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ALZHEIMER DISEASE - A SHORT REVIEW

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ABSTRACT Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and behavioral changes. It is the most common cause of dementia, accounting for 60-70% of cases. The pathology of AD is driven by amyloid- plaque accumulation, neurofibrillary tangles, oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation. While aging remains the most significant risk factor, genetic predisposition, lifestyle, and medical conditions like diabetes and hypertension also contribute to disease progression. Pharmacological treatments such as cholinesterase inhibitors and NMDA receptor antagonists provide symptomatic relief, while newer therapies like Aducanumab and Lecanemab target amyloid pathology. Non-pharmacological interventions, including cognitive stimulation, physical activity, and music therapy, are essential in improving patient well-being. Emerging biomarkers offer promising tools for early diagnosis and disease monitoring. Prevention strategies focusing on dietary interventions, particularly omega-3 fatty acids like DHA, show potential in reducing cognitive decline. A multidisciplinary approach integrating pharmacological and non-pharmacological strategies is crucial in managing AD and improving patients' quality of life.

KEYWORDS : Alzheimer's disease, amyloid- plaques, neuroinflammation, biomarkers, cognitive decline

INTRODUCTION

Dementia refers to a broad range of symptoms that impact memory, communication and cognitive abilities. Alzheimers disease (AD) is the most common form, accounting for 60-70% of dementia cases [1]. AD is a neurological condition resulting from damage to the nerve cells in the brain. According to the World Health Organization (WHO), AD and other forms of dementia were the seventh leading cause of death globally in 2021, with women accounting for 68% of these deaths [2,3,4]. Alzheimer's disease is most commonly observed in individuals over the age of 65, known as late-onset of AD (LOAD). Early-onset AD (EOAD) occurs before the age of 65 and is relatively rare, accounting for roughly 5% of AD [5]. AD is characterized by accumulation of amyloid- (A) plaques and neurofibrillary tangles (NFTs) in the brain accompained by a series of pathological changes, including neuroinflammation, synaptic and circuit dysfunction, mitochondrial and bioenergetic disturbances, epigenetic changes and vascular irregularities, ultimately resulting in the death of neurons [6,7]. In the early stages, individuals may show signs of depression, anxiety, social isolation and disturbances in sleep patterns [8,9].

As the condition progresses, memory detoriation worsens, often accompained by behavioural changes such as aggression and agitation, neuropsychiatric symptoms like hallucinations and delusions [8,10]. Diabeties mellitus and hypertension are major risk factors for dementia, especially if they develop in midlife, though they remain concerning in later life too. While these conditions may have some link to amyloid beta (A) accumulation, their main impact is through causing blood vessel damage in the brain. This vascular damage can worsen alzheimer's symptoms by reducing blood flow, rather than directly affecting A or tau proteins [10].

SYMPTOMS

Clinically, AD is classified into seven stages (Table 1). Life expectancy in Alzheimer's patients typically ranges from 3-10 years after the onset of symptoms [11].

Table 1. Seven clinical stages of Alzheimer's disease [11].

Stage 1	Patient appears cognitively normal
Stage 2	Prodromal stage: mild memory loss
Stage 3	Progresion into mild cognitive impairment (MCI).
Stage 4	Moderate dementia; poor short-term memory.
Stage 5	Cognition continues to decline. Suffer from confusion and forget personal details
Stage 6	Severe dementia. Requiring constant supervision.
Stage 7	Individuals nearing death.

ETIOLOGY AND RISK FACTORS

Various prevalence studies provide evidence that age is the major risk factor for AD [12-19], with other factors such as education, gender, social class, genetics, lifestyle, medical and psychiatric conditions, environmental influences and infections also playing a role [20]. Genetic risks include mutations in A precursor protein (APP), Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2), while the Apolipoprotein E (APOE) E4 gene significantly increases susceptibility. Individuals with Down syndrome also face a higher risk due to the presence of an extra copy of the APP gene. Additionally, conditions like inflammation, cardiovascular disease, and diabetes further elevate the risk. Environmental factors such as pollution, stress, and heavy metal exposure may also contribute [11].

PATHOPHYSIOLOGY

To develop the efficient treatment it is important to understand the pathophysiology of Alzheimer's disease. The pathophysiology of Alzheimer's disease is linked to several factors such as cholinergic dysfunction, amyloid hypothesis, tau protein, oxidative stress, neuroinflammation and mitochondrial dysfunction.

CHOLINERGIC HYPOTHESIS

The cholinergic hypothesis played a pivotal role in advancing Alzheimer's disease (AD) research. It suggests that the progressive loss of cholinergic neurons, particularly in the nucleus basalis of Meynert (NBM), contributes significantly to the cognitive decline seen in AD. The NBM is the primary

source of cortical cholinergic innervation, and its degeneration leads to reduced acetylcholine (ACh) levels. This neurotransmitter is essential for memory, learning, and attention. The discovery that cholinergic antagonists impair memory, while agonists improve it, further supported this hypothesis. Consequently, cholinesterase inhibitors like donepezil, rivastigmine, and galantamine emerged as key treatments for managing AD symptoms [21].

AMYLOID HYPOTHESIS:

The amyloid hypothesis is one of the most widely accepted theories explaining the development of Alzheimer's disease (AD). It suggests that the accumulation of amyloid- (A) peptides in the brain is a key factor in the disease's progression. These peptides are produced naturally in the body, but an imbalance between their production and clearance can lead to their buildup. This accumulation forms amyloid plaques, which are toxic to brain cells and trigger a cascade of harmful events, including inflammation and neuron damage [22].

TAU PROTEIN:

The tau protein plays a significant role in the development of Alzheimer's disease (AD). Under normal conditions, tau helps stabilize microtubules in neurons. However, in AD, tau becomes abnormally hyperphosphorylated, causing it to detach from microtubules and form neurofibrillary tangles (NFTs). This disrupts the structural integrity of neurons, leading to impaired communication between brain cells and eventual cell death. Factors such as amyloid- (A) accumulation, oxidative stress, and inflammation are believed to contribute to tau dysfunction. Research continues to explore treatments targeting tau-related pathways, including kinase inhibitors, microtubule stabilizers, and tau aggregation blockers [23].

OXIDATIVE STRESS:

Oxidative stress plays a key role in Alzheimer's disease (AD) by causing damage through an imbalance between reactive oxygen species (ROS) and the body's antioxidant defenses. The brain's high oxygen demand and lipid-rich structure make it particularly vulnerable. In AD, oxidative stress is linked to the buildup of amyloid (A) plaques and neurofibrillary tangles, contributing to neuronal damage. Metals like iron, copper, and zinc further promote ROS production, worsening oxidative damage to lipids, proteins, and DNA. This oxidative damage disrupts mitochondrial function, energy production, and calcium balance, accelerating neurodegeneration in AD [24].

NEUROINFLAMMATION HYPOTHESIS:

The neuroinflammation hypothesis links chronic brain inflammation to Alzheimer's disease (AD) progression. Immune cells like microglia and astrocytes become overactive, releasing inflammatory mediators such as cytokines and TNF, which damage neurons. While microglial activation may initially protect the brain, prolonged inflammation accelerates neurodegeneration. Age-related immune changes (immunosenescence) further worsen this process. Targeting neuroinflammation through therapies that regulate immune responses is being explored as a potential AD treatment strategy [25].

MITOCHONDRIAL DYSFUNCTION:

Mitochondrial dysfunction plays a crucial role in the pathophysiology of Alzheimer's disease (AD). Mitochondria are essential for producing cellular energy, maintaining calcium balance, and reducing oxidative stress. In AD, mitochondrial abnormalities are evident early in the disease progression. Impaired energy metabolism, particularly glucose hypometabolism, is a hallmark feature, observed even before clinical symptoms appear. Disruption in mitochondrial bioenergetics, defects in the electron transport chain (ETC), and decreased activity of key enzymes like pyruvate dehydrogenase (PDHC) and cytochrome c oxidase (COX) contribute to reduced ATP production. Furthermore, mitochondrial DNA (mtDNA) mutations, oxidative damage, and impaired mitochondrial dynamics (fusion and fission imbalance) worsen cellular energy deficits and promote neurodegeneration. These mitochondrial impairments collectively contribute to synaptic dysfunction, neuronal loss, and cognitive decline in AD [26].

PHARMACOLOGICAL TREATMENTS

Donepezil, galantamine, and rivastigmine are FDA-approved AChE inhibitors that help delay cognitive decline in Alzheimer's disease (AD). Memantine, an NMDA receptor blocker, is approved for moderate to severe AD, either alone or with AChE inhibitors, showing benefits in cognition, daily activities, and behavior [27,28]. Recent advancements in Alzheimer's treatment include FDA-approved drugs like Aducanumab and Lecanemab, targeting amyloid plaques. Ongoing trials include phase 3 studies on Donanemab, Simufilam, Fosgonimeton, Masitinib, and KarXT, focusing on disease modification, cognition, and neuroprotection. Phase 2 trials are exploring Varoglutamstat, ABBV-916, CT1812, and E2814, targeting amyloid, tau, and cognitive enhancement [29].

NON-PHARMACOLOGICAL TREATMENTS:

Non-pharmacological therapies (NPTs) play a crucial role in enhancing the quality of life for individuals with Alzheimer's disease [30]. Sleep disturbances are believed to contribute to disease progression, as inadequate sleep can lead to the accumulation of amyloid- (A) in the early stages, potentially triggering memory decline and advancing the condition to AD [31]. Evidence suggests that physical and cognitive activities are beneficial for maintaining cognitive health in older adults [32]. Additionally, music therapy has shown promise in managing behavioral and psychological symptoms of dementia. While some studies support its effectiveness, most are limited by small sample sizes and lack of control. Nevertheless, music therapy remains a valuable option due to its minimal risk of side effects [33].

BIOMARKERS FOR AD

Biomarkers play a crucial role in the early diagnosis, differential diagnosis, and monitoring of Alzheimer's disease (AD). Established biomarkers include amyloid- (A 42) and the A 42/A 40 ratio, which decrease in AD patients and correlate with amyloid plaque deposition. Tau biomarkers, such as total tau (t-Tau) and phosphorylated tau (p-Tau), are elevated in AD, reflecting neurodegeneration and tau tangle formation. Neurofilament light chain (NfL) serves as a marker for axonal damage, while inflammatory markers like YKL-40, GFAP, and sTREM2 are linked to glial activation in early disease stages. The APOE 4 genotype is a genetic risk factor associated with increased amyloid buildup. Imaging biomarkers, including amyloid PET, tau PET, FDG-PET, and MRI, provide valuable insights into amyloid deposition, tau pathology, and brain atrophy patterns. Combining these biomarkers with clinical assessment enhances diagnostic accuracy and supports early intervention strategies [34,35].

Risk management of AD

Alzheimer's disease prevention focuses on early intervention and lifestyle changes. Dietary strategies, particularly those rich in omega-3 fatty acids like DHA, have shown promise in reducing cognitive decline. DHA, found in fish oil, plays a vital role in brain health by supporting memory, neuron protection, and reducing inflammation. Studies suggest DHA may be most effective when introduced early, especially in individuals without the APOE 4 gene. While its impact in advanced AD stages is limited, regular DHA intake may help maintain brain function and reduce the risk of age-related decline [36].

CONCLUSION

Alzheimer's disease remains a significant global health challenge, especially among aging populations. While current treatments provide symptomatic relief, disease-modifying therapies are emerging as promising advancements. Understanding the complex interplay of amyloid pathology, tau dysfunction, oxidative stress, and mitochondrial impairment is vital in developing effective interventions. Lifestyle modifications, including dietary improvements, physical activity, and mental stimulation, are gaining attention for their preventive potential. Ongoing research into biomarkers is enhancing early diagnosis and personalized treatment strategies. A comprehensive approach that combines pharmacological advancements with holistic care can significantly improve outcomes and support individuals affected by AD.

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