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Alzheimer's disease: Modern Treatment & Strategy A Review

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Abstract: Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain and it is the main cause of dementia, which is characterized by a decline in thinking and independence in personal daily activities. AD is considered a multifactorial disease: two main hypotheses were proposed as a cause for AD, cholinergic and amyloid hypotheses. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease (1).In India, more than 4 million people have some form of dementia. Worldwide, at least 44 million people are living with dementia, making the disease a global health crisis that must be addressed(2).It is the fourth leading cause of death in the United States and is becoming prevalent in many other countries. The total brain size shrinks with Alzheimer's - the issue has progressively fewer nerve cells and connections. As such there is no known cure for Alzheimer's disease the death of brain cells in dementia cannot be halted or reversed. Along with an aim to improve research into prevention and treatment, the goals of the plan also include measures for present interventions. To help people suffering expand support for people with Alzheimer's disease and their families, enhance public awareness and engagement and expand your support towards them. Enhance care quality and efficiency. There are no disease-modifying drugs available for Alzheimer's disease but some options may reduce its symptoms and help improve quality of life and thereby help the patients to some extent. There are four drugs in a class called cholinesterase inhibitors approved for symptomatic relief i.e.Donepezil (brand name Aricept), Alantamine (Reminyl), Rivastigmine, and Tacrine (Cognex). A different kind of drug, memantine (Namenda), an N-methyl-D-aspartate (NMDA) receptor antagonist, may also be used, alone or in combination with a cholinesterase inhibitor. As with other types of dementia and neurodegenerative disease, a major part of therapy for patients with Alzheimer's comes from the support given by healthcare workers to provide dementia quality-of-life care, which becomes more important as needs increase with declining independence and increasing dependence(3).
Keywords: Amyloid Plaque, Cholinesterase, NMDA Antagonist, Immunotherapy.

Introduction: Alzheimer's Disease is a neurological disease where degeneration of neurons occurs. As neurons transmit nerve impulses from the brain to various parts of the body and vice versa, any damage to this neuron may result in adverse effects on the body such as Alzheimer's Disease(AD). Alios Alzheimer 1st identified an unusual disease of the cerebral cortex that had affected a woman Auguste D. This unusual disease had caused symptoms of memory loss disorientation and hallucination up until her death. In 1910 Emil Kraepelin named the disease as 'ALZHEIMER'S DISEASE 'in the 8th edition of the 'Handbook of Psychiatry [4].

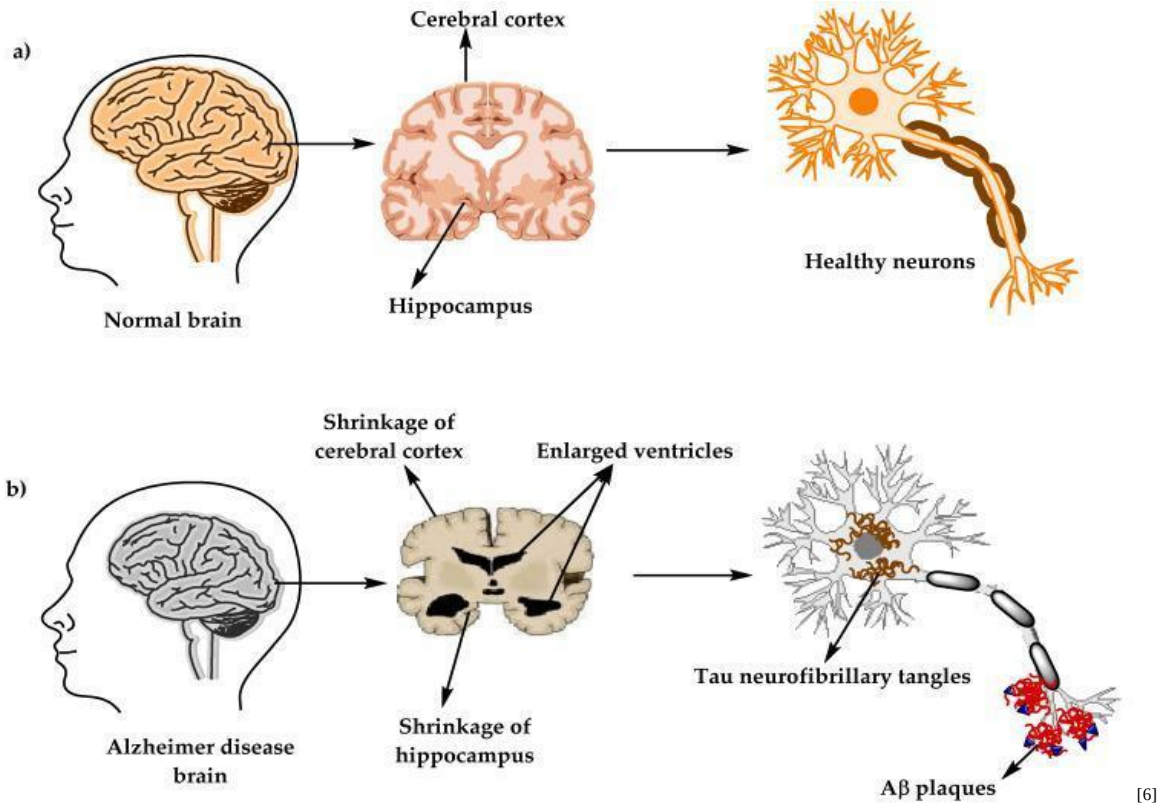
Alzheimer's disease is one cause of dementia. Dementia is an overall term for a particular group of symptoms. The characteristic symptoms of dementia are difficulties with memory, language, problem-solving, and other thinking skills. Dementia has several causes such as Alzheimer's disease, Cerebrovascular disease, Frontotemporal degeneration (FTD), Hippocampusampal sclerosis (HS), Lewy body disease, and Parkinson's disease (PD). These causes reflect specific changes in the brain.

There are various factors which may lead to AD like hypertension, diabetes, habitat, lifestyle of an individual, depression, age, etc.

In AD there is a loss of memory, loss of body function, and thinking power is also decreased. In AD there is an accumulation of abnormal proteins such as Amyloid beta peptides and phosphorylated tau in most of the affected parts of the brain, the medial temporal lobe, and neocortical structures [2]. Two types of neuropathological changes give evidence and progress of AD which are positive lesions and negative lesions. In positive lesions, there is an accumulation of neurofibrillary tangles (NFT), amyloid plagues, dystrophic neuritis, neuropil threads, and other deposits in the brain of AD patients. Whereas in negative lesions there is significant atrophy due to neural, neuropil, and synaptic loss [6,7,8].

As population in India is increasing rapidly. By 2050, there will be increase in 20% of the total Indian population of individuals of age 60 and older. This increase in aged people is a risk factor for increase in cases of AD in India. In southern part of India (Kerala), the population growth is moving towards zero as compare to the northern part of India(Uttar Pradesh). According to demographic population the people of 60 and above are contribution to 8.6%of population. Unability to perform task or any function is a major cause in aged persons which occur due to dementia. By 2030, there will be increase in cases of dementia from 52million to 82million worldwide which may increase to 152 million by 2050. As the population is increasing this leads to increase in AD cases. Countries like India, China were population is rapidly increasing are significantly contributing increase in Alzheimer's Disease.

For this it is important to study the approximate the dementia cases at state and central level, carrying out research on susceptibility of AD, evaluate the load of dementia on patients 'family. This study is carried out in by Harmonized Diagnostic Assessment of Dementia for Longitudinal Aging Study of India (LASI-DAD)[10].



[6]

[6] AD leads to nerve cell death and tissue loss and over time the brain size shrinks affecting all the functions of the brain. Cell loss in the cortex region of the brain causes damage to the thinking, planning, and remembering ability of the brain. Shrinkage is most severe in the hippocampus area of the brain important for the formation of new memories. Apart from this shrinkage in the bracellularon the ventricles, fluid-filled space in the brain, grows larger. Compared to any healthy person an AD patient's brain has fewer nerve cells and synapses but a high build-up of tangles and plaques which might be the reason for this cell death. These plaques block cell-to-cell signalling and activate immune system cells that cause inflammation and devour disabled cells. Tau proteins collapse into twisted strands called tangles because nutrients and other essential supplies no longer move through the cells and they die.

Etiology & Pathophysiology:

The causes of AD are unknown, but there are some hypotheses proposed to explain this complex neurodegenerative process. Many experts believe that this disease develops due to many causes either modifiable or non-modifiable, genetic, environmental, etc. The cause of alzheimer's disease is given by two hypothesis i.e.the amyloid cascade hypothesis and the phosphorylated hypothesis [11]

The core pathophysiology of Alzheimer's disease is unintelligible and extensive research is ongoing to clarify the fundamental pathological process involved With the current ongoing researches,numerous explanation have been proposed .The most widely recognized theories include Amyloid cascade theory and Tau hypothesis

The amyloid cascade theory/hypothesis

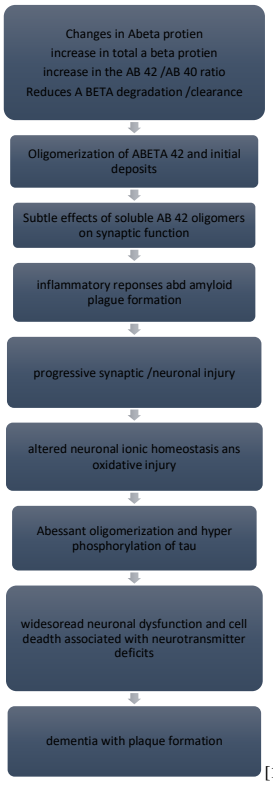
According to this hypothesis, AD onset occurs as follows:

The amyloidogenic pathway metabolizes amyloid precurssor protien, resulting in the excess synthesis of the A pepetide and poor clearance of it , thereby provoking excess production of the A peptide and defective elimination of the same.4,5 The A protein is produced by the breakdown of APP, a plasma membrane protein with a single domain found in several types of cells These cells include neurons , asterocytes ,oligodendrocytes,and glial cells[11].It is encoded by a gene on chromosome 21 that can be expressed as one of eight isoforms ;the APP695 isoform is the most prevalent in the brain.This protein is cleaved by the enzymes and secretase as well as protein complex comprising the presenilin gene.Under healthy settings , APP is catabolized by secretase via non amyloidogenic pathway results in the fragment (s)APP, which remains in the extracellular space, and a carboxy-terminal fragment of 83 amino acids (C83) attached to the plasma membrane. (s)APP regulates neural excitability, improves synaptic plasticity, learning, and memory, and increases neural resistance to oxidative and metabolic stress. Nevertheless, in a neuropathological situation, APP is metabolized by the amyloidogenic pathway in which BACE (-secretase1) cleaves APP at the N-terminus. In turn, -secretase cleaves it at the C-terminus to yield (s)APP and A40/42 fragments (which remain in the extracellular space) and a-terminal fragment with 99 amino acids (C99) that can be transported to the cell interior and translocated to the nucleus. Here, it may induce the expression of genes that promote neuronal death by apoptosis.6,7 APP regulates neuronal survival, protection against toxic

external stimuli, synaptic plasticity, and cellular adhesion. When it is transformed into A40/42, however, it affects synapse function, decreases neuronal plasticity, alters energy and glucose metabolism, induces oxidative stress and mitochondrial dysfunction, and disturbs cellular calcium homeostasis.

Differential cleavage by --secretase produces different A peptides: A40 is the predominant species, whereas A42 is the main component of senile plaques. Peptide A42 is both more likely to form aggregates and more neurotoxic than peptide A40, which gives rise to the hypothesis that it represents the pathogenic species of

A. First, A42 oligomerizes and is deposited as senile plaques in the limbic system and associative cortex, exerting toxic effects on neuronal synapses. The second stage involves glial response and activation of astrocytes and surrounding microglia; this releases cytokines or components of the complement system, resulting in inflammatory responses. Furthermore, the neuron experiences oxidative stress; calcium ion homeostasis is disrupted, which leads to hyperactivation of kinase proteins and inactivation of phosphatases. For this reason, tau protein is hyperphosphorylated and forms the neurofibrillary tangles that accumulate in synapses and neuronal bodies. These structures cause neuronal death by apoptosis and a deficit of neurotransmitters. The entire cascade of processes concludes with the onset of dementia. This being the case, both tau and A proteins (mainly A42) are recognized as the primary targets for disease-modifying therapy in AD. The hypothesis mentioned above does not give us the main cause but gives us complete information about what happens and how the pathogenesis takes place [11]



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The Tau hypothesis has also been proposed, considering AD histopathology reveals intraneuronal neurofibrillary lesions made up of tau proteins. Tau proteins are mainly found in neurons and are involved in the assembly and stabilization of the neuronal microtubule network. Tau protein becomes pathological when the phosphorylation regulation becomes unchecked and hyperphosphorylated tau proteins polymerize into filaments and become neurofibrillary tangles. This leads to malfunction of the structural and regulatory actions of the cytoskeleton and then leads to abnormal morphology, axonal transport, and synaptic function of neurons, thus leading to neurodegeneration[11]

Mitochandrial hypothesis

The reduced mitochondrial function to handle the free-radical is considered the initiating step in alzheimer's disease[14]

The genetics of AD should also be considered to play an influential role in the pathogenesis, alongside inflammation, apoptosis, and plaque buildup. The APP gene located on 21q21, mentioned above, was the first discovered causative gene of AD [12]. Advances in genetic research have identified two distinct forms of AD: Familial Alzheimer's Disease (FAD) and Sporadic Alzheimer's Disease (SAD), with the latter making up the majority of cases. Important advances in the 1990s and early 2000s revealed that FAD is the result of autosomal dominant mutations in APP, PSEN1, and PSEN2 genes, located on chromosome 21, 14, and 1, respectively [12,16]. More specifically, PSEN1 and PSEN2 contain the necessary amino acid residues required for the catalytic active site of gamma-secretase. Certain mutations of these genes lead to increased production of Ab peptides and neurodegeneration. Far more commonly, the genetic risk factor for SAD was identified as the type e4 allele on chromosome 19, of the gene for Apo lipoprotein E (APOE), a low-density lipoprotein carrier resides. APOE is present in roughly 50- 60% of patients with AD compared to 20-25% in healthy elderly adults without a history of familial AD. APOE is associated with an approximately three-fold risk of developing AD if one copy is present, and there is an eight-fold risk if two copies are present.[12]

Gene	Proposed mechanism of dysfunction contributing to pathogenesis in Alzheimer's disease
APP	Defects in synaptic development and neuronal migration, A-beta peptide synthesis defects
PSEN 1 / 2	Altered gamma-secretase activity resulting in elevated amyloid beta-42 levels
APOE – epsilon 4	Lipid and cholesterol dysmetabolism, synaptic inflammation, impaired clearance of amyloid beta-42, LDL receptor impairment
CLU	Deposition and metabolism of amyloid beta-42
ABCA7	Immune-mediated and lipid metabolic response alterations
CR1	Aggravated senile plaque formation
CD33	Influences microglia-mediated clearance of amyloid beta-42
MS4A	Deregulation of intracellular calcium concentration
EPHA1	Axonal guidance changes
SORL1, BIN, CD2AP, PICALM	Alterations in lipid metabolism

[12]

Treatments:

There is no cure for Alzheimer's disease. Only symptomatic treatment is available. Categories of drugs are approved for the treatment of Alzheimer's disease: Cholinesterase inhibitors, N-methyl D-aspartate (NMDA) antagonists, and Immunotherapy.

Cholinesterase Inhibitors: Acetylcholine is a neurotransmitter that plays a crucial role in memory, learning, and cognitive processes in the brain. It is released by neurons and acts as a chemical messenger between nerve cells. Cholinesterase inhibitors act by increasing the level of acetylcholine; a chemical used by nerve cells to communicate with each other and is important for learning, memory, and cognitive functions. Examples of cholinesterase inhibitors are - Donepezil, Rivastigmine, and Galantamine.

1) Donepezil: Donepezil is an acetylcholinesterase inhibitor. It works by blocking the action of acetylcholinesterase, the enzyme responsible for breaking down acetylcholine. By inhibiting this enzyme, donepezil increases the concentration of acetylcholine in the synaptic cleft, leading to enhanced cholinergic neurotransmission. When donepezil inhibits acetylcholinesterase, acetylcholine remains active in the synaptic cleft for a longer period. This increased availability of acetylcholine promotes improved communication between neurons in the cholinergic system. As a result, cognitive functions related to memory and learning may be enhanced [16]

2) Rivastigmine: Treats mild, moderate, and severe Alzheimer's by preventing the breakdown of acetylcholine and butyrylcholine (a chemical similar to acetylcholine) in the brain. This carbamate derivative of physostigmine inhibits both AChE and BuChE but is more selective for the GI isoform of AChE that predominates in certain areas of the brain. Rivastigmine is highly lipid-soluble and enters the brain easily. Greater augmentation of cholinergic transmission in the brain is obtained with mild peripheral effect. The carbamyl residue introduced by rivastigmine into the AChE molecule dissociates slowly resulting in inhibition of cerebral AChE for up to 10 hours despite the 2 hr plasma t½ of the drug [16]

3) Galantamine: This is primarily known for its role as an acetylcholinesterase. It is a natural alkaloid that selectively inhibits cerebral AChE and has some direct agonistic action on nicotinic receptors as well. Galantamine has produced cognitive and behavioral benefits in AD which are comparable to rivastigmine and donepezil. In Alzheimer's disease and related dementias, there is a decrease in acetylcholine levels, leading to cognitive and memory impairments. Galantamine works by binding to and inhibiting acetylcholinesterase.

N-methyl D-aspartate (NMDA) antagonists: (NMDA) antagonists are a class of compounds that interact with the NMDA receptor, a subtype of glutamate receptor in the brain. These receptors play a crucial role in synaptic plasticity, learning, and memory. NMDA antagonists are used for various purposes, including anesthesia, pain management, and treatment of certain neurological disorders. The NMDA receptor is a complex ion channel protein located in the post-synaptic membrane of neurons. It consists of multiple subunits, including GluN1, GluN2A-D, and GluN3A-B. The receptor has binding sites for the neurotransmitter glutamate and a co-agonist glycine. Activation of the NMDA receptor requires the simultaneous binding of glutamate and glycine, leading to a conformational change that allows calcium (Ca2+) and sodium (Na+) ions to enter the neuron. NMDA antagonists exert their effects by blocking the ion channel of the NMDA receptor, thereby preventing the influx of calcium ions and disrupting normal neuronal communication. This can lead to a state of functional disconnection or decreased excitability in the brain. The reduction in calcium influx can prevent excessive activation of neuronal pathways and excitotoxicity, a process where excessive calcium entry leads to cell damage and death[15].
NMDA antagonists have several clinical applications:

1. Anesthesia: NMDA antagonists like ketamine are used in anaesthesia to induce a dissociative state where the patient becomes disconnected from sensory input.
2. Pain Management: NMDA receptors play a role in the perception of chronic pain. By blocking these receptors, NMDA antagonists can help alleviate pain by interrupting pain signalling pathways.
3. Depression Treatment: Some NMDA antagonists, including ketamine, have shown rapid and potentially sustained antidepressant effects. The disruption of dysfunctional synaptic patterns and the promotion of synaptic plasticity may contribute to these effects
4. Neurological Disorders: NMDA antagonists are being studied for their potential in treating neurological disorders such as epilepsy and neurodegenerative diseases. By modulating NMDA receptor activity, these compounds may help regulate neuronal excitability and reduce neurotoxicity.

NMDA antagonists can have side effects due to their impact on normal brain function. These may include hallucinations, confusion, dissociation, and cognitive impairments. The therapeutic use of these compounds requires careful consideration of their benefits and potential risks [16].

Anti-inflammatory drugs Epidemiological evidence suggests that long-term use of NSAIDs protects against the development of AD [McGeer et al. 1996]. Despite this premise, prospective studies of rofecoxib [Reines et al. 2004], naproxen [Aisen et al. 2003], diclofenac [Scharf et al. 1999], celecoxib [Soininen et al. 2007], dapsone [Eriksen et al. 2003], hydroxychloroquine [Aisen et al. 2001] and nimesulide [Aisen et al. 2002] failed to slow progression of cognitive decline in patients with mild-to-moderate AD. By contrast, indometacin may delay cognitive decline in this subset of patients, but gastrointestinal toxicity is treatment-limiting [Rogers et al. 1993]. Because of general concerns about lack of efficacy, gastrointestinal toxicity, myocardial infarction, and stroke, NSAIDs are not considered to be viable treatment options for patients with AD[18]

Immunotherapy: -Immunotherapy is a treatment approach that harnesses the body's immune system to target specific diseases. In the context of Alzheimer's disease, which is a progressive neurodegenerative disorder characterized by the accumulation of beta-amyloid plaques and tau tangles in the brain, immunotherapy aims to target and clear these abnormal protein aggregates. The most studied form of immunotherapy for Alzheimer's disease involves the use of monoclonal antibodies. These antibodies are designed to specifically bind to and neutralize the harmful proteins associated with the disease. The goal is to enhance the clearance of beta-amyloid plaques and reduce the associated neuroinflammation and neuronal damage.

Active immunization- Aβ, phosphorylated tau (ptau) peptides, or specific artificial peptides such as polymerized British amyloidosis (ABri)-related peptide (pBri)57 are used as immunogens. ABri is a rare hereditary amyloidosis associated with a mutation that results in the production of a highly amyloidogenic protein with a unique carboxyl terminus that has no homology to any other human protein. The pBri peptide corresponds to this terminus and induces an immune response that recognizes Aβ and ptau. Antigen-presenting cells present the immunogens to B cells. The use of Ab or ptau peptides will produce antibodies to Ab or ptau epitopes, respectively. The use of pBri will produce antibodies to both Aβ and ptau epitopes. Active immunotherapy includes AADvac1 contains a synthetic tau peptide and is currently studied in a phase 2 clinical study in mild to moderate AD (NCT02579252). [20]

Passive immunization- Monoclonal Abs to Ab, ptau, or b sheet epitopes are systemically and adequately for BBB penetration infused. As antibodies cross the BBB, they act to clear, degrade, or disaggregate or neutralize their targets.56 Stimulation of innate immunity either by active or passive immunization also ameliorates the pathology of the disease by promoting microglia and macrophage function.56 Overall, Aβ-targeted strategies seem promising if used very early in the progression of the disease, before the presence of any symptoms; thus, they are developed in current trials in pre-clinical AD. Strategies that target tau pathology, although promising, bear the risk of toxicity at the moment. Nevertheless, it is hypothesized that, in sporadic late-onset AD, ptau and Aβ pathologies could be evolved by separate pathways that can affect each other synergistically.58 Consequently, it is possible that effective AD immunotherapies must be able to simultaneously target both ptau and Aβ pathologies.

Conclusion: Alzheimer's Disease (AD) is a complex and debilitating neurological disorder characterized by the progressive degeneration of neurons, leading to cognitive decline and memory loss. It is a multifactorial disease with both genetic and environmental factors playing a role in its development. The two main hypotheses explaining its pathogenesis are the amyloid cascade hypothesis and the phosphorylated tau hypothesis, both involving the accumulation of abnormal proteins in the brain.

The global impact of AD is substantial, affecting millions of individuals and their families. In India, the aging population presents a growing challenge, with dementia cases expected to rise significantly in the coming decades. Worldwide, efforts to understand, prevent, and treat AD have become critical due to its profound impact on public health and healthcare systems.

Current treatments for AD focus on alleviating symptoms and improving the quality of life for patients. Cholinesterase inhibitors like Donepezil, Rivastigmine, and Galantamine are used to enhance cholinergic neurotransmission, providing temporary relief from cognitive impairments. N-methyl D-aspartate (NMDA) antagonists, such as Memantine, target glutamate receptors to regulate neuronal excitability. Immunotherapy, a cutting-edge approach, aims to clear abnormal protein aggregates from the brain, slowing disease progression.

In this review, we focused on the etiological pathways of Alzheimer's Disease and the modern treatment strategy for Alzheimer's disease

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