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Original Research Article

Alzheimer's disease: A Comprehensive Review of Mechanisms, Diagnosis, and Treatment

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Abstract:

Background: The international leader in dementia cases, Alzheimer's disease (AD) develops as a steadily worsening brain deterioration disease. This disorder leads to declining cognition and impairments of memory and behavioral abnormalities among patients. Scientists have investigated AD at scale yet no effective medications exist for modifying the condition. This review provides substantial detail about AD's pathophysiology, genetic and environmental causes, detection approaches and existing treatment options.

Objectives: The principal objective within this review is to gather knowledge about AD by examining its fundamental processes and diagnostic and treatment aspects as well as risk factors. The text discusses active research activities and potential advancements in AD treatment development.

Methods: The research analysis employed three academic databases including PubMed, Scopus and Google Scholar. This analysis used relevant peer-reviewed articles combined with clinical studies along with systematic reviews. This analysis investigates five primary domains regarding amyloid-beta (Aβ) aggregation, tau pathology, neuroinflammation, mitochondrial dysfunction, genetic predisposition along with the development of new diagnostic and treatment methodologies.

Results & Discussion: The main cause of Alzheimer's disease development consists of Aβ plaques which accumulate together with hyperphosphorylated tau proteins in addition to neuroinflammation and mitochondrial decline and breakdown of the blood-brain barrier. Severe genetic susceptibilities to Alzheimer's disease develop when people carry the APOE ε4 allele alongside specific APP, PSEN1, PSEN2 gene abnormalities. These two conditions increase the number of risk elements that derive from cardiovascular health and stress reactions alongside individual lifestyle choices. Clinical diagnosis occurs early with the use of MRI technology and PET scans and cerebrospinal fluid biomarkers together with new blood-based detection tools. Studies have demonstrated the effectiveness of Donepezil Rivastigmine and Galantamine cholinesterase inhibitors together with Memantine as NMDA receptor antagonist and ongoing discussions about Aducanumab Aβ monoclonal antibody therapy. The core components of AD management depend on non-medical interventions that include both cognitive therapy sessions and life habit improvements.

Conclusion: Scientific advancements in AD research continue to advance yet effective cure methods prove difficult to discover. Future research needs to prioritize discovering new therapeutic targets along with enhancing early detection methods and conducting studies about precision medicine techniques. Research teams must unite genetic specialists with those who study brains and pharmacologists to achieve successful treatments.

Keywords: Alzheimer's disease, cognitive decline, amyloid plaques, tau tangles, dementia, neurodegeneration, genetic factors.

Introduction

Alzheimer's disease (often shortened to "Alzheimer's" or "AD") is a neurodegenerative disorder that primarily affects elderly individuals and represents the most common cause of dementia worldwide. Described by Alois Alzheimer in 1906, the disease is marked by a progressive decline in cognitive function, particularly memory, which significantly impacts daily life [1]. The pathophysiology of AD involves complex interactions between genetic, environmental, and lifestyle factors. It is characterized by the accumulation of amyloid plaques, neurofibrillary tangles, and neuronal cell death, leading to the progressive loss of cognitive and functional abilities.

Progressive loss of cognitive functions can be caused by cerebral disorder like Alzheimer's disease (AD) or other factors such as intoxications, infections, abnormality in the pulmonary and circulatory systems, which causes a reduction in the oxygen supply to the brain, nutritional deficiency, vitamin B12 deficiency, tumors, and others [2,3]. Alzheimer disease (AD) is one of the greatest medical care challenges of our century and is the main cause of dementia. In total, 40 million people are estimated to suffer from dementia throughout the world, and this number is supposed to become twice as much every 20 years, until approximately 2050 [4]. Because dementia occurs mostly in people older than 60 years, the growing expansion of lifespan, leading to a rapidly increasing number of patients with dementia, mainly AD, has led to an intensive growth in research focused on the treatment of the disease. However, despite all arduous research efforts, at the moment, there are no effective treatment options for the disease [5, 6]. As the global population ages, the prevalence of Alzheimer's disease continues to rise, making it a major public health challenge. According to the World Health Organization (WHO), the number of people with dementia worldwide is expected to twice by 2050 [7]. This review aims to provide a comprehensive overview of AD's pathophysiology, risk factors, clinical manifestations, diagnostic approaches, and therapeutic interventions.

Methodology:

This review article on Alzheimer's disease (AD) is based on a comprehensive analysis of existing literature, incorporating various sources to provide an in-depth understanding of the disease. The methodology followed in this review includes the following key steps:

1. **Literature Search and Selection**
    - A thorough literature search was conducted using databases such as PubMed, Scopus, Google Scholar, and other scientific repositories.
    - Keywords used for the search included *Alzheimer's disease, amyloid plaques, tau tangles, neurodegeneration, dementia, APOE, neuroinflammation, mitochondrial dysfunction, and therapeutic strategies*.
    - Studies, clinical trials, and review articles published in peer-reviewed journals were included.
2. **Inclusion and Exclusion Criteria**

Inclusion Criteria:

- Articles published in English.
- Studies focusing on AD pathophysiology, genetic and environmental risk factors, diagnosis, and treatment approaches.
- Clinical and experimental research providing significant insights into AD mechanisms.

Exclusion Criteria:

- Studies with insufficient data or small sample sizes.
- Non-peer-reviewed sources, anecdotal reports, and duplicate studies.

3. **Data Extraction and Analysis**
    - Information was categorized into major themes, including **pathophysiology, risk factors, diagnostic strategies, and treatment options.**
    - Key pathological mechanisms such as **amyloid-beta aggregation, tau pathology, neuroinflammation, and mitochondrial dysfunction** were analyzed.
    - Genetic and environmental influences were examined based on findings from genome-wide association studies (GWAS) and epidemiological research.
4. **Synthesis of Findings**
    - Data from multiple sources were synthesized to present an integrated perspective on AD.
    - The relationship between amyloid plaques, tau tangles, and neuroinflammation was explored.
    - Current and emerging diagnostic techniques and therapeutic interventions were discussed.

Discussion

Pathophysiology of Alzheimer's Disease

The pathophysiology of Alzheimer's disease is complex and involves several key pathological features, most notably the accumulation of amyloid-beta (Aβ) plaques and tau tangles. These two abnormalities are central to the most widely accepted amyloid cascade hypothesis.

Amyloid-beta Plaques:

These are extracellular deposits of a peptide derived from the amyloid precursor protein (APP). The abnormal cleavage of APP leads to the formation of Aβ peptides, which aggregate to form plaques. These plaques are toxic to neurons, disrupting synaptic function and inducing inflammatory responses that further contribute to neuronal damage [8]. When the assembly of APP fragments is disturbed, toxic oligopeptides are formed, consisting of 39 to 43 fragments, including protofibrils or fibrils. These, in turn, form deposits that are visible during microscopic examinations [9]. The formation of deposits will not occur if β-amyloid does not have a stable structure, which is related to mutations leading to the destabilization of its structure. The β-amyloid fragments, mainly the Aβ-42 isoform formed by the above-described processes, exhibits cytotoxic properties, in particular towards neurons, which promotes the formation of oxygen radicals that are toxic to nerve cells [10, 11]. Their toxicity is mainly based on the dysregulation of calcium homeostasis as a result of lipid disturbances in the cell membranes of neurons, causing their death [12, 13, 14].

Tau Tangles:

Another component of the plaque formation process is the Tau protein. It is a factor that promotes the process of the specific assembly of the tubulin protein. Tubulin, on the other hand, undergoes polymerization and forms microtubules that shape the intracellular pathway, along which the motor proteins of cells take part in cell division, acting as a dividing spindle. In the pathogenesis of Alzheimer's disease, the formed and deposited neurofibrillary fibers are the result of the hyperphosphorylation of the Tau protein [15]. The neurotoxicity of the Tau protein is based on two main pathways: the loss of physiological function by a normal Tau protein, which causes the destabilization of microtubules, or the gain of function from toxic to neurons, which leads to apoptosis [16].

In their research, many scientists have also proved the correlation between the accumulation of β-amyloid and the aggregation of the Tau protein, which is the final stage of disease pathogenesis [17].

Neuroinflammation:

In addition to Aβ and tau, neuroinflammation is a significant contributor to AD pathology. The

activation of microglia, the brain's resident immune cells, plays a role in the chronic inflammatory response observed in AD.

Astrocytes and microglia are the major types of glial cells in the CNS, and their activation involves various types of neurodegenerative processes. Reactive glial cells are closely associated with plaques and parallels tangles in AD.Once activated, their processes become hypertrophied; both astrocytes and microglia produce multiple inflammatory factors, including cytokines, prostanoids, chemokines, reactive oxygen species, and cyclooxygenase-(COX)2 [18]. Similarly, as indications of neuroinflammation, elevated levels of inflammatory cytokines are discovered in AD.

Mitochondrial Dysfunction:

Mitochondrial dysfunction is increasingly recognized as an early event in AD pathogenesis. Mitochondria are responsible for energy production, and impairments in mitochondrial function can lead to increased oxidative stress, cellular damage, and neuronal death. The accumulation of Aβ peptides has been shown to disrupt mitochondrial function, further contributing to the degenerative process [19].

Blood-Brain Barrier Dysfunction:

Another emerging area of research is the role of the blood-brain barrier (BBB) in AD. The BBB is responsible for maintaining a protective environment for neurons by regulating the entry of substances into the brain. In AD, the BBB becomes compromised, allowing neurotoxic substances to accumulate and exacerbate neurodegeneration [20].

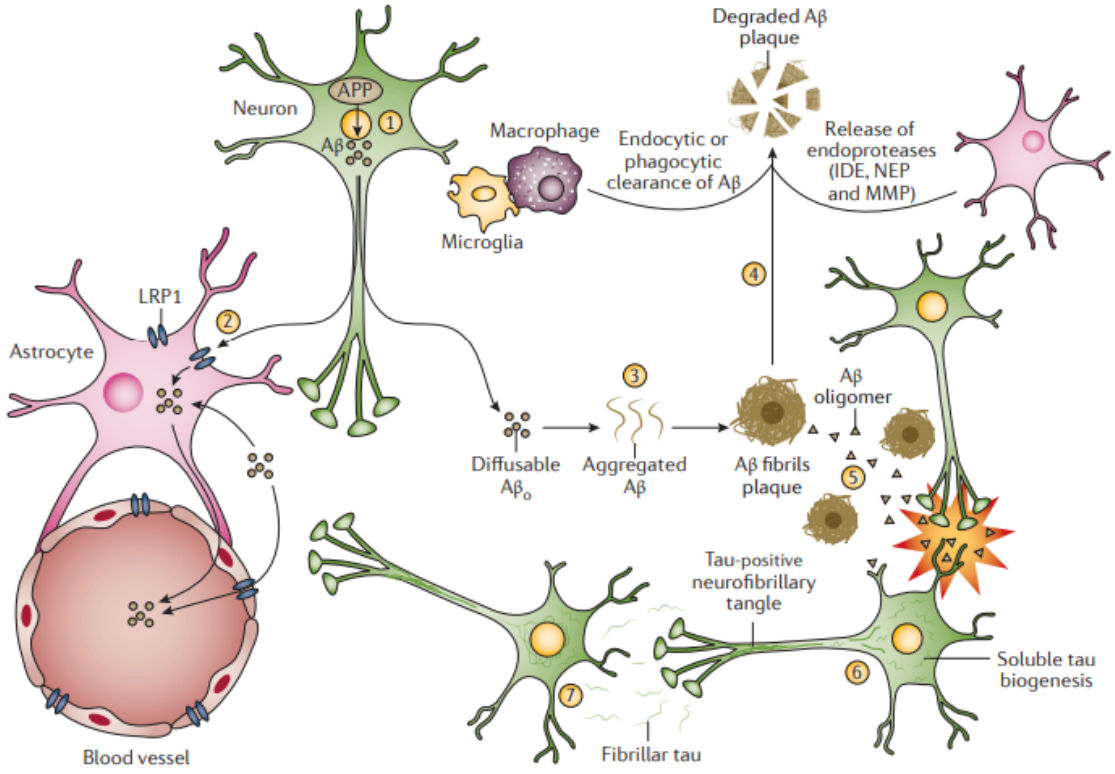

Figure1:-Pathways leading to plaques and tangles form the basis of the amyloid-β theory of Alzheimer's disease.

In the first step proteomic processing of amyloid precursor protein (APP) produces amyloid β (Aβ) while an unidentified release mechanism enables extracellular diffusion that results in diffusible oligomers (Aβo). Steps 2 and 3 employ the combination of APOE together with astrocytic LRP1 to clear Aβo proteins as a method to stop plaque development. The protein Aβo forms fibrillary structures within the cellular space to become plaques after aggregation happens. Endocytic phagocytosis enables macrophages and microglia to clear brain Aβ plaques which are then degraded by insulin-degrading enzyme (IDE) together with neprilysin (NEP) and matrix metalloproteinases (MMPs) released by astrocytes. Oligomeric Aβ conformations that separate from fibrils and plaques avoid elimination resulting in synapse damage (step 5) yet initiate the unidentified mechanism of tau aggregation. The spread of tau pathology occurs inside neurons because neurofibrillary tangles move through dendrites (step 6). Fibrillar tau that is released from damaged neurons has the ability to be taken up by healthy neurons and produce toxic effects on these cells (step 7). Under the presence of Aβ oligomers the environment becomes favorable for α-synuclein to undergo aggregation inside plaques. Janmey and Irvine indicated that disease progression requires two factors: mitochondrial impairment together with oligomeric Aβ aggregate accumulation.

Genetic Factors and Risk Genes

Genetic factors play a significant role in the development of Alzheimer's disease. Although the exact genetic causes remain unclear, several risk genes have been identified, with the most well-known being the Apolipoprotein E (APOE) gene. APOE is a lipid-binding protein that plays a role in lipid metabolism and neuronal repair. The ε4 allele of the APOE gene is associated with an increased risk of developing AD, while the ε2 allele confers a protective effect [21].

Genetic factors were discovered over the years and were found to play a major role in the development of AD. 70% of the AD cases were related to genetic factors: most cases of EOAD are inherited in an autosomal dominant pattern and mutations in the dominant genes such as Amyloid precursor protein (APP), Presenilin-1 (PSEN-1), Presenilin-2 (PSEN-2), and apolipoprotein E (ApoE) are associated with AD. In addition to APOE, mutations in other genes have been linked to familial forms of AD, which account for less than 5% of all cases. These include mutations in the Amyloid Precursor Protein (APP) gene, Presenilin 1 (PS1), and Presenilin 2 (PS2) . These mutations result in early-onset AD, typically before the age of 65 [22].

Risk Factors For Alzheimer's Disease

Several non-genetic factors contribute to the risk of developing Alzheimer's disease:

1. **Age:**

Age is the most significant risk factor for Alzheimer's disease, with the incidence increasing significantly after the age of 65. This is believed to be related to the accumulation of genetic mutations, environmental factors, and the reduced ability of the brain to compensate for neurodegeneration as individuals age. The annual incidence of AD is approximately 1% among elderly persons aged 65 to 70 years, and increases to 6 to 8% of persons older than 85 years. The prevalence of AD is higher in women than men. In men, high bioavailable testosterone levels appear to reduce the risk of AD. Education may increase the 'cognitive reserve', which reduces the risk of late-life dementia. The risk of AD is highest among those with low or limited levels of education. A positive family history of AD occurs in around 15% of AD patients, and increases the risk of AD approximately four-fold [23].

2. **Cardiovascular Factors:**

Cardiovascular health is closely linked to cognitive function. Conditions such as hypertension, diabetes, and high cholesterol increase the risk of developing AD [24]. Vascular changes in the brain, such as reduced blood flow, may contribute to the development of amyloid plaques and tau tangles. CVDs are

recognized as an important risk factor for AD, such as the stroke that is associated with increased risk of dementia due to a neural tissue loss, which enhances degenerative effect and influences amyloid and tau pathology. Atrial fibrillation also causes embolisms which leads to stroke and a decrease in memory and cognitive functions. Moreover, heart failure affects the pumping function of the heart and results in insufficient blood supply to the body and hypo-perfusion of the brain that leads to hypoxia and neural damage. The coronary heart disease's hypothesis indicates that atherosclerosis, peripheral artery disease, hypo-perfusion, and emboli are all related to increased risk of AD. Hypertension is associated with thickening of vessel walls and narrowing of the lumen which reduce the cerebral blood flow, and in chronic cases, it may cause cerebral edema, which all participate as risk factors for AD and CVD. The CVD is a modifiable risk factor and by focusing on its relationship with AD, a pathway to prevent and delay the disease can be obtained [25].

3. **Environmental Factors**:

Environmental risk factors including air pollution, diet, metals, infections, and many others may induce oxidative stress and inflammation and increase the risk for developing AD [26,27].

4. **Lifestyle Factors And others**:

Diet and lifestyle choices, such as smoking, poor nutrition, and lack of sleep, are also associated with an increased risk of AD. The protective effect of moderate alcohol intake may be related to the antioxidant properties of wine. Physical activity and exercise reduce brain tissue loss, dementia, and the risk of AD, possibly via increased neurotrophic factors. Smoking increases the risk 2 to 4 times. Depressive mood and cardiovascular risk factors are also associated with an increased risk. Severe head injury also increases the risk of AD, possibly via reduced brain reserve or increases in brain Aβ deposition. Other dietary factors may also reduce the risk of AD, including vitamin B12; folate; antioxidants including flavonoids; vitamins C and E; unsaturated fatty acids; and a Mediterranean diet pattern [28].

Clinical Symptoms:

The clinical presentation of Alzheimer's disease is characterized by a gradual onset of memory loss, followed by progressive cognitive decline. Early symptoms include:

1. **Memory Impairment:** The most prominent early symptom of AD is short-term memory loss, especially difficulty remembering recent events or conversations. As the disease progresses, long-term memory is also affected [28].
2. **Cognitive Dysfunction:** Cognitive deficits in AD affect language, executive function, and visuospatial abilities. Patients often experience difficulty with tasks such as problem-solving, decision-making, and planning [29].
3. **Behavioral Changes**: As the disease advances, patients may exhibit changes in behavior, including agitation, depression, anxiety, and apathy. These symptoms can be challenging for caregivers and may worsen over time.

Diagnosis:

Current Diagnostic Strategies:

The evaluation of a person with suspected memory impairment includes a comprehensive set of assessments aimed at characterizing the etiology of cognitivedecline and identifying treatable pathologies. These assessments include a detailed medical history, physical and mental status examinations, basic labs, and neuroimaging studies. Additional tools may also include neuropsychological testing and advanced brain imaging techniques. Once reversible causes have been ruled out, clues for specific causes of major neurocognitive disorder are sought. A history of multiple strokes, for example, may point towards a diagnosis of vascular dementia. A history of head trauma may suggest traumatic encephalopathy. A history of prolonged alcohol use disorder may

support the diagnosis of an alcohol-related dementia. In adults over 60, the most frequent cause of progressive cognitive decline is AD [30]

Emerging Diagnostics

Finding earlier and more definitive ways to diagnose AD has been the subject of significant amounts of research, and testing advances have been seen in the last decade with expanded use of positron emission tomography (PET) and magnetic resonance imaging (MRI), as well as in the identification of biomarkers in cerebrospinal fluid (CSF) and more recently serum. While limited, some of these diagnostic advances are available to the public, though typically at a high price.

A high-level overview of emerging diagnostic strategies can be found below.

Volumetric Data

In simple terms, volume changes in specific brain regions can predict the likelihood of progression from mild cognitive impairment (MCI) to AD. These volume assessments can be done by radiologists or with the help of FDA-approved MRI volumetric data software packages such as Neuroquant and Neuoreader. Hippocampal volume changes in particular are regarded as an important AD biomarker. Because of limited sensitivity of this measure in diagnosing AD, however, MRI studies are regarded as a contributor to the diagnostic process but not sufficient in themselves for determining a diagnosis [30].

Diffusion Tensor Imaging

Diffusion Tensor Imaging (DTI) is an advanced neuroimaging technique that uses the diffusion properties of water molecules to generate magnetic resonance images that correspond to changes in macroscopic axonal organization. This technique can be used to evaluate the structure of vertical cellular micro-circuits, termed “minicolumns.” Previous studies have demonstrated that minicolumns are known to be altered in a somewhat predictable and progressive manner during aging, MCI, and AD. Additionally, pathologic changes of cortex columnar architecture are associated with increased plaque load and cognitive decline. With the aid of proprietary software, DTI can be measured and used as a marker of neurodegeneration [30].

Management Strategies:

Currently, there is no cure for Alzheimer’s disease, and treatment focuses on alleviating symptoms and slowing disease progression.

1. **Cholinesterase Inhibitors**:

The most commonly used pharmacological treatments are cholinesterase inhibitors, which increase acetylcholine levels in the brain. These drugs, such as Donepezil, Rivastigmine, and Galantamine, are used to improve memory and cognitive function in mild to moderate AD [31].

Donepezil: is a reversible non-competitive acetylcholinesterase inhibitor shown to affect cognitive function, activities of daily living, and global clinical status. Benefits for the 10 mg dose appear marginally larger than for the 5 mg dose. A larger 23-mg dose form is available, with disputed clinical advantages.

Rivastigmine: is a pseudo-irreversible inhibitor of acetylcholinesterase and butyrylcholinesterase and acts by binding to two active sites of acetylcholinesterase. It is called pseudo-irreversible because it dissociates slower than acetylcholinesterase. Adverse effects of the oral preparation are significant, but the transdermal form is more tolerable for many patients, although it can cause dermatologic reactions.

Galantamine: is a reversible competitive acetylcholinesterase inhibitor and modulator of nicotinic acetylcholine receptors. Theoretically, this agent will have greater effect in areas of the brain with low levels of acetylcholine. Its effects are similar to those of the other cholinesterase inhibitors [32].

2. **NMDA Receptor Antagonist**:

Memantine is an NMDA receptor antagonist that helps regulate glutamate activity, which is

thought to be involved in excitotoxicity and neurodegeneration in AD. It is typically used in moderate to severe stages of the disease [33].

he N-methyl D-aspartate (NMDA) receptors are abundant in pyramidal cells in the hippocampus and cortex (areas involved in cognition, learning, and memory). The mechanism involved in learning and memory entails long-term potentiation, mediated by the neurotransmitter glutamate via the NMDA receptor. However, elevated glutamate levels are also undesirable and associated with excitotoxicity of the neurons. Memantine is a moderate-affinity non-competitive, NMDA-type receptor antagonist. It is postulated to decrease the glutamate-induced excitotoxicity of the neuron, while allowing the physiological actions of glutamate on learning and memory. memantine has only a marginal beneficial effect on cognition, without any benefit in terms of ADL [33].

3. **Monoclonal Antibodies**:

In recent years, immunotherapy has emerged as a promising approach for AD. Monoclonal antibodies targeting amyloid-beta, such as Aducanumab, have been developed to reduce amyloid plaque burden. Although aducanumab received FDA approval in 2021, its clinical efficacy remains a topic of debate [34].

4. **Other Investigational Therapies**:

Other investigational therapies, such as tau-targeted therapies, anti-inflammatory drugs, and gene therapy, are being explored in clinical trials. Targeting tau accumulation, inhibiting neuroinflammation, and improving mitochondrial function are considered key strategies for disease modification [34].

5. **Non Pharmacological Intervension:**

There are also non-drug treatments for the symptoms of Alzheimer's disease. Non-drug treatments do not change the underlying biology of the disease. They are often used with the goals of maintaining or improving cognitive function, overall quality of life and engagement, and the ability to perform activities of daily living. Non-drug treatments include physical activity, memory and orientation exercises, music- and art-based therapies, and many others. Non-drug treatments may be used with a more specific goal of reducing behavioral and psychological symptoms such as depression, apathy, wandering, sleep disturbances, agitation and aggression. For example, a review and analysis of nonpharmacologic treatments for agitation and aggression in people with dementia concluded that non-drug interventions seemed to be more effective than pharmacologic interventions for reducing aggression and agitation [34].

Alliance with caregivers:

An alliance between the clinician and the caregiver is essential in treating patients with Alzheimer's disease. Caregivers are responsible for supervising patients who live in the community and frequently continue to visit and provide assistance after a pa-tient has been institutionalized. Caregivers are also responsible for administering medication, implementing nonpharmacologic treatment, and promoting the patient's general health and well-being and a meaningful quality of life. Caregivers must make decisions regarding driving, advance directives, financial management, removal of firearms, home safety, and programs such as Safe Return, nationwide network created by the Alzheimer's Association. Studies show that caregivers of patients with Alz-heimer's disease rate their own health as relatively poor. Furthermore, they endure a greater number of illnesses, have more somatic symptoms, have more depression and anxiety, use more health care, and engage in fewer preventive-health activities than people who are not caregivers. Self-help groups, support groups, education, skills training, counseling, and psychotherapy may help caregivers. Most of these interventions have been associated with reduced psychological distress and improved knowledge on the part of caregivers, yet they have failed to reduce the caregiver's burden. Referring caregivers to a family assistance organization is an important element of their care [35].

Conclusion:

Alzheimer's disease remains one of the most debilitating and widespread neurodegenerative disorders. Although there have been significant advancements in understanding its molecular underpinnings, effective disease-modifying therapies remain elusive. Continued research into the genetics, biomarkers, and pathophysiology of AD is essential to develop novel therapeutic approaches. In the meantime, early diagnosis and symptom management are critical to improving the quality of life for patients and their families.

References

1. Alzheimer's Association. (2021). Alzheimer's Disease Facts and Figures. Alzheimer's & Dementia, 17(3), 1-76.
2. Terry RD, Davies P. Dementia of the Alzheimer type. Annu Rev Neurosci. 1980;3:77-95. doi: 10.1146/annurev.ne.03.030180.000453. PMID: 6251745.
3. Rathmann KL, Conner CS. Alzheimer's disease: clinical features, pathogenesis, and treatment. Drug IntellClin Pharm. 1984 Sep;18(9):684-91. doi: 10.1177/106002808401800902. PMID: 6383752.
4. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement. 2013 Jan;9(1):63-75.e2. doi: 10.1016/j.jalz.2012.11.007. PMID: 23305823.
5. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM. Alzheimer's disease. Lancet. 2016 Jul 30;388(10043):505-17. doi: 10.1016/S0140-6736(15)01124-1. Epub 2016 Feb 24. PMID: 26921134.
6. Cummings, Jeffrey, et al. "Alzheimer's disease drug development pipeline: 2019." Alzheimer's & Dementia: Translational Research & Clinical Interventions 5 (2019): 272-293.
7. Prince, M., Wimo, A., Guerchet, M., & Ali, G. (2015). World Alzheimer Report 2015: The Global Impact of Dementia. Alzheimer's Disease International.
8. Selkoe DJ. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev. 2001 Apr;81(2):741-66. doi: 10.1152/physrev.2001.81.2.741. PMID: 11274343.
9. Mitra A, Sarkar N. Sequence and structure-based peptides as potent amyloid inhibitors: A review. Arch BiochemBiophys. 2020 Nov 30;695:108614. doi: 10.1016/j.abb.2020.108614. Epub 2020 Sep 30. PMID: 33010227.
10. Forloni G, Balducci C. Alzheimer's Disease, Oligomers, and Inflammation. J Alzheimers Dis. 2018;62(3):1261-1276. doi: 10.3233/JAD-170819. PMID: 29562537; PMCID: PMC5869993.
11. Jankovska N, Olejar T, Matej R. Extracellular Amyloid Deposits in Alzheimer's and Creutzfeldt-Jakob Disease: Similar Behavior of Different Proteins? Int J Mol Sci. 2020 Dec 22;22(1):7. doi: 10.3390/ijms22010007. PMID: 33374972; PMCID: PMC7792617.
12. Tuppo EE, Arias HR. The role of inflammation in Alzheimer's disease. Int J Biochem Cell Biol. 2005 Feb;37(2):289-305. doi: 10.1016/j.biocel.2004.07.009. PMID: 15474976.
13. Pendin D, Fasolato C, Basso E, Filadi R, Greotti E, Galla L, Gomiero C, Leparulo A, Redolfi N, Scremin E, Vajente N, Pozzan T, Pizzo P. Familial Alzheimer's disease presenilin-2 mutants affect Ca2+ homeostasis and brain network excitability. Aging ClinExp Res. 2021 Jun;33(6):1705-1708. doi: 10.1007/s40520-019-01341-0. Epub 2019 Oct 12. PMID: 31606858.
14. Rossi A, Galla L, Gomiero C, Zentilin L, Giacca M, Giorgio V, Calì T, Pozzan T, Greotti E, Pizzo P. Calcium Signaling and Mitochondrial Function in Presenilin 2 Knock-Out Mice: Looking for Any Loss-of-Function Phenotype Related to Alzheimer's Disease. Cells. 2021 Jan 21;10(2):204. doi:

10.3390/cells10020204. PMID: 33494218; PMCID: PMC7909802.
15. Guan PP, Cao LL, Wang P. Elevating the Levels of Calcium Ions Exacerbate Alzheimer's Disease via Inducing the Production and Aggregation of β-Amyloid Protein and Phosphorylated Tau. Int J Mol Sci. 2021 May 31;22(11):5900. doi: 10.3390/ijms22115900. PMID: 34072743; PMCID: PMC8198078.
16. Sebastián-Serrano Á, de Diego-García L, Díaz-Hernández M. The Neurotoxic Role of Extracellular Tau Protein. Int J Mol Sci. 2018 Mar 27;19(4):998. doi: 10.3390/ijms19040998. PMID: 29584657; PMCID: PMC5979432.
17. Sies H, Berndt C, Jones DP. Oxidative Stress. Annu Rev Biochem. 2017 Jun 20;86:715-748. doi: 10.1146/annurev-biochem-061516-045037. Epub 2017 Apr 24. PMID: 28441057.
18. Zhang, F., & Jiang, L. (2015). Neuroinflammation in Alzheimer's disease. Neuropsychiatric Disease and Treatment, 11, 243–256. https://doi.org/10.2147/NDT.S75546
19. Swerdlow RH. Mitochondria and Mitochondrial Cascades in Alzheimer's Disease. J Alzheimers Dis. 2018;62(3):1403-1416. doi: 10.3233/JAD-170585. PMID: 29036828; PMCID: PMC5869994
20. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, Toga AW, Jacobs RE, Liu CY, Amezcua L, Harrington MG, Chui HC, Law M, Zlokovic BV. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015 Jan 21;85(2):296-302. doi: 10.1016/j.neuron.2014.12.032. PMID: 25611508; PMCID: PMC4350773.
21. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993 Aug 13;261(5123):921-3. doi: 10.1126/science.8346443. PMID: 8346443.
22. Levy-Lahad E, Wijsman EM, Nemens E, Anderson L, Goddard KA, Weber JL, Bird TD, Schellenberg GD. A familial Alzheimer's disease locus on chromosome 1. Science. 1995 Aug 18;269(5226):970-3. doi: 10.1126/science.7638621. PMID: 7638621.
23. Chu LW. Alzheimer's disease: early diagnosis and treatment. Hong Kong Med J. 2012 Jun;18(3):228-37. PMID: 22665688
24. Sparks, D. L., et al. (2000). Alzheimer's disease and cardiovascular disease: A review of the literature. American Journal of Geriatric Cardiology, 9(2), 91-98.
25. Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24):5789. doi: 10.3390/molecules25245789. PMID: 33302541; PMCID: PMC7764106.
26. Wainaina MN, Chen Z, Zhong C. Environmental factors in the development and progression of late-onset Alzheimer's disease. Neurosci Bull. 2014 Apr;30(2):253-70. doi: 10.1007/s12264-013-1425-9. Epub 2014 Mar 24. PMID: 24664867; PMCID: PMC5562669.
27. Grant WB, Campbell A, Itzhaki RF, Savory J. The significance of environmental factors in the etiology of Alzheimer's disease. J Alzheimers Dis. 2002 Jun;4(3):179-89. doi: 10.3233/jad-2002-4308. PMID: 12226537.
28. McKhann, G. M., et al. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7(3), 263-269.
29. Neugroschl J, Wang S. Alzheimer's disease: diagnosis and treatment across the spectrum of disease severity. Mt Sinai J Med. 2011 Jul-Aug;78(4):596-612. doi: 10.1002/msj.20279. PMID: 21748748; PMCID: PMC3315348.
30. Bomasang-Layno E, Bronsther R. Diagnosis and Treatment of Alzheimer's Disease:: An

Update. Dela J Public Health. 2021 Sep 27;7(4):74-85. doi: 10.32481/djph.2021.09.009. PMID: 34604768; PMCID: PMC8482985

31. Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev. 2006 Jan 25;2006(1):CD005593. doi: 10.1002/14651858.CD005593. PMID: 16437532; PMCID: PMC9006343.
32. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003 Apr 3;348(14):1333-41. doi: 10.1056/NEJMoa013128. PMID: 12672860.
33. Sevigny J, Chiao P, Bussière T, Weinreb PH, Williams L, Maier M, Dunstan R, Salloway S, Chen T, Ling Y, O'Gorman J, Qian F, Arastu M, Li M, Chollate S, Brennan MS, Quintero-Monzon O, Scannevin RH, Arnold HM, Engber T, Rhodes K, Ferrero J, Hang Y, Mikulskis A, Grimm J, Hock C, Nitsch RM, Sandrock A. The antibody aducanumab reduces Aβ plaques in Alzheimer's disease. Nature. 2016 Sep 1;537(7618):50-6. doi: 10.1038/nature19323. Update in: Nature. 2017 Jun 21;546(7659):564. doi: 10.1038/nature22809. PMID: 27582220.
34. 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024 May;20(5):3708-3821. doi: 10.1002/alz.13809. Epub 2024 Apr 30. PMID: 38689398; PMCID: PMC11095490.
35. Cummings, J.L. Alzheimer’s Disease. N. Engl. J. Med. 2004, 351, 56–67.