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ALZHEIMERS UNVEILED – A HOLISTIC JOURNEY THROUGH SCIENCE AND CARE

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ABSTRACT

Alzheimer's disease (AD) represents a significant and expanding global health challenge, with projections indicating a doubling of affected individuals every five years by 2050. This neurodegenerative disorder is delineated by the accumulation of amyloid plaques, neurofibrillary tangles, and subsequent neuronal and synaptic degeneration, leading to progressive cognitive decline. While the exact etiology of AD remains elusive, age, genetics, cardiovascular disease, traumatic brain injury, type 2 diabetes mellitus, obesity, and environmental factors are recognized as key risk factors. This review provides a comprehensive overview of AD, encompassing epidemiology, pathogenesis, risk factors, clinical stages, and treatment options. Despite the absence of a cure, current pharmacological interventions aim to alleviate symptoms and improve quality of life. Emerging disease-modifying treatments targeting amyloid-beta offer promise for slowing disease progression. Understanding the multifaceted nature of AD is essential for developing effective interventions and mitigating its devastating impact on individuals, families, and society.

Keywords: Alzheimer's disease, Amyloid plaques, Neurodegeneration, risk factors, disease - modifying treatments

INTRODUCTION

Alzheimer's disease (AD), credited to the German physician Alois Alzheimer, stands as the predominant form of dementia. It is typified by a slowly advancing neurodegenerative illness that results in neuritic plaques and neurofibrillary tangles due to the accumulation of amyloid-beta peptide (Aβ) in the neocortical structures and medial temporal lobe, the two most afflicted parts of the brain **[17]**. A decline in cognitive function can stem from various conditions, such as infections, alcoholism, malnourishment, low vitamin B12, tumours, abnormalities in the pulmonary and circulatory systems, which lower the amount of oxygen reaching the brain, and cerebral disorders like Alzheimer's disease (AD) **[53] [45]**. Around 50 million people worldwide suffer with AD today; by 2050, that figure is predicted to have quadrupled every five years to 152 million. The annual global costs of AD are projected to exceed $1 trillion, impacting individuals, their families, and the economy. There is yet no known treatment for Alzheimer's disease however some drugs can help with symptoms **[58] [34]**. A succinct synopsis of AD pathogenesis, etiology, risk factors, and current treatments is intended to be provided by this review.

EPIDEMIOLOGY

Global estimates predict that by mid-century, the number of individuals with dementia will reach 152 million, with the most substantial rise in cases anticipated in low- and medium-income countries **[43]**. The number of Americans over 65 who suffer from Alzheimer's disease (AD) could raise significantly from 5.8 million to 13.8 million by 2050, according to 2020 Alzheimer's disease data [1]. There has been a noticeable rise in the prevalence of AD during the last few decades, according to community-dwelling studies carried out in China and Japan **[40] [15]**. Women dominated the world in particular not just because they lived longer lives than men, but also because their prevalence rates within specific age groups were 1.17 times higher than those of men’s, and their age-adjusted death rate was also higher **[38]**. Moreover, Alzheimer's disease has emerged as the fifth most common cause of death in older Americans in 2018 with death tolls rising by 146.2% between 2000 and 2018 **[1]**. Notably, there would be a greater mental strain and adverse emotional effects on carers. As a result, providing care for the AD population will place a heavy and unsustainable strain on society and families **[1]**.

Well-being is often the main objective of AD care. Confusion-inducing symptoms and concerns would appear in multiple domains for AD patients. Additionally, some epidemiological Extensive research has demonstrated that Environmental and behavioral factors significantly contribute to the etiology and progression of the disease. Since preexisting conditions are more common in AD patients than in people their own age, maintaining physical health is crucial to safeguarding cognitive function. Furthermore, some risk factors may both be thought of as AD symptoms and as variables that lead to the development of AD. Reverse causality may concurrently be responsible for this. Consequently, it is critical to have an accurate diagnosis for people who are experiencing cognitive dysfunction **[34]**.

PATHOGENESIS

The four primary neuropathologic features of AD are intracellular neurofibrillary tangles, **[7]**. extracellular amyloid plaque, synaptic deterioration, and neuronal death. According to the amyloid cascade theory, a build-up of amyloid plaques obstructs synaptic function and sets off a sequence of subsequent events that result in intra- and interneuronal dysfunction and, eventually, death of the cell **[56]**.

1. Amyloid plaques

B-amyloid protein (Aβ) is present in every amyloid plaque. When β and γ-secretase cleaves APP, an amino acid peptide known as Aβ is created. Ab1e40 and Ab1e42 are the primary byproducts of this cleavage. A relative excess of Ab1e42 makes amyloid more likely to organize into fibrils and oligomers, which eventually form amyloid plaques. However, a number of lines of evidence point to the possibility that AD may have more than one origin besides amyloid plaques

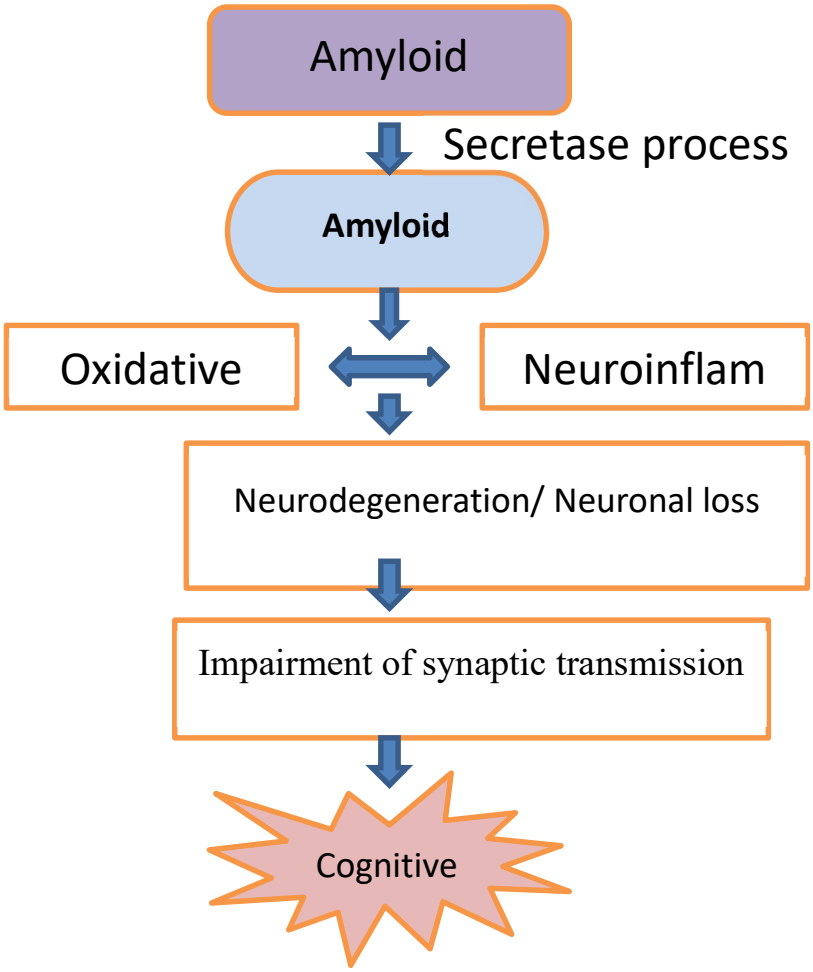

Figure 1: Pathogenesis of Alzheimer's disease

2. NFTs

Tau is one protein that plays a role in microtubule assembly. It is an essential component for healthy neuronal development and axonal growth. The hyperphosphorylated tau proteins that form helical filamentous NFT are mostly found in neurons located in the lateral parietotemporal area, the frontal association cortices, and the mesial temporal lobe, particularly in the hippocampus. NFT appears to play a crucial part in the pathophysiology of AD, as evidenced by the link between tau NFT density and location and the severity and symptoms of AD dementia **[7]**. According to the amyloid cascade theory, tau pathogenic changes result from Aβ deposition, yet research indicates that tau can also cause neurodegeneration on its own when it acts alone. Therefore, it is plausible that tau and Aβ work in concert to induce AD and intensify the deleterious effects of one another **[50]**.

3. Synapse and Neuron Loss

Acetylcholine (Ach) synthesis and release are reduced consequently destruction of neuron in the nucleus basalis of Meynert brought on by Aβ plaque in AD. Additionally, acetylcholinesterase activity is elevated, muscarinic acetylcholine signaling pathways are disrupted, and cholinergic signaling and function are compromised. These alterations cause glutamate neurotoxicity by indirectly impairing the action of the NMDA receptor. Due to the basal ganglia's concentration of plaque, executive function, memory, neocortex and portions of the temporal lobe are impacted **[10]**. Loss of locus ceruleus neuron and brainstem median raphe causes deficiencies in norepinephrine and serotonin, respectively. Dysphoria and sleeplessness in AD are brought on by aberrant brain adrenergic and serotonergic activity **[56]**.

CAUSES OF AD

The pathogenic changes (Aβ, NFTs, and synaptic loss) linked to Alzheimer's disease are presently unknown in their cause. There are several theories explaining AD, but only two are considered to be major: one proposes that modifications in the production and processing of amyloid proteins are the main cause of the disease, while another suggests that cholinergic dysfunction is a significant risk factor. As of yet, the pathophysiology of AD is not explained by an acknowledged hypothesis **[5] [2]**.

1. Cholinergic hypothesis

The cholinergic hypothesis of Alzheimer's disease was suggested due to the crucial involvement of ACh in cognitive processes. The cholinergic neuron's cytoplasm contains the ChAT enzyme, which transforms acetyl-coenzyme A and choline into acetylcholine (ACh). The vesicular acetylcholine transporter (VAChT) facilitates the transport of ACh to synaptic vesicles. In the brain, Acetylcholine is essential for learning, memory, attention, processing of sensory data, and other physiological processes. Cholinergic neuron degeneration has been found to be a hallmark of AD, leading to alterations in cognition and decline of memory. According to theory, B-amyloid affects cholinergic neurotransmission, which lowers choline absorption and releases ACh. According to research findings, amyloid fibrils and cholinergic synaptic loss are linked to the neurotoxicity of Aβ oligomers and the Aβ peptides and AChE interactions. Other factors that contribute to the development of Alzheimer disease include a decrease in nicotinic and muscarinic (M2) Ach receptors, which are found on presynaptic cholinergic terminals, and a decline in excitatory amino acid (EAA) neurotransmission, which is

characterized by markedly decreased D-aspartate uptake and glutamate concentration in various regions of cortex of AD brains. Furthermore, scopolamine and other cholinergic receptor antagonists have been demonstrated to trigger amnesia. To counteract this impact, substances that increase acetylcholine synthesis can be utilized **[6] [24] [36]**.

Therefore, the three concepts that form the basis of the cholinergic hypothesis are as follows: reduced levels of cortical cholinergic innervation originating from the nucleus basalis of Meynert (NBM) in the basal forebrain; severe neurodegeneration of this neuronal source; and the function of cholinergic antagonists in memory loss as opposed to agonists' opposite impact **[25]**.

2. Amyloid hypothesis

Decades of research revealed a strong correlation between aberrant -sheet deposition in the central nervous system and dementia, leading to the development of the amyloid hypothesis. But amyloid plaques (AP) were also discovered to gradually develop in normal, healthy brains with ageing, which begs the question: Is Amyloid plaque build up the cause of onset of AD or not?? Therefore, the amyloid hypothesis remains the most widely recognised pathogenic explanation for inherited AD (IAD), despite the fact that a number of theories have lately been proposed addressing the non-inherited kind of AD (NIAD). The Aβ peptides (Aβ40 and Aβ42) aggregation is thought to be caused by the amyloid hypothesis, which states that ageing or pathological conditions decrease the amount of β and γ –secretase capacity to break down Aβ, which is produced from APP. Elevating the Aβ42/Aβ40 ratio results in the development of Aβ amyloid fibrils, that subsequently result in tau pathology and neurotoxicity, neurodegeneration, and death of neuronal cells. The catabolism and anabolism of Aβ have been found to be impacted by risk factors for Alzheimer's disease and mutation in several genes, including APP, PSEN1, and PSEN2. This results in an Aβ build up and a rapid development of neurodegeneration **[42] [27] [47]**.

RISK FACTORS OF AD

1. Age

The principal risk factor for Alzheimer's disease is definitely becoming older. Less frequently do younger people get this condition; most cases of AD begin after the age of 65 **[23]**. A number of cell systems and organ are involved in the complex, irreversible process of ageing, which also include the shrinkage of volume and mass of the brain, the decline in synapses, and the

swelling of ventricles in certain regions due to NFT and SP deposition. It can be hard to differentiate between cases of early ons*et al*zheimer's disease and those of normal ageing due to the presence of a number of conditions that can develop with ageing, such as, cholesterol dyshomeostasis, dysfunction of mitochondria, depression, glucose hypometabolism and decline in cognition **[48] [26]**. Two categories can be distinguished by the age at which AD manifests itself: early-onset AD (EOAD), which represents only 1-6% of cases and is incredibly rare; the majority of cases in this category are familial AD, which is characterized by the presence of multiple AD cases in multiple generations and can manifest in individuals as young as 30 or as old as 65. Individuals with onset ages over 65 are more likely to have the second type of AD, which is referred to as late-onset AD (LOAD). Both forms of AD can affect people, depending on whether they come from a family with a favorable history of AD or not **[8]**.

2. Genetics

According to Ballard *et al*. (2011), genetics is responsible for around 70% of the risk of developing AD. Apolipoprotein E gene variation, especially the existence of the ε4 allele, is primarily related to late-form AD; in contrast, early AD is often resulting from mutations in the PSEN1, PSEN2 and APP (genes of, Presenilin 1, 2 and amyloid precursor protein respectively) **[21] [12]**.

In the APP gene (chromosome 21q21), over 30 dominant mutations have already been identified; these mutations are linked to approximately 15% of early-onset autosomal dominant AD cases. Eighty percent of cases of AD with an early onset are related to mutations in the PSEN1 gene (chromosome 14q24.3), and five percent of cases are related to PSEN2 mutations (chromosome 1q31–q42) **[13]**.

The Aβ42:Aβ40 ratio is elevated by most mutations in the APP gene and PSEN1.This can be credited to either reduction in Aβ40 or an elevation in Aβ42 expression. This dysregulation promotes the amyloidogenic cascade by promoting early Aβ deposition in brain tissue **[21]**. Campion *et al*.'s (1999) research suggests that additional genes may be implicated in the pathophysiology of early-onset AD in addition to APP, PSEN1, and PSEN2 **[14]**.

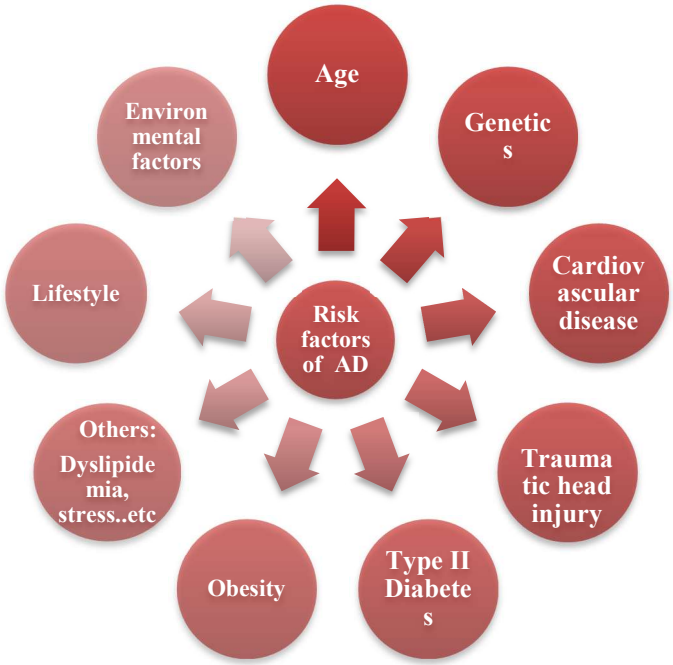

Figure 2: Risk factors of AD

3. Cardiovascular disease

It is well known that CVDs pose a significant risk for AD. Examples of these include stroke, which increases the risk of dementia by causing a loss of tissue of neuron, which exacerbates the degenerative effect and affects the pathologies of tau and amyloid. In addition to causing emboli, atrial fibrillation also affects memory and cognition and raises the possibility of stroke. In addition, heart failure hinders the heart's capacity to pump blood throughout the body, and brain's hypo-perfusion results in hypoxia and neurological harm. The coronary heart disease theory links peripheral artery disease, emboli, hypo-perfusion and atherosclerosis to an elevated risk of AD. In addition to reducing blood flow to the brain, hypertension is linked to thickening of the artery walls, lumen constriction, and, in chronic situations, cerebral edoema. These conditions all serve as risk factors for CVD and AD. Since the cardiovascular disease is a controllable risk factor, a strategy to delay and prevent AD can be found by concentrating on how the two conditions are related **[49] [16]**.

4. Traumatic brain injury

In both the Swedish research and the Danish trial, participants who had experienced traumatic injury of brain had a higher AD developing risk. These findings may have been reinforced by specific findings about TBI, such as TBI involving the skull or spine, younger individuals with the injury, and severe and multiple TBIs **[19] [39]**. Based on their death certificates, athletes who had

sustained repeated head injuries were more at risk of dying from AD **[35]**. Moreover, women with traumatic brain injuries (TBI) had an increased incidence of dementia among US military veterans **[57]**. Positively, stain medications, particularly rosuvastatin, may lower the incidence of dementia in patients who have had concussions due to their possible neuroprotective properties **[46]**. Therefore, additional research is needed to clarify the likelihood that persons with TBI would develop AD and to develop treatment plans aimed at reducing the likelihood and severity of AD. The public has to take precautions to appropriately safeguard their heads from accidents when participating in risky activities or jobs, given the detrimental consequences that traumatic brain injury (TBI) has on cognition.

5. Type II DM

The increased risk of AD is clearly linked to Type 2 diabetes mellitus, according to epidemiological studies. Various mechanisms have been anticipated to explain this association, involving insulin deficiency and resistance, affected insulin receptor, hyperglycemia toxicity, negative impact from end products advanced glycation, vascular inflammation, and cerebrovascular damage **[33]**.

It was possible to show through the use of animal models that insulin resistance or insufficiency can promote the activity of γ and β-secretase in addition to enhancing a decrease in the clearance of Aβ, which causes an accumulation of the protein in brain tissue. Hyperphosphorylation of tau protein, which results in NFT production, can still be caused by insulin shortage or resistance. Insulin receptor autophosphorylation and activation are caused by the binding of insulin and growth factor like insulin. The tau protein's phosphorylation is dependent on the phosphorylation and inhibition of enzyme glycogen synthase kinase 3β (GSK3β), that is mediated by the enzyme phosphoinositide 3-kinase (PI3K), that is phosphorylated when this receptor is activated. Hence, aberrant GSK3β activation resulting from insulin shortage or resistance raises the production of p-tau **[28]**.

Apart from the previously mentioned mechanisms, studies have demonstrated that advanced glycation end products (AGEs) trigger the processing of APP by upregulating the expression of complexes β and γ-secretases (BACE and PSEN1), a procedure that results in the production of reactive oxygen species, and they also induce neuronal death by initiating pathways that cause cell death **[29]**. Furthermore, Aβ peptide can

undergo non-enzymatic glycation, which makes it a more neurotoxic advanced glycation end product than its counterpart that is not glycated **[32]**.

6. Obesity

Research findings regarding the association between obesity and the onset of AD have been somewhat inconsistent. Profenno, Porsteinsson, and Faraone (2010) **[44]** conducted a meta-analysis and found that obesity (Body Mass Index less than 30 kg/m2) is independently and significantly related to the risk of AD development. But according to Fitzpatrick *et al*. Meta analysis (2009) **[20]**, middle age obesity is related to a greater possibility of dementia development whereas obesity in later life is related with a lower possibility of dementia. Lowered BMI, less than 20 kg/m2 has too been related to a greater chance of developing dementia, according to research by the same authors. As people age, low weight often coincides with other medical conditions and is a sign of poor health. It can even occur ten years before dementia symptoms appear. Low weight, overweight, and obesity in middle age are all linked to an increased chance of getting AD in later life, according to another meta analysis by Anstey *et al*. (2011) **[3]**.

7. Environmental Factors

Genetic risk factors and ageing are insufficient to account for all occurrences of AD. Oxidative stress and inflammation are resulted due to various environmental aspects, comprising diet, metal, infections, and air pollution. These factors increase the likelihood of developing AD.

STAGES OF AD

Sr. No.	Clinical stage	Description	Reference
1	Preclinical or Presymptomatic Stage	Initial signs include mild loss of memory and early alteration in the hippocampus and cortical region, without affecting daily activities or showing clinical symptoms of Alzheimer's disease.	[17][18][30]
2	Early or mild Stage	Symptoms emerge such as difficulties in daily activities, memory loss, disorientation, mood fluctuation, and possibly depression.	[30][55]
3	Moderate Stage	Memory loss intensifies, along with difficulty recognizing loved ones, impulse control issue, and challenges in communication and comprehension.	[30]
4	Late or severe Stage	The infection spreads throughout the cortical region, leading to significant cognitive decline, an inability to recognize family members, and eventually, severe physical complications and death.	[17,4]

TREATMENT

While there isn't a recognised cure for AD at this time, there are several therapy options that can improve patients' quality of life and reduce the disease's progression. Though it is ultimately believed that a person's genetic predisposition to AD plays a larger part in the progression of the condition, there are ways to strengthen cognition and reduce the possibility of AD, including eating a plant-

based diet **[52]**, maintaining cardiovascular fitness **[37]**, and participating in ongoing intellectual activity **[51]**.

Pharmacologically, two licensed drug classes can be used to lessen the symptoms of AD: antagonist of NMDA receptor, that stop glutamate from connecting to NMDA receptors to avoid death of cell from overactivation of neuron **[41]**, and inhibitors of acetylcholinesterase , that block the of acetylcholine's enzymatic breakdown **[9]**. While memantine is the sole NMDA receptor antagonist that has been approved, approved acetylcholinesterase inhibitors include rivastigmine, galantamine and donepezil.

Since these medications cannot stop or cure Alzheimer's disease, research on disease-modifying treatments, which impede or slow the pathophysiological progression of AD is gaining momentum **[22]**. Numerous of these are mAb (Monoclonal antibodies) that target Aβ; the FDA has approved Aducanumab and Lecanemab respectively, for AD and early AD treatment. The AD patient's cognitive impairment rate was found to be moderately reduced by both of these therapies in clinical studies **[11] [54]**. The differences between the treatments and the placebo group were −0.39 and −0.45, respectively, in terms of the alteration in the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score. Because of these medications' small (and maybe clinically irrelevant) impact on declined cognition and elevated possibility of neurological consequences, there is a considerable deal of debate around their approval **[31]**.

CONCLUSION

Alzheimer's disease (AD) stands as a formidable confront in healthcare, with its prevalence projected to escalate dramatically in the coming decades. This review has illuminated key aspects of AD, from its neuropathologic underpinnings to its societal impact. Despite substantial progress in understanding the disease, effective interventions remain elusive. Current treatment strategies focus on symptom management, underscoring the urgent need for disease-modifying therapies. Environmental and genetic risk factors underscore the intricate interplay of factors contributing to AD onset and progression. As research continues to unravel the mysteries of AD, there is hope for novel therapeutic avenues. However, addressing the multifaceted nature of AD requires a concerted effort from researchers, healthcare providers, policymakers, and society at large. By advancing our understanding and developing targeted interventions, we can strive to alleviate the burden of AD on

individuals, families, and healthcare systems worldwide.

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