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AN UPDATE ON PATHOPHYSIOLOGY AND MANAGEMENT OF ALZHEIMER'S DISEASE

Tejal Mahale[1], Vishakha Gangwal[1], Akshada Shinde[1], Charulata T. Nemade[1*], Hitesh V. Shahare[2]

1. Department of Pharmacognosy, SNJB's SSDJ College of Pharmacy, Chandwad, Nashik
2. Department of Pharmaceutical Chemistry, SNJB's SSDJ College of Pharmacy, Chandwad, Nashik

***Corresponding author- Dr. Charulata T. Nemade,**

Associate Professor, Head of Pharmacognosy Department

SNJB's SSDJ College of Pharmacy, Neminagar, Chandwad, Nashik,

Maharashtra, India.
Tejal Mahale- B.Pharmacy
Vishakha Gangwal- B.Pharmacy
Akshada Shinde- B.Pharmacy
Charulata T. Nemade[1*] - Ph.D
Hitesh V. Shahare - Ph.D

ABSTRACT

Alzheimer's disease (AD), the most common neurodegenerative condition, produces growing problems in memory, cognition, and behaviour and ultimately leads in death. In addition to neuronal and synaptic loss, intracellular neurofibrillary tangles and extracellular senile plaques also develop in the brain as a result of Alzheimer's disease. Alzheimer's disease, the most common form of dementia, is the only one of the top 10 causes of death in the US for which there is no effective treatment. Numerous studies show that factors such as age, some genetic components, diet, and nutrition all raise the risk of AD.

Several hypotheses explain the pathophysiology of AD including *amyloid cascade hypothesis, Tau hypothesis, cholinergic hypothesis, mitochondrial cascade theory, metabolic hypothesis.* Genetic factors play a role in the development of Alzheimer's disease; characterised by *insulin/IGF resistance and insufficiency in the brain.* In mild Alzheimer's disease patient suffers memory loss that disrupts daily life, losing track of dates or knowing current location etc. while in severe cases patient in unable to communicate, have no awareness of recent experiences or surroundings, increased sleeping, loss of bowel and bladder control etc. Alzheimer's, physicians may use medical history, mental status tests, physical and neurological exams, diagnostic tests and brain

imaging to diagnose the disease. Cerebral spinal fluid tests for low beta-amyloid 42 and increased tau is helpful to diagnose preclinical stage AD treatment aims to enhance the patient's functioning and quality of life. Tacrine, donepezil, galantamine, and rivastigmine are the four medications that have received FDA approval for the treatment of Alzheimer's disease. In this overview, we discuss the various theories regarding its onset, symptoms, and treatments, including cholinesterase inhibitors, beta-amyloid ligands, antioxidants, antipsychotics, novel drug delivery systems, and the effects of diet and exercise on AD.

Keywords: Alzheimer's disease; memory; *cholinergic hypothesis*; cerebral spinal fluid; Tacrine; antioxidants

INTRODUCTION

Alzheimer's disease (AD) is defined clinically by a gradual decline in memory and other cognitive functions and neuropathologically by gross atrophy of the brain and the accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles.[1] AD is the most common form of dementia in the elderly population[2] and is characterized clinically by a progressive decline in memory and other cognitive functions as well as neuropathologically by gross atrophy of the brain and the buildup of extracellular amyloid plaques and intracellular neurofibrillary tangles.[3]

AD is a neurological condition that mainly affects persons over the age of 65 and progresses fatally. Neuropsychiatric problems and a steady decline in everyday functioning are the most common symptoms of AD.[4] The World Alzheimer Report from 2018 estimated that roughly 50 million people worldwide suffer from dementia and that this number is likely to rise to 152 million by 2050, which would represent more than a 3-fold increase compared to today. As life expectancy rises, it is expected that the number of AD cases globally will rise.[5]

There are two major types of Alzheimer's disease, early onset and the more common late onset. Both types have a genetic component. Early onset AD is very rare, usually caused by changes in gene passed from parents to child. The signs first appear between a person's 30 and mid-60 years age. Late onset AD is the most common type, and may involve a gene called APOE ε4. The first sign appears in person's mid-60 year's age.[6]

SIGNS AND SYMPTOMS[7]

Early (mild) dementia symptoms

Learning and keeping new information become challenging due to the impairment of recent memory. The development of linguistic issues, particularly word finding issues, mood swings, and personality changes. Patients may gradually struggle with independent daily life skills (such balancing their chequebook, getting about, or remembering where they put things). It's possible to have poor judgement, insight, or abstract thinking. Patients may become agitated, hostile, and irritable in response to losing their independence and memory.

Early-onset AD is brought on by mutations in the presenilin 1 (PSEN1), 2 (PSEN), and b-amyloid precursor protein (APP) that are dominantly inherited (AD)

Intermediate (moderate) dementia symptoms

Patients lose their ability to remember and learn new knowledge. Remote experiences are remembered less clearly but not entirely. Patients may need assistance with routine everyday tasks like eating, dressing, and using the restroom.

Patients may more easily experience feelings of agitation, anxiety, self-centeredness, rigidity, or anger. They could acquire sadness, become irrational, lose their spontaneity, become more passive, have a flat affect, or just generally retreat from social situations. Exaggerated personality traits or routines could develop.

Late (severe) dementia symptoms

Patients may develop incontinence if they are unable to walk, feed themselves, or perform any other activities of daily living. Memory from the past is fully gone. Some patients may have trouble swallowing. They are susceptible to malnutrition, pneumonia (particularly from aspiration), and pressure sores and may develop muteness.Coma and death accompany end-stage dementia and are typically brought on by infection.

PATHOPHYSIOLOGY

The neurobiological changes that cause AD includes synaptic loss, specific neuronal brain lesions (senile neuritis plaques and neuroticbrillary tangles), and vascular amyloid deposits within the cerebral cortex.A significant first stage in the onset of AD is the formation of b-amyloid (Ab), according to genetic, biochemical, and neuropathological evidence. The amyloid precursor protein (APP) fragment Ab is generated by the sequential activity of the b- and g-secretases. The two primary neuropathologic features that underlie the symptoms of AD are neurofibrillary tangles (NFTs) and senile plaques, which are extracellular deposits of filamentous 3-amyloid, a protease cleavage result of amyloid precursor protein.[8]

Several hypotheses addressing the pathophysiology of AD are supported by epidemiologic, clinical, and experimental data, including the following.

The *amyloid cascade hypothesis* asserts that the buildup of neuritic plaques, diffuse plaques, or oligomeric forms in the brain is the primary pathogenic process.[9] The amyloid hypothesis for AD postulates direct causes and effects in a cascade starting with Ab deposition and moving on to Tau pathology, synaptic dysfunction, inflammation, neuronal death, and, in the end, dementia.

The *cholinergic hypothesis* states that areas with lower levels of acetylcholine and choline acetyltransferase activity include the cerebral cortex.

The main event, according to the *Tau hypothesis,* is tau hyperphosphorylation.[10, 11] The microtubules and tau, a protein that is abundant in axons, are related. Neurodegeneration results from tau aggregation under pathological conditions because it harms the axons of neurons.[12] In its hyperphosphorylated state, the soluble tau protein has a propensity to take on an abnormal shape and aggregate into insoluble fibrillary material, which appears as neuropil threads (NTs) in cellular processes and neurofibrillary tangles (NFTs) in neuronal somata.[13]

The *mitochondrial cascade theory* postulates that the first pathogenic event leading to neurodegeneration is brain mitochondrial malfunction.[14]

According to the *metabolic hypothesis*, diseases including obesity, diabetes, and hypercholesterolemia are brought on by metabolic imbalances. Alterations in glucose transport systems, altered glycolysis, oxidative stress, and diminished mitochondrial activity are all indicators of alterations in glucose metabolism. The disease's pathological abnormalities, which include hypometabolism, disruption of the blood-brain barrier (BBB), oxidative stress, mitochondrial dysfunction, and neuroinflammation, can be brought on by a number of metabolic disorders that are important risk factors for AD.[15] The primary histopathological feature of the aggregation of soluble proteins into insoluble clumps.[16]

One explanation explaining the *gender disparities in ADD* claims that women's brains are more prone to the condition. This is supported by research showing sex variations in volumetric change over time, memory trajectories, and tau accumulation rates.[17] Inflammation in AD has emerged as a significant pathology that likely plays a role in the onset and progression of the condition.[18] Numerous investigations have demonstrated that persistent brain inflammation accelerates other fundamental diseases.[19]

Dysregulated lipid homeostasis, which significantly contributes to AD aetiology, is associated with ageing. Lipid dysregulation to AD include changes in the gut-brain axis, the neuronal signalling system.[20]

AD is characterised by *insulin/IGF resistance and insufficiency in the brain.* In the early stages of AD, cerebral glucose uptake and blood flow are both reduced by up to 45%. Later, when metabolic and physiological issues worsen, there is a 55–65% reduction in cerebral blood flow. The two main pathophysiological mechanisms of brain insulin/IGF resistance in AD are 1) the gradual loss of insulin/IGF responsive neurons caused by the removal of trophic factors and 2) impaired insulin/IGF ligand-receptor binding caused by pathological changes in membrane lipid composition, along with probably decreased membrane receptor expression.[21]

Oxidative stress and mitochondrial pathology in AD: The onset of AD is accompanied with an increase in oxidative damage, indicating the significance of mitochondrial dysfunction which affects normal synaptic function and for the transmission of brain impulses. Alzheimer's fibroblast mitochondria have damaged calcium transport pathways and have increased sensitivity to oxygenic free radicals.[22] The mitochondrial abnormalities present in AD is increased by the fact that oxidative damage in the illness, including damage to nucleic.[23]

The *Ca2+ theory* of AD states that amyloid metabolism increases Ca2+ signalling by increasing both the entry of external Ca2+ and the sensitivity of the channels (InsP3 and ryanodine receptors) that release Ca2+ from the internal reserves.[24]

GENES INVOLVE IN AD

Genetic factors play a role in the development of AD, especially early-onset (familial) AD, which accounts for 5% to 10% of all AD cases.[25]Through molecular genetic research (AD), four separate genes have been connected to inherited susceptibility to AD. It is estimated that at least two, and possibly many more, AD

susceptibility loci still need to be identified because only about 50% of FAD cases are connected to the four FAD loci that have so far been identified.Presenilin, The Amyloid Precursor Protein, Presenilin 1, and Apolipoprotein E.The long arm and pericentromeric region of chromosome 10q, as well as the pericentromeric region of chromosome 12 (Alzheimer Type 5), may contain additional susceptibility loci. (Type 6 Alzheimer's).[26, 27]

SIGNS AND SYMPTOMS[28]

Signs of Mild Alzheimer's disease

Memory loss that disrupts daily life, Poor judgment, leading to bad decisions, Loss of spontaneity, losing track of dates or knowing current location, taking longer to complete normal daily tasks, Repeating questions, trouble in handling money and paying bills, misplacing things, increased anxiety.

Signs of moderate Alzheimer's disease

Increased confusion and memory loss, such as forgetting events or personal history, Withdrawal from social activities, Inability to learn new things, Difficulty organizing thoughts, Problems coping with new situations, Difficulty carrying out familiar, multistep tasks, such as getting dressed, Impulsive behaviour, Inappropriate emotional outbursts, hallucinations, delusions and paranoia, Occasional problems recognizing family members and friends, Restlessness, agitation, anxiety, tearfulness, wandering especially in late afternoon or evening.

Signs of severe Alzheimer's disease

Inability to communicate, no awareness of recent experiences or surroundings, Weight loss with little interest in eating, Seizures, Difficulty swallowing, Groaning, moaning, or grunting, Increased sleeping, Loss of bowel and bladder control

DIAGNOSIS

To diagnose Alzheimer's, physicians may use medical history, mental status tests, physical and neurological exams, diagnostic tests and brain imaging.

Standard laboratory tests reveal no particular abnormalities. To rule out other causes, complete blood count (CBC), complete metabolic panel (CMP), thyroid-stimulating hormone (TSH), and B12 are typically examined.[29, 30, 31]

On a CT scan, the third ventricle is enlarged and there is cerebral atrophy. In order to diagnose the preclinical stage, cerebral spinal fluid (CSF) tests for low beta-amyloid 42 and increased tau is important. Neuropsychological testing is the most reliable tool for identifying mild cognitive impairment in the early stages of disease.Volumetric MRI reveals shrinkage in the medial temporal lobe in Alzheimer's disease. However, the efficacy of volumetric MRI for early identification of AD is debatable because hippocampal atrophy is also connected to typical age-related memory impairment. Patterns of dysfunction in smaller brain regions of the medial temporal and parietal lobe are being mapped using functional brain imaging techniques like PET, fMRI, and SPECT. Recent advancements in brain imaging technologies have made it possible to

identify the amyloid plaques and neurofibrillary tangles that are the primary histological signs of Alzheimer's disease.[32]

When evaluated serially, neuroimaging employing MRI and PET (Positive Emission Tomography) can provide accurate assessments of preclinical illness and the rate of change. PET may be more effective than clinical evaluation at distinguishing between persons with AD and dementia with Lewy bodies.[33]

TREATMENT

At this moment, there is no known way to prevent or treat Alzheimer's disease. Any type of AD treatment aims to enhance the patient's functioning and quality of life.

Antipsychotic medications can be used to treat psychosis, agitation, and some behavioural issues. Treatment options for behavioural problems include the mood stabilisers carbamazepine and valproate, the sedating antidepressant trazodone, the atypical anxiolytic buspirone, and SSRIs.[34]The majority of drug candidates being developed at the moment are for anti-amyloid therapy. One of the key targets is beta-amyloid, whose accumulation in the brain is thought to have a role in the development of Alzheimer's disease, and tau protein.[35]

Cholinesterase Inhibitors

According to the cholinergic hypothesis of AD, cholinergic systems in the basal forebrain are harmed on early in the disease process, including loss of acetylcholine neurons causing memory loss and deterioration of other cognitive and noncognitive functions like neuropsychiatric symptoms. Donepezil, rivastigmine and galantamine are a brain-selective drug.[36] Cholinesterase inhibitors act by increasing the level of acetylcholine; helps to improve learning, memory and cognitive functions. FDA approved tacrine, the first drug for the 1995 saw the introduction of tacrine as a therapy for AD.[37] Galantamine, donepezil, and rivastigmine are examples of the second generation AChEI medications that are currently in widespread usage.[38]Donepezil is used once daily, starting at a dosage of 5 mg daily. 1.5 mg twice daily is the starting dose of rivastigmine.[39]

N-Methyl-D-aspartate Receptor (NMDA) Antagonist.

It is well known that glutamate-mediated excitotoxicity causes calcium excess, mitochondrial malfunction, and increased nitric oxide production. These effects can be harmful to cells because they cause high amounts of oxidants and trigger neuronal death. NMDA receptor antagonists, such as memantine, which the Food and Drug Administration licenced in 2003, can prevent this overstimulation. It is approved by the FDA for treating moderate to severe Alzheimer's disease. Dizziness, body aches, headache, and constipation are common side effects. It can be taken in combination with cholinesterase inhibitors.[40]

Glutamatergic-System Modifiers

In people with AD, glutamatergic neurotransmission, which is crucial for learning and memory, is significantly disturbed. The decline in glutamatergic function seen in AD may be linked to the Abeta peptide's increased oxidative stress. Supplementing with oestrogen and antioxidants like vitamin E are treatments for oxidative damage brought on by glutamate receptor activation.[41]

Herbal medicine in the treatment of Alzheimer's disease-

Ginkgobiloba-

Ginkgo biloba extract (GBE) can lessen AD symptoms and slow the disease's progression. The first phases of AD appear to be when GBE is most effective. GBE has shown the ability to boost cholinergic activity and ameliorate many symptoms of the condition. Ginkgo biloba must be taken continuously for at least 12 weeks in all forms. In patients with mild to moderate AD, cholinesterase inhibitors are advised above Ginkgo biloba as a treatment.[42]

HuperzineA

Huperzine A, an alkaloid was produced from a specific kind of club moss (*Huperzia serrata*). It is marketed as a dietary supplement for memory loss and mental impairment, despite being more of a medication than an herb. Vincamine, found in the leaves of periwinkle (Vinca minor) and the seeds of other African plants, is the source of the chemical known as vinpocetine. Vinpocetine does not exist in nature in any substantial amounts, but it is utilised as a therapy for memory loss and mental disability. It needs a large amount of laboratory-based chemical effort to product.[42]

Melissa officinalis

Melissa officinalis (lemon balm) has been demonstrated to improve cognitive function and reduce agitation in people with mild to severe AD. Patients receiving *M. officinalis* have reportedly shown central nervous system ACh receptor activation with nicotinic and muscarinic binding properties.[42]

Salvia officinalis

After ingesting *Salvia officinalis* (sage) extract for 16 weeks, patients with mild to moderate AD demonstrated statistically significant improvements in cognition. The adverse effects of salvia were mostly those that would be anticipated from cholinergic stimulation and were comparable to those that have been associated with cholinesterase inhibitors.[42]

Curcuma longa

The active components of *Curcuma longa*is curcumin which has anti-inflammatory, antioxidant, anticancer, and antibacterial effects, among others. By reducing oxidative damage and tau hyperphosphorylation, curcumin (at a dosage of 5–10 M) shielded PC12 cells against the neurotoxicity caused by A. This shows that curcumin might work as a medication to treat ADC.[43]

Bacopa monnieri

*Monnieri*is used for memory and mental acuity improvement. According to research, bacopa inhibits AChE activity. Additionally, *B. Monnieri* harvests neuronal cells that have been protected from amyloid-induced damage. Additionally, reactive oxygen species (ROS)concentrations in neurons treated with *B. monnieri* extract decreased, indicating that *monnieri*reduced oxidative stress in the cells.[43]

Zingiber officinalis

In vitro experiments have shown that it has an AChE inhibiting effect. By suppressing the AChE enzyme, ACh levels in synapses can be increased. This increases cholinergic pathway activity and enhances cognitive function in AD patients.[44]

Disease modifying therapies

Disease modifying therapies (DMTs) are still being developed in preclinical and early AD due to the urgent need for preventive therapies that stop the progression of AD before the onset of symptoms or when symptoms are first appearing.[45]

Antioxidants in the treatment of AD

Exogenous antioxidant therapy may be beneficial for those with early-stage AD or for those who are at risk for developing AD, according to recent studies.[46] High levels of protein oxidation, lipid oxidation, DNA oxidation, and glycoxidation are the key signs and symptoms of AD. Antioxidant therapy is a promising way to halt the advancement of the illness since oxidative stress is brought on by an imbalance between the creation of ROS and the antioxidative defence system, which is in charge of eliminating ROS. A promising drug for the therapy of AD is silibinin, an isolated flavonoid from *Silybum marianum*, which has been shown to lessen memory loss and the oxidative damage caused by ageing in mice.[43]

Vitamin E treatment

AD manifestly generates ROS, which promotes the oxidation of all macromolecules. Vitamin E has more antioxidant action against peroxyl radicals than other antioxidants like glutathione or -carotene.[47]

Polyphenols

Numerous studies on animals have demonstrated that polyphenols delay cognitive ageing and stop the development of AD. Data from a 100-person, double-blind, randomised clinical trial suggests that antioxidant drinks' polyphenol content may benefit AD patients by reducing their homocysteine levels.[48]

FUTURE DIRECTIONS

A crucial area of research for AD diagnosis is the development of person-specific diagnostic models.[48] Amyloid is the main aim of trials for prodromal (or moderate cognitive impairment) and pre-symptomatic Alzheimer's disease. A4 study (Anti-Amyloid Treatment in Asymptomatic Alzheimer's) in cognitively normal 65–85-year-olds with aberrant amyloid accumulation as measured by PET scans is one of the pre-symptomatic AD trials using monoclonal medicines targeting amyloid.[46] The idea that anti-amyloid medications should be begun as early in the disease process as possible is in keeping with the notion that genetic diversity in how the brain responds to amyloid deposition is a potential treatment target for the illness.[49]

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Ethical approval

There is no ethical issue.

Author contribution

TBM, VMG and AVS have read and collected the information about Alzheimer's disease. CTN carried out the conceptualization, drafting and communication for publication. HVS read and approved the content. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Conflict of interest

We have no conflict of interest to declare.

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