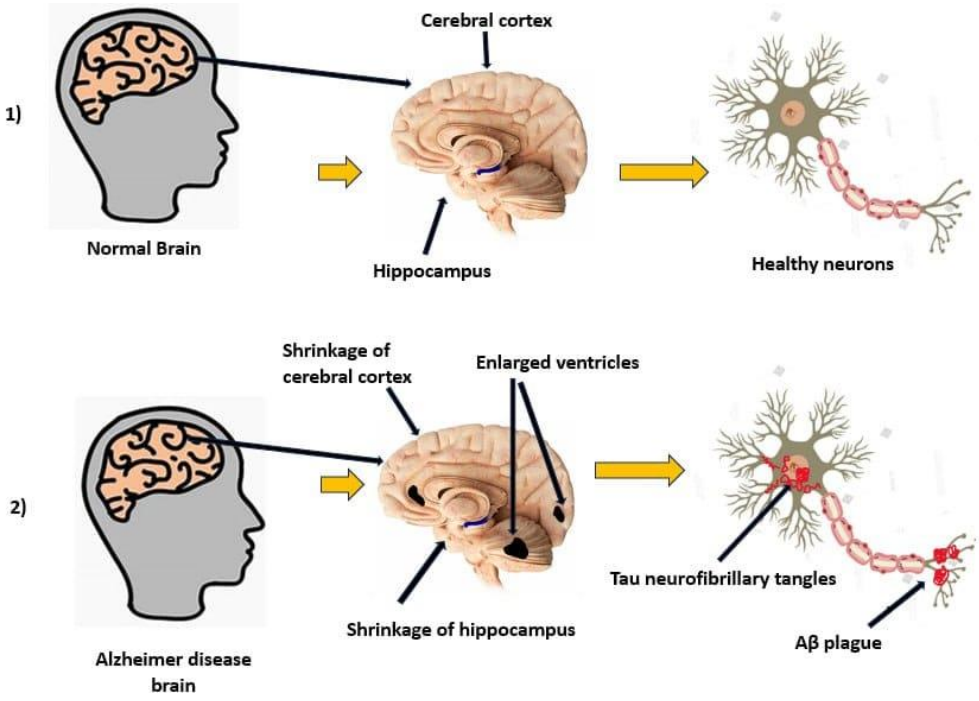
Mechanisms and drivers of pathology

There is more knowledge available on the biologic mechanisms related with protein aggregation and neurodegeneration associated with aging and Alzheimer's disease, notably for both hereditary and environmental variables in the pathogenesis of Alzheimer's disease as represented in figure 2. However, the evolution of many crucial elements of Alzheimer's disease have not been examined or have barely been touched upon utilizing imaging tools. Pathological investigations, for example, have shown that synapse loss is a prominent characteristic of Alzheimer's disease, although imaging of synapses has just recently been performed. Changes in cholinergic function, meantime, have gotten some attention with positron emission tomography (PET) imaging but have primarily been thought to represent secondary processes (8). Although this chapter concentrates on Aβ and tau, additional proteins such as α-synuclein and TDP43 have been shown to group together in the brains of the elderly and those suffering from dementia. Because in vivo imaging techniques for these proteins are not yet accessible, their roles in life have not yet been examined; development of such novel ways is a top priority in the imaging area. Finally, because amyloid imaging was accessible for years before tau imaging, illness mechanisms linked with tau are mostly unknown, and the majority of data represent relationships with Aβ (9).

Multimodal imaging tools have revolutionized studies on human aging and dementia by allowing researchers to investigate the complex interconnected pathways that govern the development of Alzheimer disease (AD). The two aggregated proteins implicated in the cause of Alzheimer's disease AD - amyloid-β (Aβ) and tau may be seen using positron emission tomography (PET), and the suggested downstream consequence of neurodegeneration can be investigated using structural MRI, functional MRI, and glucose metabolism PET. These pathophysiological mechanisms have been largely clarified in studies of cognitively healthy older persons and those with cognitive impairment or dementia, in a method that might be used to investigate various degenerative neurological illnesses (10).AD is a slowly progressive condition that generally begins with dementia and the inability to acquire new memories, indicating impairment of the medial temporal lobe (MTL)

episodic memory system. Alzheimer's disease (AD) is characterized by dementia in its late stages and is linked with extensive Aβ plaques and tau aggregates as neurofibrillary tangles. Because plaque and neurofibrillary tangle pathology are frequently observed in the brains of cognitively healthy older adults, it is widely assumed that the molecular mechanisms underlying Alzheimer's disease are present for decades before symptoms appear. Thus, imaging has the potential to explain the progression of Alzheimer's disease (AD) from normal aging to the stage of mild cognitive impairment (MCI) to dementia (11). Such research has fueled a commonly used model of biomarker change, which proposes a systematic set of empirically verifiable processes. This model starts with Aβ deposition, which corresponds to the amyloid cascade theory of AD. One of the primary goals of this chapter is to assess the imaging evidence gathered thus far in order to determine how well these data correspond to this model and how departures from the model may or may not be tolerated. It is critical to understand that each imaging modality has been accessible for a different amount of time; this is important since techniques that have been used for years fail to account for factors that have just been measurable (12).

Figure 2. Mechanism and drivers of Alzheimer's disease



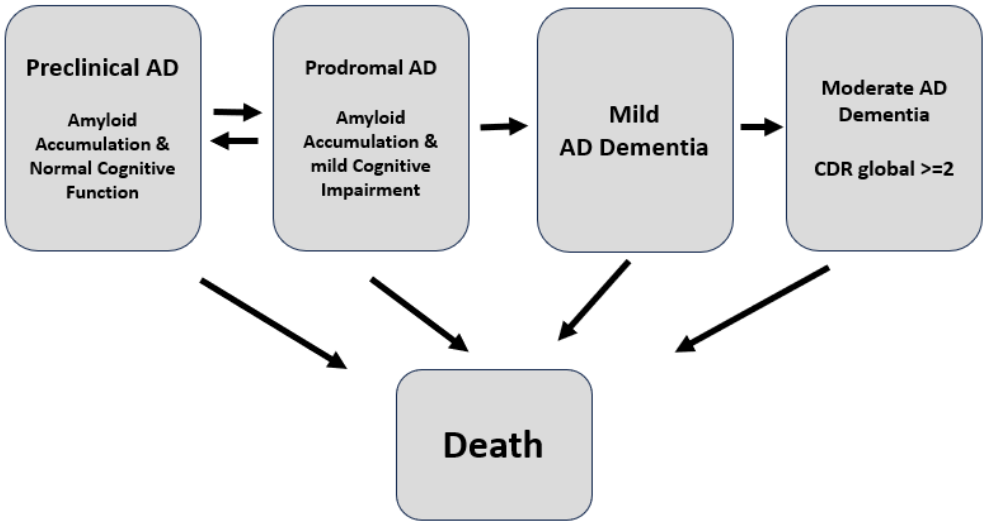
A new Frontiers in Aging Neuroscience paper gives an update on Alzheimer's disease as well as insights into its pathogenesis. The chapter focuses on the JAK2/STAT3 signaling pathway's position in the hippocampus and its relevance in Alzheimer's disease. Key proteins that activate the system include p-JAK2-Tyr1007 and p-STAT3-Tyr705, both of which have been reported to be increased in Alzheimer's disease models. The chapter also examines the significance of glial cells like astrocytes in Alzheimer's disease development. The JAK2/STAT3 pathway has a behavioral influence in animal models of Alzheimer's disease in reactive astrocytes but has no effect on tau and amyloid pathology. Cholinergic atrophy in Alzheimer's disease has been linked to trophic failure in the Nerve growth factor (NGF) metabolic pathway, which is required for the survival and maintenance of basal forebrain cholinergic neurons (BFCN). In Alzheimer's disease, there is a change in the conversion of proNGF to mature NGF (mNGF), as well as an increase in the degradation of physiologically active mNGF. Thus, the use of exogenous mNGF in experimental investigations was demonstrated to promote the recovery of atrophic BFCN. Vascular dysfunction has long been linked to cognitive decline and an elevated risk of Alzheimer's disease. Vascular risk factors are related with increased tau and cerebral beta-amyloid (Aβ) load, whereas Aβ acts synergistically to cause cognitive impairment (13).

Stages of Alzheimer's Disease

The clinical stages of Alzheimer's disease can be divided into four categories: (1) pre-clinical or pre-symptomatic, which can span several years or longer. This stage is distinguished by a slight reduction in memory and early degenerative alterations in the cortex and hippocampus, as well as little functional impairment in everyday activities and the lack of clinical signs and symptoms of Alzheimer's disease. (2) The moderate or early stage of Alzheimer's disease in which various symptoms emerge in patients, such as difficulty with everyday activities due to loss of attention and memory, confusion of location and time, a change in mood, and the development of depression. (3) Moderate Alzheimer's disease stage, in which the illness extends to parts of the cerebral cortex, causing increasing memory loss, difficulty recognizing relatives and friends, loss of impulse control, and difficulties reading, writing, and speaking. (4) Severe or late-stage

Alzheimer's disease, which involves the disease spreading to the entire cortex area with a severe accumulation of neuritic plaques and neurofibrillary tangles, resulting in a progressive functional and cognitive impairment where patients cannot recognize their family at all and may become bedridden with swallowing and urination difficulties, eventually leading to the patient's death due to these complications as represented in figure 3 (14).

Figure 3. Stages of dementia



Alzheimer's Disease Cause

AD has been considered a multifactorial disease associated with several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors (heavy metals, trace metals, and others). The underlying cause of pathological changes in Alzheimer's disease (Aβ, NFTs, and synaptic loss) is still unknown. Several hypotheses were proposed as a cause for AD but two of them are believed to be the main cause: some believe that an impairment in the cholinergic function is a critical risk factor for AD, while others suggest that alteration in amyloid β-protein production and processing is the main initiating factor. However, at present, there is no accepted theory for explaining the AD pathogenesis (15).

6. Alzheimer's Disease Risk Factors

6.1. Aging

Aging is the most major risk factor in Alzheimer's disease. Younger people are infrequently affected by this condition, and the majority of cases begin beyond the age of 65. Aging is a complicated and irreversible process that affects various organs and cell systems, resulting in a decrease in brain volume and weight as well as synaptic loss. Furthermore, various disorders such as glucose hypometabolism, cholesterol dyshomeostasis, mitochondria malfunction, depression, and cognitive decline may occur as we age. These changes are also seen in normal aging, making it difficult to identify cases with early AD. Early-onset AD (EOAD), the uncommon variety with roughly 1-6% of cases, most of which are familial AD characterized by having more than one relative in more than one generation with AD, and spans from 30-60 or 65 years, is the most common kind of AD. The second form is late-onset Alzheimer's disease (LOAD), which occurs beyond the age of 65. Both forms can arise in adults with a positive family history of Alzheimer's disease and in families with a late-onset illness (16).

Genetics

Over time, genetic variables were identified to have a significant influence in the development of Alzheimer's disease. Most instances of EOAD are inherited in an autosomal dominant manner, and mutations in dominant genes such as Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2), and apolipoprotein E (ApoE) are associated with AD (17).

Herein, we discuss the strong genetic risk factors in AD.

a) Amyloid Precursor Protein (APP)

The APP gene on chromosome 21 encodes a type I transmembrane protein that is cleaved by α-, β-, and γ-secretase to release Aβ and other proteins. Thirty mutations in the APP gene have been discovered, twenty-five of which are linked to Alzheimer's disease and produce an increase in Aβ levels. Meanwhile, A673T is a protective mutation that reduces Aβ, Aβ40, and Aβ42 secretion and hence protects against AD. All mutations that surround the secretase cleavage site, for example, the KM670/671NL mutation have exhibited an increase in amyloid plaques in the hippocampus and cortex with

no NFTs in mice models. Neuropathological reports for the A673V mutation revealed the presence of Neurofibrillary tangles (NFTs) and Aβ, activation of microglia and astrocytes, and neuronal loss, in contrast to the other mutations mentioned, which showed no change in intracellular Aβ. Other mutations that affect the γ-secretase cleavage site and cause polymorphic aggregates with the ability to disrupt bilayer integrity include T714I, V715A, V715M, V717I, V717L, L723P, K724N, and I716V, while E693G, E693K, D694N, and A692G. Furthermore, the E693delta deletion mutation promotes the production of synaptotoxic Aβ (18).

b) Presenilin-1 (PSEN-1) and Presenilin-2 (PSEN-2)

PSEN1 and PSEN2 genes are also autosomal dominant forms of EOAD, situated on chromosomes 14 and 1, respectively. PSEN-2 and PSEN-1 are homologous, with 67% similarity, with differences in the N-terminus and the hydrophilic region. The PSEN1 gene has more than 200 mutations, but the PSEN2 gene has an uncommon variant with less than 40 mutations. PSEN1 is a key protein that activates the -secretase complex and is essential for the synthesis of Aβ from APP. PSEN1 knockout mice demonstrated synaptic dysfunction and memory impairment, indicating that it plays an important role in the maintenance of memory and neurons. PSEN1 mutations can be mild, resulting in a single amino acid replacement, or severe, resulting in two amino acid alterations. Mutations in the PSEN1 gene enhance the ratio of Aβ42/Aβ40 via reducing Aβ40 levels. Sun et al. found that C410Y or L435F mutations in PSEN1 knock-in mice enhanced the Aβ42/Aβ40 ratio due to a larger drop in Aβ40 (19).

PSEN-2 mutations, on the other hand, are uncommon and have only a minimal impact in Aβ production. In the context of normal PSEN-1 alleles, any mutation in PSEN-2 might have a substantial influence on the Aβ 42/40 ratio, resulting in familial AD. Some PSEN-2 mutations, such as N141I, T122P, M239V, and M239I, cause a significant increase in γ-secretase activity with an increase in the Aβ-42 and Aβ 42/40 ratio levels, whereas others are rare polymorphisms that have no effect on the Aβ-42, -40, and Aβ 42/40 ratio levels and are not considered pathogenic mutations (20).

c) Apolipoprotein E (ApoE)

ApoE protein is a glycoprotein that is extensively expressed in the liver, brain astrocytes, and certain microglia and functions as a receptor-mediated endocytosis ligand for lipoprotein particles such as cholesterol, which is required for myelin synthesis and appropriate brain function. Because of single-nucleotide polymorphisms (SNPs) that induce alterations in the coding sequence, the ApoE gene on chromosome 19 has three isoforms: ApoE2, ApoE3, and ApoE4. The ApoE4 allele is a substantial risk factor for both EOAD and LOAD when compared to the ApoE2 and ApoE3 alleles, which are linked with a reduced risk and protective effect, respectively. ApoE4 is involved in Aβ deposition as a senile plaque and induces cerebral amyloid angiopathy (CAA), which is a hallmark for AD. ApoE4 has also been linked to vascular injury in the brain, which contributes to the etiology of Alzheimer's disease (21).

d) ATP Binding Cassette Transporter A1 (ABCA1)

Adenosine triphosphate (ATP)-binding cassette transporter A1 (ABCA1) is a member of the vast ABC transporter family that regulates cholesterol efflux in the circulation, like ApoAI, and into the brain, like ApoE. Furthermore, ABCA1 is a mediator for high-density lipoprotein (HDL) production and maintains the stability of ApoE lipidation, which highlights its function in atherosclerosis and cardiovascular disease. ABCA1 deficiency promotes amyloid plaques and prevents ApoE lipidation in the AD mouse model. Tangier illness, which is characterized by low levels of high-density lipoprotein (HDL) and ApoAI in plasma, cholesterol buildup in tissues, and AD pathogenesis, is caused by an ABCA1 mutation in humans (22).

e) Clusterin Gene (CLU) and Bridging Integrator 1 (*BIN1*)

In contrast to PSEN1, PSEN2, and APP mutations, which cause familial or EOAD, clusterin (CLU) and Bridging Integrator 1 (BIN1) genes are unique risk factors for LOAD. In 2009, Genome-Wide Association Studies (GWAS) found the CLU gene on chromosome 8, which is elevated in the cortex and hippocampus of AD brains, as well as AD cerebrospinal fluid (CSF) and plasma, making the CLU a prospective biomarker for AD. The CLU may play a protective function by interacting with A and boosting its clearance, or it may play a neurotoxic role by lowering A clearance. The A ratio values decide whether the CLU function is neuroprotective or neurotoxic.

BIN1 is a Bin-Amphiphysin-Rvs (BAR) adaptor protein that is involved in the formation of membrane curvature and other endocytosis biological processes. BIN1 contains multiple isoforms, some of which are present in the brain and interact with proteins such as clathrin, synaptojanin, and amphiphysin 1, and others of which control synaptic vesicle endocytosis. BIN1 was recently identified as the second most significant risk factor for LOAD after ApoE, where it plays a function in Aβ production as well as a tau and NFT pathology modulator (23).

f) Evolutionarily Conserved Signaling Intermediate in Toll pathway (ECSIT)

Aβ buildup in AD brains enhances protein oxidation, indicating the importance of mitochondria in Aβ cytotoxicity and AD pathogenesis. The ECSIT (evolutionarily conserved signaling intermediate in the Toll pathway) gene is found on chromosome 19 and has been linked to an increased risk of Alzheimer's disease. ECSIT encodes an adaptable protein that

acts as a cytoplasmic and signaling protein and is crucial for the mitochondrial respiratory complex's stability. The adaptor protein also plays a role in the activation of nuclear factor (NF)-κB, interferon regulatory factors (IRFs), and activating protein-1. It also helps to connect the immunological toll-like receptor (TLR), the homeostatic bone morphogenetic pathway (BMP), and the transforming growth factor-beta (TGF-b) pathways.

ECSIT interacts with mitochondrial proteins such as Lon protease homolog (LONP1) and glutaryl-CoA dehydrogenase (GCDH), which are involved in intra-mitochondrial proteolysis and redox signaling, respectively, before interacting with AD seed nitric oxide synthase (NOS3). Furthermore, investigations have revealed ECSIT interactions with the AD genes ApoE, PSEN-1, and PSEN-2. These interactions indicate the significance of ECSIT as a molecular link in oxidative stress, inflammation, and mitochondrial dysfunction in AD (24).

g) Estrogen Receptor Gene (ESR)

Both men and women are affected by Alzheimer's disease, however women account for roughly two-thirds of all cases. Several studies have found that women with Alzheimer's disease had greater mental impairment than males. Furthermore, genetic variations in some genes, such as the ApoE4 allele, considerably enhance AD risk in women compared to males. Other studies have found that the loss of ovarian hormones during menopause increases the risk of Alzheimer's disease in women. Estrogen regulates several activities in the brain, including neurotransmission, neural development, survival, protection against oxidative stress, reduction of Aβ peptide levels, and attenuation of tau hyperphosphorylation. Estrogen action is mediated by estrogen receptors (ERs), which can be intracellular, transmembrane, or membrane-bound. The two primary subtypes of these receptors are ERα and Erβ, which are encoded by two separate genes on chromosomes 6 and 14, respectively. ERα receptors are located in the hypothalamus and amygdala, while ERβ receptors are found in the hippocampus and cortex. Single nucleotide polymorphisms (SNPs) in the ERβ and ERα genes have the potential to alter exogenous estrogen in older women and effect cognitive aging. PvuII (rs9340799) and Xbal (rs223493) are two examples of SNPs discovered in ERα that are linked to AD and cognitive impairment. In addition, numerous SNPs in ERβ have been shown to enhance the risk of AD in women (25).

h) Other Genes

Vitamin D receptor (VDR) gene polymorphism, which changes the binding of vitamin D to its receptor and may induce neurodegenerative disorders and neuronal damage, is another gene polymorphism linked to an increased risk of AD. Furthermore, epigenetic variables such as DNA methylation, histone, and chromatin alterations have been shown to be implicated in AD (26).

Environmental Factors

Alzheimer's disease cannot be attributed to aging or genetic risk factors alone. Air pollution, diet, metals, infections, and other environmental risk factors can all produce oxidative stress and inflammation, increasing the probability of developing Alzheimer's disease. We have included the most significant environmental components and their connections with AD in this section (27).

a) Air Pollution

Air pollution is described as modifying the character of the atmosphere by the introduction of chemical, physical, or biological pollutants. It has been connected to respiratory and cardiovascular diseases, and it has recently been linked to Alzheimer's disease. In the United States, National Ambient Air Quality Standards (NAAQSs) have designated six air pollutants as harmful to human health: ozone (O3), nitrogen oxides (NOx), carbon monoxide (CO), particulate matter (PM), sulfur dioxide (SO2), and lead. Animal and cellular model studies have demonstrated that high levels of air pollution can induce damage to the olfactory mucosa and bulb, as well as the frontal brain region, similar to that found in Alzheimer's disease. In those exposed to air pollution, there is a link between oxidative stress, neuroinflammation, and neurodegeneration, as well as the formation of hyperphosphorylated tau and Aβ plaques in the frontal cortex. Air pollution can increase Aβ42 production and buildup while also impairing cognitive ability (28).

b) Diet

The number of studies on the effect of diet in AD has risen in recent years. Several dietary supplements, including antioxidants, vitamins, polyphenols, and fish, have been linked to a lower risk of Alzheimer's disease, but saturated fatty acids and a high calorie consumption have been linked to an increased risk. Food processing results in the degradation of heat-sensitive micronutrients (e.g., vitamin C and folates), the loss of large amounts of water, and the formation of toxic secondary products (advanced glycation end products, AGEs) from the non-enzymatic glycation of free amino groups in proteins, lipids, and nucleic acids. The harmful impact of AGEs is defined as their capacity to cause oxidative stress and inflammation by altering the structure and function of cell surface receptors and body proteins. Several investigations have found that higher AGEs serum levels are linked to cognitive loss and the advancement of Alzheimer's disease. The AGE receptor (RAGE) is found in a variety of tissues, including microglia and astrocytes, and has been shown to be overexpressed in the brains of Alzheimer's disease patients, where it functions as a transporter and a cell surface receptor for Aβ. Another risk factor for Alzheimer's disease is malnutrition. Nutritional deficiencies such as folate, vitamin B12,

and vitamin D may impair cognitive performance, in addition to the fact that people with Alzheimer's disease have difficulties eating and swallowing, which may increase the risk of malnutrition (29).

c) Metals

Metals may be found in nature and biological systems, and they are classified as bio-metals, which have a physiological purpose in living creatures (e.g., copper, zinc, and iron), and toxicological metals, which have no biological function (e.g., aluminum and lead). Aluminum is widely employed in a variety of sectors, including processed foods, cosmetics, medical preparations, medications, and others. Aluminum is attached to plasma transferrin and citrate molecules in the body, which can promote aluminum transfer to the brain. Al accumulates in the cortex, hippocampus, and cerebellum, where it interacts with proteins and causes misfolding, aggregation, and phosphorylation of highly phosphorylated proteins like tau protein, which is hallmark of Alzheimer's disease. Lead competes with the binding site of bio-metals such as calcium and can quickly pass the blood-brain barrier (BBB), where it can alter neuronal differentiation and synaptogenesis and cause serious harm. Acute lead exposure was linked to Alzheimer's disease, with an increase in β-secretase expression and Aβ buildup, according to research. Cadmium is a carcinogenic, water-soluble metal that may penetrate the BBB and induce neurological illnesses like Alzheimer's. Cadmium ions were shown to be implicated in the aggregation of Aβ plaques and the self-aggregation of tau in the AD brain. Metal findings support the concept that they are one of the risk variables implicated in the development of AD (30).

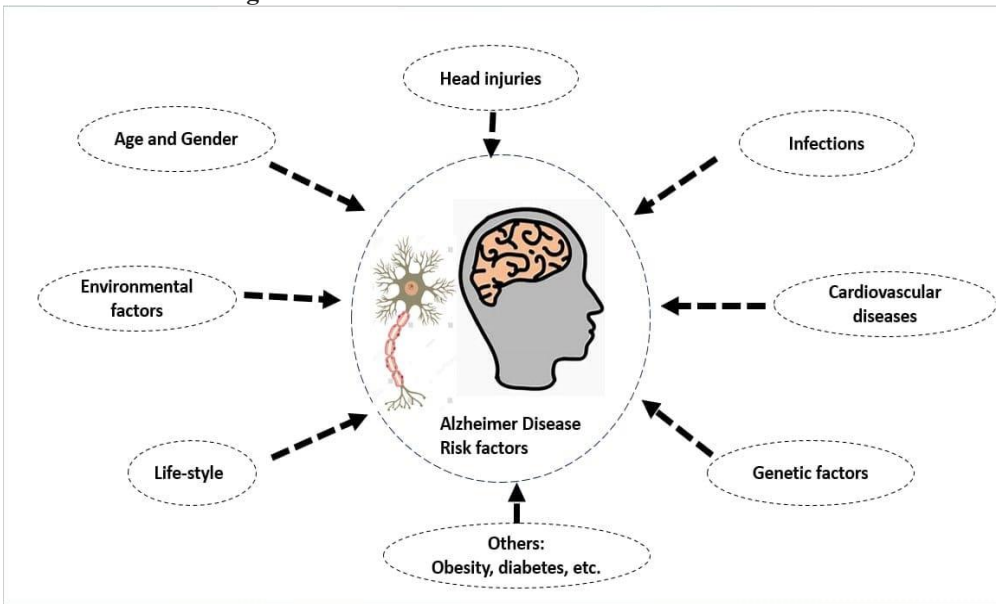
d) Infections

Chronic infections of the central nervous system (CNS) can result in the formation of A plaques and NFT, hence they are considered risk factors for Alzheimer's disease. Researchers discovered herpes simplex virus (HSV-1) DNA in ApoE-ε4 allele carriers, explaining the significant risk of developing AD. HSV-1 can proliferate in the brain, activating the inflammatory response and increasing Aβ deposition, causing in neurodegeneration and the slow development of AD. Miklossy and Balin's research, on the other hand, has highlighted the involvement of persistent bacterial infections in Alzheimer's disease. For example, syphilitic dementia caused by spirochete bacteria (Treponema pallidum) accumulating in the cerebral cortex created lesions resembling neurofibrillary tangles, leading to catastrophic neurodegenerative illnesses. Furthermore, the Chlamydia pneumonia bacteria can cause late-onset Alzheimer's disease by activating astrocytes and cytotoxic microglia, disrupting calcium regulation and apoptosis, resulting in cognitive function impairment, and increasing the risk of Alzheimer's disease (31).

7. Medical Factors

Alzheimer's disease is associated with a number of risk factors as represented in figure 4. To this list, older persons with AD are more likely to have medical disorders including cardiovascular disease (CVD), obesity, diabetes, and others. All of these disorders are linked to an increased risk of Alzheimer's disease (32).

Figure 4 The risk factors for Alzheimer's disease



a) Cardiovascular Disease (CVDs)

CVDs are recognized as a key risk factor for Alzheimer's disease, such as stroke, which is associated with an increased risk of dementia owing to brain tissue loss, which amplifies the degenerative impact and effects amyloid and tau pathology. Atrial fibrillation can also result in embolisms, which can lead to stroke and a decline in memory and cognitive functioning. Furthermore, heart failure impairs the heart's pumping capacity, resulting in inadequate blood flow to the

body and hypo-perfusion of the brain, which leads to hypoxia and neural damage. According to the coronary heart disease hypothesis, atherosclerosis, peripheral artery disease, hypo-perfusion, and emboli are all linked to an elevated risk of Alzheimer's disease. Hypertension is related with thickening of vessel walls and narrowing of the lumen, both of which restrict cerebral blood flow and, in chronic situations, may produce cerebral edema, all of which are risk factors for AD and CVD. CVD is a controllable risk factor, and by concentrating on its association with AD, a pathway to preventing and delaying the illness can be found (33).

b) Obesity and Diabetes

Obesity is defined as having too much body fat in a person as a result of ingesting more calories than they burn, and it may be quantified using the body mass index (BMI). Body fat accumulation is linked to reduced brain blood flow, which increases cerebral ischemia, memory loss, and vascular dementia. Obesity, a poor diet, and other factors can all lead to impaired glucose tolerance (IGT) or diabetes, all of which are characterized by hyperglycemia that damages peripheral tissues and blood vessels. Chronic hyperglycemia can impair cognition by increasing amyloid-beta buildup, oxidative stress, mitochondrial dysfunction, and neuroinflammation. Obesity is characterized by an increase in the release of pro-inflammatory cytokines from adipose tissue, which stimulates macrophages and lymphocytes and eventually leads to local and systemic inflammation. Insulin resistance, hyperinsulinemia, and, as a result, hyperglycemia are all promoted by this inflammation. Obesity is a well-known risk factor for type 2 diabetes, CVDs, and cancer, all of which have been linked to dementia and Alzheimer's disease. Inflammation in the brain generates an increase in microglia, which leads to decreased synaptic plasticity and poor neurogenesis. Microglia have the ability to influence insulin receptor substrate 1 (IRS-1) and prevent intracellular insulin signaling, which is critical for neurological health. As a result, changes in insulin action can cause Aβ buildup and inhibit tau protein breakdown associated with AD (34).

Treatment approaches for AD

Alzheimer's disease cases are currently predicted to be over 24 million globally, with the total number of dementia patients expected to more than 4 times by 2050. Despite the fact that Alzheimer's disease is a public health concern, only two kinds of medications are currently licensed to treat it: inhibitors of the cholinesterase enzyme (naturally occurring, synthetic, and hybrid variants) and antagonists of N-methyl D-aspartate (NMDA). Several physiological mechanisms in Alzheimer's disease damage Ach-producing cells, reducing cholinergic transmission through the brain. Acetylcholinesterase inhibitors (AChEIs), which are classed as reversible, irreversible, and pseudo-reversible, work by preventing cholinesterase enzymes (AChE and butyrylcholinesterase (BChE)) from breaking down ACh, resulting in increased ACh levels in the synaptic cleft. Overactivation of NMDAR, on the other hand, results in increased quantities of influxes Ca2+, which promotes cell death and synaptic dysfunction. NMDAR antagonist reduces overactivation of the NMDAR glutamate receptor and hence Ca2+ influx, and restores normal function. Despite their therapeutic impact, these two classes are only useful in treating the symptoms of Alzheimer's disease and do not cure or prevent the illness. Unfortunately, just a few clinical studies on Alzheimer's disease have been conducted in the recent decade, and the results have been disastrous. Several mechanisms have been postulated to explain AD pathophysiology in order to change its process and create effective therapies, including aberrant tau protein metabolism, β-amyloid, inflammatory response, and cholinergic and free radical damage.

Most AD modifiable risk factors, such as cardiovascular or lifestyle behaviors, may, on the other hand, be prevented without medical intervention. Physical exercise has been shown in studies to promote brain health and prevent AD by stimulating brain vascularization, plasticity, neurogenesis, and lowering inflammation by decreasing Aβ production, all of which result in improved cognitive performance in older adults. Furthermore, the Mediterranean diet (MD), intellectual exercise, and higher education may all slow the course of Alzheimer's disease and memory loss while increasing brain capacity and cognitive functioning. Several studies have shown that a multi-domain strategy involving lifestyle (diet, exercise, and cognitive training), depression of AD symptoms, and management of cardiovascular risk factors can improve or preserve cognitive performance and prevent new instances of AD in older people. We outline the currently existing medications and hypotheses for the development of novel AD therapeutics in this chapter (35).

Current therapies

The present Alzheimer's disease treatment is only symptomatic. The only four FDA-approved treatments for Alzheimer's disease are AChE inhibitors (donepezil, galantamine, and rivastigmine) and NMDA antagonists (memantine). Tacrine, a fifth AChE inhibitor, has been withdrawn off the market due to hepatotoxicity. The loss of cholinergic neurons, according to the cholinergic hypothesis, explains cognitive impairment and other symptoms of Alzheimer's disease. AChE inhibitors enhance cholinergic neurotransmission by inhibiting acetylcholine hydrolysis and thereby increasing synaptic levels. Donepezil, galantamine, and rivastigmine have all been demonstrated to be helpful in persons with mild to severe Alzheimer's disease. While their pharmacokinetics and pharmacodynamics differ, there is no significant difference in efficacy across the three medications. AChE inhibitors are generally well tolerated by patients. The most common side effects are gastrointestinal issues such as nausea, vomiting, diarrhea, and anorexia. The most current FDA-approved medicine, memantine, is a non-competitive NMDA antagonist. Its precise mechanism of action is uncertain, although it is thought to block glutamate's excitatory neurotoxicity. Memantine has a modest efficacy and safety profile when used as monotherapy in the treatment of moderate to severe Alzheimer's disease. Combination therapy with AChE inhibitors (typically added to an existing AChE inhibitory medicine) has benefits over non-combination therapy (36).

Future advanced therapy options

Due to the inefficiency of present medicines un regulating the progression of Alzheimer's disease, tremendous efforts have been made to find novel molecules with the potential to affect the course of the illness: disease-modifying medications. A search on Clinical trial.gov for ongoing Phase I through III interventional studies revealed 226 trials in progress at this moment. These prospective disease-modifying medicines primarily target the two pathological hallmarks of Alzheimer's disease: amyloid plaques (Aβ) and the NFT (tau-protein). As a result, we will divide future Alzheimer's disease medicines into two categories: anti-amyloid therapy and anti-tau therapy (37).

1. Anti-amyloid therapy

Anti-amyloid treatment is a type of Alzheimer's disease drug that targets the protein fragments that aggregate in the brain and form plaques, which is a defining feature of the illness. The most recent Alzheimer's disease drug to be approved is an anti-amyloid medication. They concentrate on what may cause the problem rather than just the symptoms. Anti-amyloid medications target the protein fragments that aggregate in your brain and form plaques, which is a hallmark of Alzheimer's disease. Acuranumab-avwa (Aduhelm) and lecanemab-irmb (Leqembi) are now available. They are not without controversy since they can cause brain enlargement and neither is widely available. Anti-amyloid medicines work by attaching to and removing beta-amyloid, a protein that builds plaques in the brain. Each medicine works differently and targets beta-amyloid at a different stage of plaque formation. The drugs have not been shown to impede or reverse development, nor have they been shown to increase cognitive performance (38).

1.1. Reduction of Aβ production

The activities of enzyme β-secretase (BACE1, β-site amyloid precursor protein cleaving enzyme 1) and γ-secretase appear to have a crucial role in Aβ production. Hence, their inhibition has been a potential strategy to reduce Aβ production (39).

1.2. Prevention of Aβ aggregation

The aggregation of Aβ in oligomers, fibrils, and deposition into amyloid plaques is thought to be the cause of synaptic dysfunction and neuronal death in Alzheimer's disease. Although amyloid plaques have been identified as the primary harmful species, they are very weakly associated to the severity of Alzheimer's disease. According to current studies, soluble oligomers are the most hazardous form of Aβ. As a result, anti-aggregation medicines are a sound technique in disease-modifying treatment. They bind to soluble Aβ peptides, preventing oligomerization and consequent neurotoxicity. Scyllo-inositol and tramiprosate have been explored as Aβ aggregation inhibitors throughout the years. Despite encouraging preclinical results, scyllo-inositol failed to demonstrate clinical benefit in a phase II trial of mild to moderate Alzheimer's disease patients. At the highest dosages, the results also indicated significant side consequences (infections and fatalities). A recent study found that the lowest dosage of scyllo-inositol (250 mg) has an acceptable safety profile. However, further study is needed to determine effectiveness. In a phase III trial of mild to moderate Alzheimer's disease patients, tamiprosate did not reveal a meaningful difference in cognitive scores between the treatment and control groups. A further reanalysis of the study data revealed therapeutic improvements in the ApoE4 homozygotic participant subgroup. ALZ-801, a tramiprosate prodrug, is currently being studied (40).

1.3. Promotion of Aβ clearance

Given that Aβ buildup and aggregation is the primary cause of the neurodegenerative process of Alzheimer's disease, increasing its clearance using particular anti-A antibodies is a sound strategy. In fact, immunotherapy targeting Aβ has been identified as the most promising treatment for slowing the course of Alzheimer's disease. This therapy may be separated into two approaches: inducing the immune system to produce its own antibodies or directly injecting foreign antibodies, known as active and passive immunization. Both methodologies have been extensively researched during the previous decade (41).

1.3.1. Active immunotherapy (vaccination)

By injecting Aβ or its fragments, active immunotherapy induces the patient's immune system to develop antibodies against Aβ. The first anti-Aβ vaccination to be clinically tested was AN-1792. AN-1792 is a synthetic pre-aggregated Aβ42 with an immunogenic adjuvant (QS-21) that is injected intramuscularly (IM). A phase II experiment including mild to severe Alzheimer's disease patients was halted in 2002 when 6% of the participants got aseptic meningoencephalitis. Because Aβ42 of AN-1792 contains a domain important for T-cell activation, this significant unfavorable impact is assumed to be produced by the immunological response of T-cells. Despite this, AN-1792 shown promising outcomes in the removal of amyloid plaques from the brain. As a result, a new series of active immunotherapy drugs based on Aβ peptides lacking the part responsible for T-cell activation has been produced. After demonstrating a generally benign profile and an acceptable antibody response in early studies, amilomotide (CAD106), consisting of several copies of a short segment of Aβ (A1-6), is now in phase II/III testing with preclinical AD subjects. Several phase II studies were conducted with vanutide cridificar (ACC-001), an N-terminal fragment of Aβ (A1-7). The findings indicated a satisfactory safety and tolerability profile. However, no significant variations in cognitive or functional ratings, as well as levels of CSF biomarkers, were seen between the treatment and control groups. The clinical testing of vanutide cridificar has been halted.

One of the first medications targeting the Aβ40 peptide was ABvac40, a C-terminal fragment of Aβ40. A phase I trial including mild to moderate Alzheimer's disease patients found that the vaccine was safe, well-tolerated, and elicited an adequate antibody response. As a result, a phase II trial is already recruiting individuals with prodromal Alzheimer's disease to evaluate clinical effectiveness (42).

1.3.2. Passive immunotherapy

The infusion of monoclonal antibodies directed against Aβ and/or its aggregated forms is used as passive immunotherapy. This method has received the greatest attention in clinical studies to far. Six antibodies have progressed to phase III trials: bapineuzumab, solanezumab, crenezumab, gantenerumab, aducanumab, and BAN2401. Unfortunately, until recently, the outcomes of the usage of these monoclonal antibodies have showed a lack of clinical benefit, despite modest success in lowering CSF biomarkers levels and Aβ plaques. The first two monoclonal antibodies tested in phase III trials were apineuzumab and solanezumab. Both medications failed to slow mild to moderate cognitive or functional deterioration. Concerns have been raised about the safety of bapineuzumab due to an increased incidence of amyloid-related imaging abnormalities (ARIA) in the therapy group. Based on these findings, bapineuzumab research was halted. Solanezumab, on the other hand, had a safer profile, with a decreased frequency of ARIA seen. This discrepancy might be explained by solanezumab's particular affinity to soluble Aβ rather than fibrils (insoluble) (43).

2. Anti-tau therapy

Over the last 25 years, anti-amyloid treatment has dominated research, but the lack of clinical effectiveness seen in recent clinical studies has raised doubts about that method. As a result, researchers are refocusing their attention on tau pathology. Although the function of tau protein is not fully known, investigations have shown that it plays a vital role in the assembly and stability of cytoskeletal microtubules. Furthermore, aberrant hyperphosphorylation of tau (p-tau) has been shown to impair its propensity to bind microtubules. This breakdown of the tau-microtubule connection causes microtubule malfunction and raises cytosolic p-tau levels, resulting in aggregation and the creation of NFT. NFT, which is made up of paired helical filaments of p-tau, as well as other aggregated forms, are linked to synapse dysfunction and neuronal death. Similarly, to Aβ, soluble oligomers appear to be the most damaging type of p-tau. According to the amyloid cascade theory, Aβ buildup causes tau disease. Several in vitro and in vivo investigations have shown that A precedes and promotes tau hyperphosphorylation through kinase activation. However, the dismal outcomes of anti-Aβ treatments led researchers to speculate that tau pathology may potentially play a role in the development of AD. Furthermore, the presence or accumulation of tau is more closely associated to the severity of cognitive impairment in AD than Aβ. As a result, the development of disease-modifying medicines targeting tau has gained prominence in recent years. Anti-tau therapy includes tau hyperphosphorylation and aggregation prevention, microtubule stability, and tau clearance promotion. (44).

2.1. Prevention of abnormal tau hyperphosphorylation

The aberrant tau protein hyperphosphorylation caused by an imbalance in the activities of phosphatases and kinases is regarded to be the crucial stage in tau pathology. Tau phosphorylation is mediated by a number of protein kinases. Glycogen synthase kinase 3-beta (GSK3β) appears to play the most essential part in this process, since its dysregulation is linked to the production of p-tau and consequent neurodegeneration in Alzheimer's disease. Thus, inhibiting GSK-3β has been proposed as a sensible technique in Alzheimer's disease treatment. Tideglusib is an irreversible GSK-3β inhibitor that has been shown in preclinical tests to reduce tau phosphorylation, Aβ deposition, and neuronal death. However, it did not delay cognitive or functional decline in a phase II study of mild to severe Alzheimer's disease patients. As a result, tideglusib research in Alzheimer's disease has been halted. Lithium is a well-established medication for bipolar illness, and its function in Alzheimer's disease has also been investigated because to its ability to inhibit GSK. (45).

2.2. Prevention of Tau aggregation

Tau aggregation spread and accumulation are linked to neuronal death and clinical impairment in Alzheimer's disease. In this regard, tau aggregation inhibition is a logical strategy in AD disease modification treatment. In vitro, the salt of the oxidized form of methylthioninium, methylthioninium chloride (commonly known as "methylene blue") inhibited tau aggregation. A phase II clinical trial found cognitive advantages in people with mild to severe Alzheimer's disease. However, there were limits in the absorption of the greatest dosage and low tolerability in the absence of meals. These discoveries led to the invention of leuco-methylthioninium bis (hydromethanesulfonate) (LMTM), a reduced derivative of methylene blue that is more stable and tolerable. (46).

2.3. Microtubule stabilization

Microtubules are engaged in a variety of biological functions. One of them is the mediation of the transport of proteins, organelles, synaptic vesicles, and other macromolecules across cells. Tau protein ordinarily stabilizes microtubules, however hyperphosphorylation causes it to lose its function. Microtubule malfunction in neurons and associated axonal transport impairment are hypothesized to play a critical role in AD neurodegeneration. Davunetide is a peptide that appears to stabilize microtubules in neurons and glial cells, while its specific mode of action is unknown. Davunetide advanced to clinical trials following the excellent outcomes of preclinical research. A phase II experiment with intranasal treatment in prodromal AD participants revealed an acceptable safety profile but no meaningful improvement in cognitive score.

Another microtubule stabilizer, epothilone D (BMS-241027), improved cognitive function while decreasing axonal degeneration in transgenic animal models of tau disease. (47).

2.4. Promotion of tau clearance

Following the failure of this technique in Aβ, tau immunotherapy has gained increased interest in recent years. Both active and passive vaccination procedures attempt to create or employ antibodies that precisely target abnormal tau protein conformers without reacting against normal tau protein (non-pathologic tau). Promoting the elimination of aberrant tau is thus predicted to lessen neuronal loss and clinical symptoms. Because tau aggregates typically develop inside neurons, there are some worries concerning anti-tau antibodies' ability to infiltrate neurons. Recent research has shown that antibodies may traverse the blood-brain barrier and enter neurons. This entrance is mostly accomplished by the Fc receptor (receptor-mediated endocytosis), but it can also occur via bulk endocytosis. Currently, the bulk of anti-tau treatments in clinical trials are immunotherapies. However, they are in the early phases of clinical development and have not yet reached phase III. Data is mostly derived from conference communications or news announcements issued by study sponsors (48).

2.4.1. Active immunotherapy

Anti-tau vaccinations stimulate patients' immune systems to produce antibodies against harmful versions of tau protein. Synthetic peptides that imitate pathological tau epitopes have been employed as antigen in this situation. AADvac1 was the first anti-tau vaccination to undergo clinical testing. It advanced to a phase II study in mild Alzheimer's disease after demonstrating a satisfactory safety profile in two phase I studies. The preliminary findings of this phase II study were reported in September 2019. AADvac1 was shown to be safe and well-tolerated, with positive immunogenicity (98.2% of patients acquired specific anti-tau antibodies). Furthermore, AADvac1 caused statistically significant alterations in blood and CSF indicators, showing that it has the ability to halt the course of tau pathology. These encouraging results support the progression to phase III. In preclinical investigations, ACI-35, another anti-tau vaccination, displayed an acceptable safety profile and a decrease in tau pathology indices. A phase I study with ACI-35 in mild to moderate Alzheimer's disease patients began in 2013, but no findings have been reported as of yet (49).

2.4.2. Passive immunotherapy

A monoclonal antibody directed against aberrant types of tau protein is administered during passive immunotherapy. Because this technique looks to be safer than tau vaccinations, it has received a lot of attention. Gosuranemab, Tilavonemab, Semorinemab, and Zagotenemab are the four anti-tau antibodies that have achieved phase II studies. In two phase I studies, gosuranemab (BIIB092) was shown to be safe and well-tolerated. Gosuranemab is now being investigated in a phase II study with prodromal to moderate Alzheimer's disease patients. The research is scheduled to last until 2024. Tilavonemab (ABBV-8E12) is another anti-tau monoclonal antibody. AbbVie initiated a phase II trial based on the positive safety profile demonstrated in the phase I trial. The experiment aims to evaluate the effectiveness and safety of tilavonemab in individuals with prodromal to moderate Alzheimer's disease and is scheduled to conclude in 2021. An extension study of this phase II experiment was also launched with the goal of evaluating long-term safety and tolerability. Another anti-tau antibody, Semorinemab (RO7105705), began a phase I study in 2016. Although the trial findings have not been publicly published, a satisfactory safety profile was presented at a conference in 2017.

These findings prompted Genentech to initiate two phase II studies. One trial is enrolling prodromal to mild Alzheimer's patients, while the other is recruiting intermediate Alzheimer's patients. The studies are expected to be finished in 2022 and 2023, respectively. The phase I trials for zagotenemab (LY3303560) were just completed, although the data have yet to be released. Zagotenemab is now being tested in a phase II study with prodromal to moderate Alzheimer's disease patients, which is scheduled to be completed in 2021. Other anti-tau antibodies in phase I studies include RG7345, UCB0107, JNJ-63733657, and BIIB076 (50).

11. Conclusion

For almost three decades, researchers have focused on the amyloid hypothesis. So far, medicines targeting Aβ have failed to demonstrate clinical effectiveness, raising doubts about this notion. Even the good findings of aducanumab are unclear given the scant data supplied by Biogen thus far. The most often cited reason for these disappointing results is that the medications were evaluated in the late stages of Alzheimer's disease, when the condition is incurable. However, studies undertaken in the early stages of Alzheimer's disease (prodromal) or even in preclinical Alzheimer's disease revealed no clinical effect. Some Aβ immunotherapies are still being evaluated in clinical trials, and the findings are expected.

Despite these shortcomings, evidence of Aβ aggregates in post-mortem analysis, neuroimaging diagnosis, and data from genetic and biochemical investigations leads researchers to believe that the Aβ function in AD cannot be ruled out. However, it is evident that novel targets and therapeutic procedures are required. Tau pathology appears to have a key role in AD neurodegeneration rather than being a secondary effect of the amyloid cascade. As a result, tau-targeting medicines have garnered more interest in recent years. However, the majority of anti-tau medicines are still in the early phases of clinical studies. Another new technique recommended by several writers is combination treatment. Given the intricate etiology of Alzheimer's disease and the possible synergy between Aβ and tau, combining these therapies may be more

beneficial than monotherapy. Furthermore, the involvement of glial cells (mostly astrocytes and microglia) in AD pathogenesis must be elucidated since it may offer a possible new therapy.

In conclusion, while promising medications are now being tested, more study is needed to better understand the pathophysiology of Alzheimer's disease and, as a result, to identify novel biomarkers and targets that will allow the creation of really disease-modifying therapies (51).

Consent for publication
Not applicable.

Funding
None.

Conflict of interest
The authors declare no conflicts of interest, financial or otherwise.

Acknowledgements
Declared none.

References
1. Kumar A, Sidhu J, Goyal A, Tsao JW. Alzheimer Disease. 2022 Jun 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.
2. Vermunt L, Sikkes SAM, van den Hout A, Handels R, Bos I, van der Flier WM, Kern S, Ousset PJ, Maruff P, Skoog I, Verhey FRJ, Freund-Levi Y, Tsolaki M, Wallin ÅK, Olde Rikkert M, Soininen H, Spiru L, Zetterberg H, Blennow K, Scheltens P, Muniz-Terrera G, Visser PJ; Alzheimer Disease Neuroimaging Initiative; AIBL Research Group; ICTUS/DSA study groups. Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. Alzheimers Dement. 2019 Jul;15(7):888-898. doi: 10.1016/j.jalz.2019.04.001. Epub 2019 Jun 1.
3. Tang, Y., Lutz, M. W., & Xing, Y. (2019). A systems-based model of Alzheimer's disease. Alzheimer Dement, 15(1), 168–171. https://doi.org/10.1016/j.jalz.2018.06.3058
4. Maccioni, R. B., González, A., Andrade, V., Cortés, N., Tapia, J. P., & Guzmán-Martínez, L. (2018). Alzheimer´s Disease in the Perspective of Neuroimmunology. The open neurology journal, 12, 50–56.
5. Nebel, R. A., Aggarwal, N. T., Barnes, L. L., Gallagher, A., Goldstein, J. M., Kantarci, K., Mallampalli, M. P., Mormino, E. C., Scott, L., Yu, W. H., Maki, P. M., & Mielke, M. M. (2018). Understanding the impact of sex and gender in Alzheimer's disease: A call to action. Alzheimer's & dementia: the journal of the Alzheimer's Association, 14(9), 1171–1183.
6. Chaudhary K, Patel MM, Mehta PJ. Long-Acting Injectables: Current Perspectives and Future Promise. Crit Rev Ther Drug Carrier Syst. 2019;36(2):137-181.
7. Ridge, P. G., Ebbert, M. T., & Kauwe, J. S. (2013). Genetics of Alzheimer's disease. BioMed research international, 2013, 254954.
8. Jagust W. Imaging the evolution and pathophysiology of Alzheimer disease. Nat Rev Neurosci. 2018 Nov;19(11):687-700.
9. Chen, M. K. et al. Assessing synaptic density in Alzheimer disease with synaptic vesicle glycoprotein 2A positron emission tomographic imaging. JAMA Neurol.
10. Small, S. A., Schobel, S. A., Buxton, R. B., Witter, M. P. & Barnes, C. A. A pathophysiological framework of hippocampal dysfunction in ageing and disease. Nat. Rev. Neurosci. 12, 585–601 (2011).
11. Jack, C. R. Jr. et al. Tracking pathophysiological processes in Alzheimer’s disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–216 (2013).
12. Hardy, J. & Selkoe, D. J. The amyloid hypothesis of Alzheimer’s disease: progress and problems on the road to therapeutics. Science 297, 353–356 (2002).
13. Abubakar MB, Sanusi KO, Ugusman A, Mohamed W, Kamal H, Ibrahim NH, Khoo CS, Kumar J. Alzheimer's Disease: An Update and Insights into Pathophysiology. Front Aging Neurosci. 2022 Mar 30; 14:742408.
14. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24):5789.
15. Armstrong R.A. Risk factors for Alzheimer’s disease. *Folia Neuropathol.* 2019; 57:87–105.
16. Hou Y., Dan X., Babbar M., Wei Y., Hasselbalch S.G., Croteau D.L., Bohr V.A. Ageing as a risk factor for neurodegenerative disease. *Nat. Rev. Neurol.* 2019;15: 565–581.
17. Van Cauwenberghe C., Van Broeckhoven C., Sleegers K. The genetic landscape of Alzheimer disease: Clinical implications and perspectives. *Genet. Med. Off. J. Am. Coll. Med Genet.* 2016;18:421–430.
18. Li N.M., Liu K.F., Qiu Y.J., Zhang H.H., Nakanishi H., Qing H. Mutations of beta-amyloid precursor protein alter the consequence of Alzheimer’s disease pathogenesis. *Neural Regen. Res.* 2019;14:658–665.

19. Dai M.H., Zheng H., Zeng L.D., Zhang Y. The genes associated with early-onset Alzheimer's disease. *Oncotarget.* 2018;9:15132–15143.
20. Cai Y., An S.S., Kim S. Mutations in presenilin 2 and its implications in Alzheimer's disease and other dementia-associated disorders. *Clin. Interv. Aging.* 2015;10:1163–1172.
21. Giau V.V., Bagyinszky E., An S.S., Kim S.Y. Role of apolipoprotein E in neurodegenerative diseases. *Neuropsychiatr. Dis. Treat.* 2015;11:1723–1737.
22. Koldamova R., Fitz N.F., Lefterov I. ATP-binding cassette transporter A1: From metabolism to neurodegeneration. *Neurobiol. Dis.* 2014;72 Pt A:13–21.
23. Andrew R.J., De Rossi P., Nguyen P., Kowalski H.R., Recupero A.J., Guerbette T., Krause S.V., Rice R.C., Laury-Kleintop L., Wagner S.L., et al. Reduction of the expression of the late-onset Alzheimer's disease (AD) risk-factor BIN1 does not affect amyloid pathology in an AD mouse model. *J. Biol. Chem.* 2019;294:4477–4487.
24. Mi Wi S., Park J., Shim J.H., Chun E., Lee K.Y. Ubiquitination of ECSIT is crucial for the activation of p65/p50 NF-kappaBs in Toll-like receptor 4 signaling. *Mol. Biol. Cell.* 2015;26:151–160.
25. Goumidi L., Dahlman-Wright K., Tapia-Paez I., Matsson H., Pasquier F., Amouyel P., Kere J., Lambert J.C., Meirhaeghe A. Study of estrogen receptor-alpha and receptor-beta gene polymorphisms on Alzheimer's disease. *J. Alzheimer's Dis. Jad.* 2011;26:431–439. doi: 10.3233/JAD-2011-110362.
26. Khorram Khorshid H.R., Gozalpour E., Saliminejad K., Karimloo M., Ohadi M., Kamali K. Vitamin D Receptor (VDR) polymorphisms and late-onset Alzheimer's disease: An association study. *Iran. J. Public Health.* 2013;42:1253–1258.
27. Grant W.B., Campbell A., Itzhaki R.F., Savory J. The significance of environmental factors in the etiology of Alzheimer's disease. *J. Alzheimer's Dis. Jad.* 2002;4:179–189.
28. Croze M.L., Zimmer L. Ozone atmospheric pollution and Alzheimer's disease: From epidemiological facts to molecular mechanisms. *J. Alzheimer's Dis. Jad.* 2018;62:503–522.
29. Koyama A., Hashimoto M., Tanaka H., Fujise N., Matsushita M., Miyagawa Y., Hatada Y., Fukuhara R., Hasegawa N., Todani S., et al. Malnutrition in Alzheimer's disease, dementia with lewy bodies, and frontotemporal lobar degeneration: Comparison using serum albumin, total protein, and hemoglobin level. *PLoS ONE.* 2016;11:e0157053.
30. Huat T.J., Camats-Perna J., Newcombe E.A., Valmas N., Kitazawa M., Medeiros R. Metal toxicity links to Alzheimer's disease and neuroinflammation. *J. Mol. Biol.* 2019;431:1843–1868.
31. Muzambi R., Bhaskaran K., Brayne C., Smeeth L., Warren-Gash C. Common bacterial infections and risk of incident cognitive decline or dementia: A systematic review protocol. *BMJ Open.* 2019;9:e030874.
32. Santos C.Y., Snyder P.J., Wu W.C., Zhang M., Echeverria A., Alber J. Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis. Alzheimer's Dement. 2017;7:69–87.
33. De Bruijn R.F., Ikram M.A. Cardiovascular risk factors and future risk of Alzheimer's disease. BMC Med. 2014;12:130.
34. Anjum I., Fayyaz M., Wajid A., Sohail W., Ali A. Does obesity increase the risk of dementia: A literature review. Cureus. 2018;10:e2660.
35. Crous-Bou M., Minguillon C., Gramunt N., Molinuevo J.L. Alzheimer's disease prevention: From risk factors to early intervention. Alzheimer's Res. Ther. 2017;9:71.
36. Alzheimer's Association, 2020. 2020 Alzheimer's disease facts and figures. Alzheimer's Dementia 391–460.
37. Selkoe, D.J., 2019. Alzheimer disease and aducanumab: adjusting our approach. Nat. Rev. Neurol. 15, 365–366.
38. Lane, C.A., Hardy, J., Schott, J.M., 2018. Alzheimer's disease. Eur. J. Neurol. 25, 59–70.
39. Henley, D., Raghavan, N., Sperling, R., Aisen, P., Raman, R., Romano, G., 2019. Preliminary results of a trial of atabecestat in preclinical Alzheimer's disease. N. Engl. J. Med. 380, 1483–1485.
40. Penke, B., Szucs, M., Bog´ ar, F., 2020. Oligomerization and conformational change turn monomeric β-amyloid and tau proteins toxic: their role in Alzheimer's pathogenesis. Molecules 25.
41. Plotkin, S.S., Cashman, N.R., 2020. Passive immunotherapies targeting Aβ and tau in Alzheimer's disease. Neurobiol. Dis. 105010.
42. Plotkin, S.S., Cashman, N.R., 2020. Passive immunotherapies targeting Aβ and tau in Alzheimer's disease. Neurobiol. Dis. 105010.
43. Klein, G., Delmar, P., Voyle, N., Rehal, S., Hofmann, C., Abi-Saab, D., Andjelkovic, M., Ristic, S., Wang, G., Bateman, R., Kerchner, G.A., Baudler, M., Fontoura, P., Doody, R., 2019. Gantenerumab reduces amyloid-β plaques in patients with prodromal to moderate Alzheimer's disease: a PET substudy interim analysis. Alzheimer's Res. Ther. 11, 1–12.
44. Barbier, P., Zejneli, O., Martinho, M., Lasorsa, A., Belle, V., Smet-Nocca, C., Tsvetkov, P. O., Devred, F., Landrieu, I., 2019. Role of tau as a microtubule-associated protein: structural and functional aspects. Front. Aging Neurosci.
45. Lauretti, E., Dincer, O., Pratico, ` D., 2020. Glycogen synthase kinase-3 signaling in Alzheimer's disease. Biochim. Biophys. Acta Mol. Cell Res. 1867
46. Penke, B., Szucs, M., Bog´ ar, F., 2020. Oligomerization and conformational change turn monomeric β-amyloid and tau proteins toxic: their role in Alzheimer's pathogenesis. Molecules 25.
47. Venkatramani, A., Panda, D., 2019. Regulation of neuronal microtubule dynamics by tau: implications for tauopathies. Int. J. Biol. Macromol. 133, 473–483.

48. Sandusky-Beltran, L.A., Sigurdsson, E.M., 2020. Tau immunotherapies: lessons learned, current status and future considerations. Neuropharmacology 175.
49. Bittar, A., Bhatt, N., Kayed, R., 2020. Advances and considerations in AD tau-targeted immunotherapy. Neurobiol. Dis. 134, 1–26.
50. Boxer, A.L., Qureshi, I., Ahlijanian, M., Grundman, M., Golbe, L.I., Litvan, I., Honig, L.S., Tuite, P., McFarland, N.R., O'Suilleabhain, P., Xie, T., Tirucherai, G.S., Bechtold, C., Bordelon, Y., Geldmacher, D.S., Grossman, M., Isaacson, S., Zesiewicz, T., Olsson, T., Muralidharan, K.K., Graham, D.L., O'Gorman, J., Haeberlein, S.B., Dam, T., 2019. Safety of the tau-directed monoclonal antibody BIIB092 in progressive supranuclear palsy: a randomised, placebo-controlled, multiple ascending dose phase 1b trial. Lancet Neurol. 18, 549–558.
51. De Strooper, B., Karran, E., 2016. The cellular phase of alzheimer's disease. Cell 164, 603–615.