NANOPARTICULATE DRUG DELIVERY SYSTEMS IN THE TREATMENT OF NEURODEGENERATIVE ALZHEIMER'S DISEASE

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ABSTRACT

Alzheimer's disease is a multifactorial Neurodegenerative central system disease with a high prevalence among the elderly and is the most common form of dementia. lt is characterized by gradual mental failure, abnormal cognitive functioning, personality changes, diminished verbal fluency and speech impairment. Alzheimers's are consider the most debilitating as they cause memory and cognitive loss, as well as severely affecting basic physiological conditions such as the ability to move, speak and breathe. Deposition of the amyloid beta plaques has been identified as the most common alzheimer's disease pathology; however the excessive accumulation of phosphorylated or total tau proteins reactive oxygen species, and higher acetylcholinesterase activity are also strongly associated alzheimer's dementia. The nanoparticles (NPS)mediated drug delivery systems improve drug solubility and bioavailability thus genders as superior alternatives Nanoparticles can cause acute toxicity damaging cellular and tissue architecture therefore nanoparticle material should be carefully selected. Additionally, several risk factors such as head injuries, vascular diease, infections increasing age genitic factors and environmental play a role in the diease Tradional anti-alzheimer drugs such as acetyl cholinesterase inhibitors help improve memory and attention defictits. Although none of the existent compounds or drug can completely arrest the disease's progression, nanocarrier development of anti-alzheimer drugs could help delaying the initial or late stages of neurodegeneration. The discovery of new and more complex nanosystems with multiple apporches in alzheimer disease treatment is needed. currently there are only two classes of approved drugs to treat alzheimer disease, including inhibitors to cholinesterase enzyme and antagonists to N- methly D-aspartate (Nmda), where they are effective only in treating symptoms of alzheimer disease, but do not cure the disease. In this review discusses currently available drugs and future therapies foe alzheimer disease such as disease modifying therapeuties (DMT), chaperones.

KEYWORDS: Alzheimer's disease, Blood- Brain Barrier, Amyloidal protein, Dementia, Neurodegenerative disease, Nanoparticles.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative central system disease with a high prevalence among the older people and is the most common form of dementia. In 2005, 24.2 million people had dementia worldwide, and approximately 70% of the cases were associated with AD.[1] AD affects memory, thought, and language processes; in the early phase, short- and medium-term memory is affected, and patients have problems executing complex activities; in the middle phase, the patient is unable to remember for specific periods, impairing their communication, and they experience disorientation on the familiar environment; on the late phase, memory, language, and thought processes are impaired, and AD patients are unable to execute basic activities.[2] The main hypotheses that explain this pathology are (i) amyloid-beta (Aβ) deposition, (ii) neurofibrillary tangles (NFT) formation, (iii) Ca2+ homeostasis dysregulation, (iv) cholinergic axis dysfunction, and (v) oxidative stress-related Aβ and NFT deposition. AD is considered a mixed proteinopathy with the deposition of amyloid and Tau protein.[3]
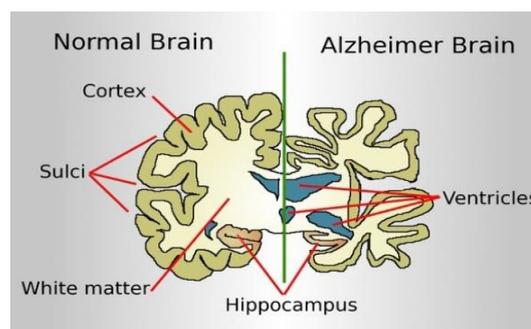

Fig. 1: Alzheimer's Disease changes in the brain.

Tau proteins stabilize the microtubule under normal conditions; hyperphosphorylation and cleavage of these proteins lead to their accumulation, aggregation, and neuronal toxicity.[4] Aβ deposition is one of the more accepted hypotheses that explain familial AD, mutations in the genes encoding amyloid precursor protein (APP), ε4 allele of apolipoprotein E (APOE4), and presenilin 1/2 (PSEN1/2) result in aberrant Aβ monomer and Aβ fibril production.[5] Cholinergic neurons within the nucleus basalis and septal diagonal band complex are important in memory and attentional function.[6] Patients with AD and mild cognitive impairment show higher levels of lipid peroxidation metabolites in the brain and reduced levels of glutathione peroxidase and superoxide dismutase.[7]

Among the different nanoparticles (NPs) being explored for therapeutic applications, gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) have gained significant attention due to their unique properties and potential benefits in combating these disorders.[8] AuNPs and AgNPs possess several characteristics that make them suitable for targeted drug delivery and imaging in neurological diseases these NPs have shown promise in reducing the aggregation and toxicity of amyloid-beta (Aβ) plaques, which are hallmark pathological features of the disease. By binding to Aβ peptides and inhibiting their aggregation, these NPs can potentially prevent the formation of toxic oligomers and fibrils, thereby slowing down the progression of Alzheimer's pathology.[9] The pathogenesis of AD is associated with the formation of amyloid-β (Aβ) plaques extracellularly and neurofibrillary tangles intracellularly.[10,11] AD is the sixth-leading cause of death in the United States, as official death certificates recorded 121,499 deaths from AD in 2019.

First, AD therapeutics must enter the brain by overcoming the blood–brain barrier (BBB). BBB is one of the most specialized biological barriers in the human body. Polymeric NPs are able to open tight junctions in the BBB and provide loaded substances with a camouflaging membrane barrier, which protects drugs from enzymatic degradation and achieves sustained drug release.[12] This review discusses different strategies for nanocarrier conjugation for brain targeting and delivery of traditional and non-traditional therapies for AD according to the principal hypotheses of AD pathogenesis.

However, in Alzheimer's disease, there is an overproduction of this amyloid beta protein that disturbs these cells and eventually causes the death of the cells. The death of the old cells causes the loss of old memories and information. The blocking of nerve cells can stop the production of new connections, which means short term memories are not being accurately encoded in the brain to become long term memories. It causes functional as well as structural disturbance of brain's nerve cells. In early means of disease, it also causes synaptic dysfunction of nerve cells thereby affecting the communication within neural circuits which is important for memory and other cognitive functions.[13]

Dementia is a clinical syndrome linked with progressive downturn of the intellectual function of the brain and the person affected is not able to carry out the daily activities properly.[14] Memory deficit also contributes to the tendency to repeat words and concepts which can result in communication errors, lower coherence, and information density.[15] Memory impairment typical in AD contributes to many of these dysfunctions. For example, word retrieval difficulties may be the earliest signs of AD.[16] By 2050, with the combination of an aging population and 3 increases in longevity, an estimated 11.3 to 16 million Americans will suffer from Alzheimer's,[17] whose course can run from two to over 20 years. The illness and recent death of former President Reagan brought wider atten- tion to the disease and its impact on patients and their families.

NPs across the BBB: The NP-assisted delivery of drugs across the BBB must overcome these mechanisms to efficiently accumulate in the brain. NPs can cross the BBB by active and passive transport that depends on size, charge, and surface modification. Ultra-small NPs (<3 nm) can cross the BBB by paracellular diffusion, while larger NPs (<200 nm) are transported by transcytosis.[18,19] Another strategy for NP transport across the BBB is targeting carrier proteins. GLUT1 is highly expressed on the BBB endothelial cells, and so mannose and glucose surface modification can be used as targeting ligands.[20,21] The BBB is a semi-permeable barrier formed by microvascular endothelial cells, supported by astrocytes, pericytes, neurons, and the basement membrane.[22]

The BBB also plays an important metabolic role by disposing waste products, metabolizing different chemical compounds, both drugs and toxics, and protecting the brain from changes in the ionic composition of the cerebrospinal fluid. One of the main characteristics of the BBB is the presence of a very high electrical resistance across itself. This high resistance is caused by the presence of intercellular tight junction complexes that keep together adjacent endothelial cells, and which are formed by different proteins including claudins, ZO-1 and occludin[23] Taking advantage of transport- and receptor-mediated transcytosis, as indicated above. In this sense, ligands for targets such as GLUT1 or albumin transporters.[24] It is estimated that, at best, less than 5% of the initially administered nanoparticle dose can be found in the brain .The usual method for nanoparticle administration to achieve an effect in the CNS is intravascular (generally intravenous) administration. However, nanoparticles face rapid clearance from circulation, leading to a limited circulation time and thus to a reduced BBB crossing.[25]
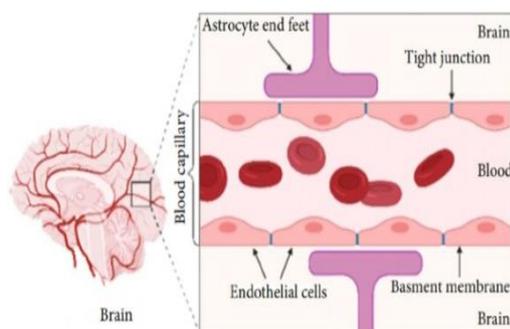
Fig. 2: Anatomy of blood brain barrier.

Diseases of the CNS constitute a significant burden in terms of both personal suffering of the patients and also in economic terms for the health systems. It has been estimated that the cost of brain diseases in Europe amounted to €798 billion in 2010.[26] The cost in the USA was similar, about US$789 billion in 2014.[27] Moreover, the increase in lifespan in Western countries predicts that CNS diseases will have a much more profound impact on both their society and economy.

The BBB is a specialized part of the vascular system which comprises the basal lamina, containing different extracellular matrix proteins such as laminin, heparan sulfate or collagen, which in turn encompasses microvessel endothelial cells and pericytes. In addition, astrocyte endfeet and interneurons also contribute to the BBB structure. These structures prevent toxic substances or pathogens from entering the CNS, also markedly limiting in turn the brain uptake of therapeutic and diagnostic compounds. Moreover, the presence in BBB endothelial cells of ATP-binding cassette transporters (ABC transporters),[28] expelling back to the blood stream some compounds that might cross the BBB, further limits the availability of drugs and imaging probes in the CNS. Accordingly, very few molecules are transported efficiently into the brain.

Since new therapeutic compounds are needed for many CNS diseases where mostly symptomatic treatments are available, different approaches have been used to overcome the limits that BBB poses for compounds, intended for CNS diseases diagnostic and therapeutic procedures, to reach their target sites. One of the most promising alternatives is the use of nanoparticles to deliver such compounds through the BBB into the brain. Several reviews have been focused on this subject in recent years.[29]

In Alzheimer's, the neurons damaged first are those in parts of the brain responsible for memory, language and thinking. As a result, the first symptoms tend to be memory, language and thinking problems. Although these symptoms are new to the individual affected, the brain changes that cause them are thought to begin 20 years or more before symptoms start.1-8. Beta-amyloid and tau have different roles in Alzheimer's. Plaques and smaller accumulations of beta-amyloid may damage neurons by interfering with neuron-to-neuron communication at synapses. Inside neurons, tau tangles block the transportation of nutrients and other molecules essential for the normal function and survival of neurons.

Etiology: The main neuropathological features of AD appear to be senile plaques and neurofibrillary tangles. The senile plaques seem to develop first in brain areas associated with cognition, and spread to other cortical areas as the disease progresses. The senile plaques consist, among other components, of insoluble deposits of amyloid p-peptide (Aβ), a fragment of the amyloid precursor protein (APP). Aβ peptide is generated from APP by two consecutive cleavage events: proteolytic activity by β-secretase generates one end of the Ap peptide, while γ-secretase generates the other end, also by proteolysis. There appear to be two types of Aβ: a longer species, Aβ42, and a shorter species, Aβ40. Aβ42 seems to be deposited initially and may have a role in initiating the events that ultimately lead to amyloid deposition. It is still not clear if the senile plaques are the cause or a by-product of AD, although there are increasing data that dysfunction in the metabolism of APP with subsequent increase in the insoluble Aβ is responsible for AD. Aβ seems toxic to the neuron either directly, or indirectly by causing inflammation or increasing the production of free radicals.[30]

The accumulation of neurofibrillary tangles in neurons is a second distinguishing feature of AD. Neurofibrillary tangles are mostly formed by chemically altered (abnormally folded and phosphorylaled) tau protein, a protein involved in microtubule formation. Tangle formation is related to the severity of disease; the more advanced the stage of disease, the more tau tangles in the brain. Despite the presence of neurofibrillary tangles in AD, no cases of AD secondary to mutations in the tau gene on chromosome 174 have been reported, although frontotemporal dementias with parkinsonism were found in some families with that mutation. The finding that the tau alteration follows Aβ accumulation in patients with AD is supported by recent data.[31]

Epidemiology of AD: With a substantial financial, social, and health cost to society, AD is a major health concern in the US and many other nations. An AD diagnosis is made in United States every 68 seconds, affecting an estimated 5 million people.[32] The prevalence of Alzheimer's disease is higher in women than in men, however this difference is probably because women live longer.Both sexes experience Alzheimer's disease at similar rates when age is taken into account.[33] Numerous studies indicate that cerebrovascular risk factors are important in the onset and course of AD; individuals with a history of diabetes, hypertension, obesity, and smoking are significantly more likely to acquire AD.[34] Family members with history of AD and head injuries.

There are additional risk factors for the development of AD together with loss of consciousness.[35] The disease's main risk factor is growing older, and incidence rates vary depending on age. After 65, the chance of getting the condition about doubles every five years, going from 3 to 69 cases per thousand person years.[36,37] The etiology of AD is unknown, as it is a complex disease with a number of risk factors linked to its onset and progression.

The biggest risk factor for the onset of AD is age. After the age of 65, the chance of acquiring AD increases exponentially with age, roughly doubling every five years.[38,39] According to estimates, the prevalence of Alzheimer's dementia in the US in 2020 was 5.3% for those in the 60–74 age range, rising to 13.8% in the 7484 age group and 34.6% for people over 85.[40]

Pathophysiology: The two pathologic hallmarks of Alzheimer disease are
1) Extracellular beta-amyloid deposits (In neuritic plaques)
2) Intracellular neurofibrillary tangles (Paired helical filaments)

The loss of synapses and neurons caused by beta amyloid deposition and neurofibrillary tangles causes extensive atrophy in brain, usually beginning in the mesial temporal lobe.

It is not fully known how beta amyloid peptide and neurofibrillary tangles generate this kind of harm.

According to the amyloid hypothesis, the brain's gradual buildup of beta amyloid causes a complicated series of processes that culminate in the loss of synapses, the death of individual neurons, and growing deficiencies in neurotransmitters.

These consequences collectively exacerbate dementia's symptoms.

Alzheimer disease patients' brains have been shown to have inflammation and a persistent immunological response. According to some scientists, inflammation is third main pathologic characteristic of Alzheimer's disease.[41]

Alzheimer's disease has been linked to specific prions.A normal brain protein known as prion protein can misfold into apathogenic form known as a prion in prion disease. There is a noticeable rise in the aberrant proteins as a result of the prioninduced misfolding of other prion proteins, which damages the brain. It is believed beta-amyloid in cerebral amyloid deposits and tau in neuro fibrillary tangles in Alzheimer's disease possess selfreplicating, prionlike characteristics.

Alzheimer's disease has been demonstrated to be potentially significantly influenced by a disruption in glucose metabolism.[42] The loss of synapses and neurons

caused by beta-amyloid deposition and neurofibrillary tangles causes gross atrophy in the affected areas of the brain, usually beginning in the mesial temporal lobe. There is a strong correlation between cognitive decline and brain atrophy, including hippocampal atrophy, and the accumulation of tau proteins.

Alzheimer's disease causes inflammation, the deposition of amyloid plaques, an aberrant cluster of protein fragments, and tangled fiber bundles due to neuronal loss and atrophy in the temporofrontal cortex.

As a result, the number of monocytes and macrophages in the cerebral cortex rises, and the parenchymal microglial cells become activated.[43]

Each of the billions of neurons in the brain has numerous dendrites and an axon.

Neurones need to communicate with one another, perform metabolism, and self-repair in order to remain healthy. All three of these vital tasks are interfered with by AD.

Neuritic plaques: Deposits of amyloid, a protein fragment that builds up in the gaps between nerve cells (neurons).The precursor to amyloid plaque is called APP, or amyloid precursor protein. The APP pierces the membrane of the neuron. The APP is broken up into protein fragments (the neurotoxic A42 fragment), which includes -amyloid, by enzymes such as α-secretase and a-secretase. B-amyloid fragments coalesce into plaque-forming clumps. Many of these clumps form in AD, impairing neuron function. The hippocampal region and other cerebral cortex regions are impacted by this.
1) Amyloid precursor protein, or APP
2) Divided by a- and M-secretases
3) Amyloid precursor protein mutation on chromosome number 21
4) A higher level of amyloid precursor protein synthesis
5) Generates amyloid protein
6) Build-up of -amyloid protein (caused by elevated APP production)
7) Neurotoxin 1 directly
8) The illness Alzheimer's

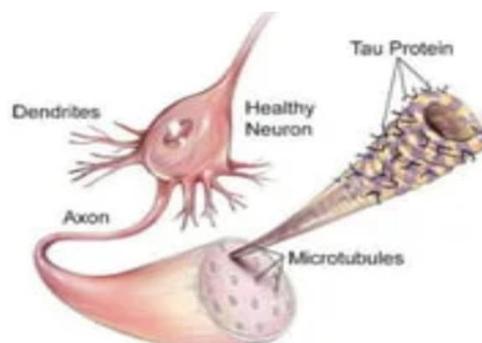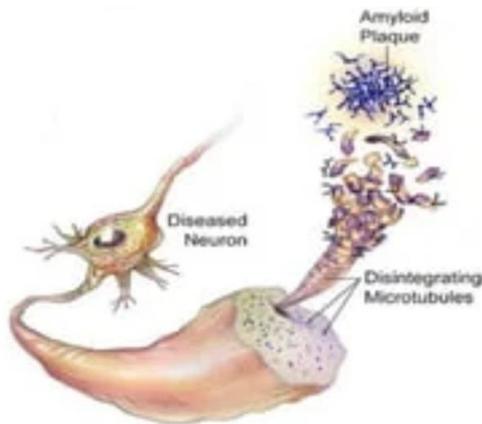**Fig. 3: Healthy neuron carrying tau Protein and Microtubules.**

Fig. 4: Diseased neuron with Amyloid Plaque and Disintegrating microtubules.

Neurofibrillary tangles (NFT'S): Microtubules are a component of the internal support structure of neurons. The "tau" protein aids in the stabilization of microtubules. Tau alterations in AD lead to the collapse of microtubules and the clumping of "tau" proteins into neurofibrillary tangles.
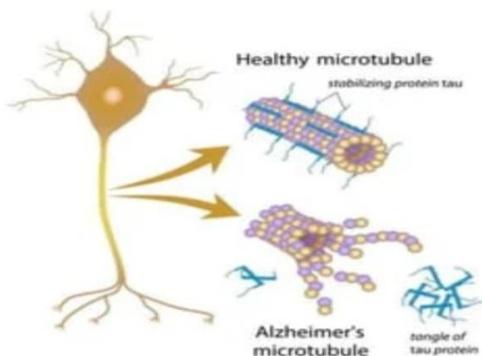

Fig. 5: Neuron with stabilizing tau Protein and Alzheimer's microtubules.

Genetic basis of alzheimer disease: Alzheimer's disease has almost complete penetrance and is inherited as an autosomal dominant disorder. Mutations in the 3 genex AAP gene on chromosome 21, Presenilint (PSENI) on chromosome 14, and Presenilin 2 (PSENZ) on chromosome 1 are associated with the autosomal dominant form of the disease. PSENI and PSENZ mutations cause beta amyloid aggregation by interfering with gamma-secretase processing, while APP mutations may result in increased production and aggregation of beta-amyloid peptide. Most cases of early-onset Alzheimer's disease and approximately 5–10% of all cases are caused by mutations in these three genes.

Families with certain disorders have variations in the sortilin receptor SORT1 gene, which is necessary for moving APP from the cell surface to the Golgi-endoplasmic reticulum complex., have been discovered in both sporadic and familial forms of Alzheimer's disease.[44]

Another genetic marker that raises the risk of Alzheimer's disease is apolipoprotein E, a regulator of lipid metabolism with an affinity for beta-amyloid protein. The APOE gene isoform e4, which is found on chromosome 19, has been linked to a higher number of familial and sporadic types of Alzheimer's disease that manifest after the age of 65. Alzheimer's disease is not always caused by the presence of one APOEe4 allele; however, in those who carry one allele, about 50% get Alzheimer's disease, and in those who carry two alleles, 90% get Alzheimer's disease. The age of disease onset is also lowered by each APOE e4 allele. An essential risk factor for Alzheimer's disease is the APOE e4 allele.

Symptoms: The symptoms of Alzheimer's disease worsen with time because the illness is progressive. One important aspect is that memory loss is often one of the initial symptoms to appear. Over months or years, the symptoms gradually become apparent. A person may need to see a doctor if they appear over several hours or days, as this could be a sign of a stroke. Alzheimer's disease symptoms include: Loss of memory: It's possible for someone to struggle to retain knowledge and absorb new information. This may result in: asking the same queries or having the same talks over losing things forgetting appointments or events straying or becoming disoriented Cognitive deficits: An individual may struggle with judgment, reasoning, and difficult tasks. This may result in: a diminished comprehension of risks and safety financial difficulties or settling invoices having trouble decidingfinding it difficult to finish multi-stage tasks, like dressing Recognition issues: An individual may lose their ability to identify faces or objects or to operate simple tools.

These problems are not related to visual issues. Issues related to spatial awareness include trouble balancing, falling or spilling objects more frequently, and having trouble lining up clothes with the body when getting dressed. Difficulties with reading, writing, or speaking: An individual may experience trouble remembering everyday words or may experience an increase in spelling, grammar, or speech mistakes.

Changes in personality or behavior: A person may exhibit the following changes in personality or behavior: becoming more agitated, furious, or anxiousa decrease in empathy, a loss of interest in or drive for activities they typically enjoy, or compulsive, obsessive, or socially inappropriate behavior more frequently.
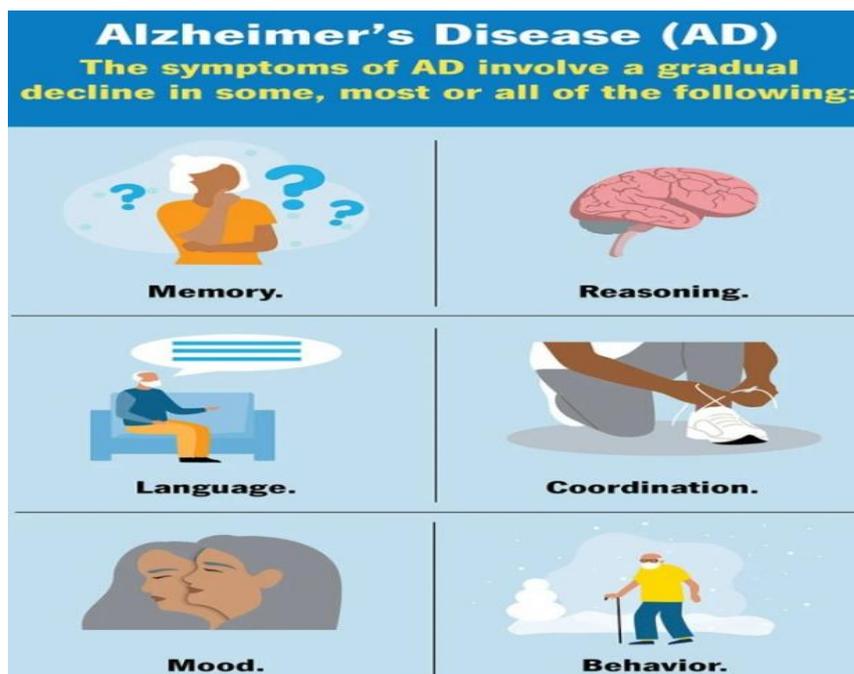
Fig. 6: Alzheimer's disease symptoms.

Pathogenesis: The cholinergic hypothesis is among the many theories that have served as a foundation for our understanding of the disease's etiology. Based on the observation that AD patients exhibit decreased cerebral cortex activity of acetylcholinesterase and choline acetyltransferase in comparison to normal brain activity, this hypothesis is put forth. Reduced neurotransmitter pathway activity was verified by postmortem brain tissue from AD patients, which also showed that cholinergic neuron degeneration and neurotransmission loss are major contributors to the cognitive impairment observed in AD patients.[45] When the regulation of phosphorylation is disrupted, hyperphosphorylated tau proteins form filaments and develop into neurofibrillary tangles, which is when tau protein turns pathological. This causes the cytoskeleton's structural and regulatory functions to malfunction, which in turn causes aberrant neuronal morphology, axonal transport, and synaptic function, all of which contribute to neurodegeneration.[45]

According to this theory, the overproduction or decreased clearance of amyloid beta (Ab) is responsible for the disease's clinical sequelae. Ab40 and Ab42 are the two primary types of Ab polymers that are directly involved in the pathology of AD. Following oligomerization, Ab40/Ab42 visits synaptic clefts where it obstructs synaptic signaling. These finally undergo additional polymerization to form insoluble amyloid fibrils, which then combine to form amyloid plaques.[46] Together with inflammation, apoptosis, and plaque accumulation, the genetics of AD should be taken into consideration as a significant contributor to the pathophysiology. As previously mentioned, the APP gene on 21q21 was actually the first gene linked to AD.[47] AD is a multifaceted, intricate neurodegenerative illness that arises from intricate interactions between an

individual's age, environment, education level, and genetic composition. Given that AD histopathology reveals intraneuronal neurofibrillary lesions composed of tau proteins, the tau hypothesis has also been put forth. Tau proteins are primarily present in neurons and play a role in the microtubule network assembly and stability of the neuron.

Genetic research has revealed two different types of Alzheimer's disease (AD): sporadic Alzheimer disease (SAD), which accounts for most cases, and familial Alzheimer's disease (FAD). Significant discoveries in the 1990s and early 2000s demonstrated that autosomal dominant mutations in the APP, PSEN1, and PSEN2 genes—which are found on chromosomes 21, 14, and 1, respectively—cause familial AD disease (FAD).[45,48] The type e4 allele of the gene encoding the low-density lipoprotein carrier apolipoprotein E (APOE), located on chromosome 19, has been identified as a genetic risk factor for sickle cell disease (SAD).

Stages of Alzheimer's disease: Organizations dedicated to Alzheimer's disease and medical professionals refer to the different stages of the disease using different terms depending on the symptoms. The stages all follow the same pattern, despite differences in terminology: AD symptoms get worse over time. Alzheimer's disease typically progresses in three stages, each characterized by a growing pattern of cognitive and functional impairment. are examples. Early or mild, middle or moderate, and late or severe are the terms used to describe the three stages. The hippocampus, which is linked to memory, is the target of the disease and is what causes the initial signs of memory impairment. However, no two people have the same experience with AD. Every Alzheimer's patient will go through the stages at a

different rate. Not every person will experience every change. Since stages may overlap, it can occasionally be challenging for caregivers to assign a person with AD to a particular stage.

The phases of dementia are used by certain organizations and providers to describe Alzheimer's disease: 1) Preclinical Alzheimer's disease, 2) Mild cognitive impairment (MCI) due to Alzheimer's disease, 3) Moderate dementia due to Alzheimer's disease, 4) Severe dementia due to Alzheimer's.

Preclinical or presymptomatic: At this point, there is clear laboratory evidence but no symptoms in the patients. Finding the biomarkers will aid in the diagnosis of Alzheimer's at this stage. In the early stages of Alzheimer's disease, subtle issues with planning, flexibility, attentiveness, and abstract thought, as well as impairment in semantic memory, may also be present. As stated in.[26] Although they are not unique to Alzheimer's disease, low levels of amyloid and elevated tau proteins in CSF function as biomarkers. According to a different analysis, a number of factors, including ApoE4 positivity, scores on the digits symbol substitution test and the paired associates immediate recall test, elevated tau protein in CSF, and right entorhinal cortex thickness and right hippocampal volume on MRI, can predict the development of MCI. Nevertheless, the utility of such an early "preclinical" diagnosis is still debatable because the methods for detecting the early changes of Alzheimer's disease are developing faster than the available treatments. The entorhinal cortex, which is connected to the hippocampus directly, is where AD starts. The hippocampus, a structure crucial to the formation of both short- and long-term memories, is the next structure discussed. Affected areas start to shrink, or atrophy. These alterations in the brain most likely begin 10 to 20 years before any outward symptoms or indicators show up. The primary symptom of mild cognitive impairment (MCI) is memory loss. Many scientists believe that MCI frequently represents the first stage of brain aging that occurs between normal aging and AD.
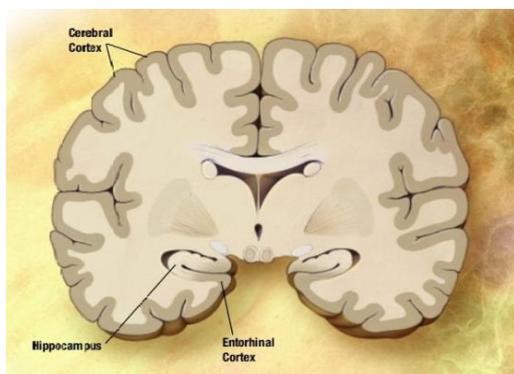

Fig. 7: Alzheimer's changes in mild cognitive impairment (MCI).

Mild cognitive impairment
Patients experience impairment in non-memory domains like language function or executive ability, as well as memory. These people carry on with their independent work, social lives, and daily activities. 10% of MCI patients experience dementia each year. In addition to the other risk factors for Alzheimer's disease, the degree of impairment at the time of diagnosis is a risk factor for dementia progression. A different name for the third stage of Alzheimer's is mild cognitive impairment (MCI). At this point, there might be more overt indications of memory loss, attention problems, and cognitive difficulties. Those who exhibit two or more of the following symptoms are classified as being in stage 3 by the GDS.

A noticeable drop in output that coworkers can observe
1) Fear of forgetting things
2) Ignorance of memory problems or other cognitive disorders
3) Difficulty interacting socially
4) Getting lost the first time you visit a place
5) Losing names or "losing words"
6) Misplacing a sentimental item, like a social security card or wedding ring
7) Retaining or recalling very little of the information that was just read, as determined by a clinical evaluation.

The stable phase of mild cognitive impairment ends with a detectable decline in cognitive function, lasting two to five years, in which semantic memory (the store of facts and general knowledge) and implicit memory (the non-conscious influence of past experience on subsequent performance) also becomes degraded(9). As the disease begins to affect the cerebral cor- tex, memory loss continues and changes in other cognitive abilities emerge. The clinical diagnosis of AD is usually made during this stage. Signs of mild AD can include:
1) Loss of memory
2) Perplexity regarding where familiar
3) locations (becoming lost starts to happen) Taking longer to complete everyday chores
4) Difficulty managing finances and making payments
5) Bad judgment resulting in poor choices Absence of initiative and spontaneity
6) Shifts in mood and personality, elevated anxiety.

The brain regions responsible for memory, language, and reasoning are initially harmed by the increasing quantity of plaques and tangles. Physical abilities do not deteriorate until much later in the disease. As a result, a person with mild AD may appear healthy at first but may be experiencing increasing difficulties understanding the world around them. Since the early signs can be mistaken for aging-related changes, the realization that something is amiss frequently happens gradually. For patients and their families, accepting these symptoms and choosing to undergo diagnostic testing can be very difficult decisions.
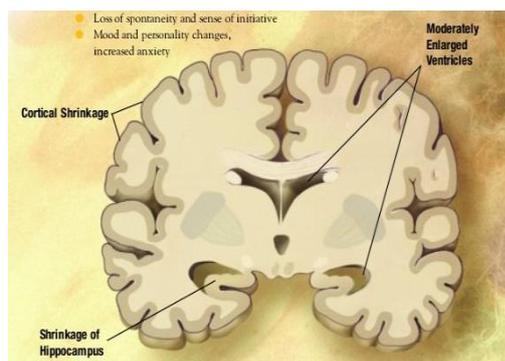
Fig. 8: Alzheimer's changes in moderate AD.

Moderate AD
The parts of the cerebral cortex responsible for language, reasoning, sensory processing, and conscious thought have already been further affected by AD damage at this point. Affected areas keep atrophying, and the disease's signs and symptoms get worse and spread farther. Behavior issues can arise, including restlessness and restlessness. It becomes necessary to provide more stringent supervision and care, which can be challenging for many spouses and families.

This stage's symptoms can include
1) Growing disorientation and memory loss
2) Reduced capacity for sustained focus
3) Difficulties identifying loved ones and friends
4) Language difficulties, including issues with writing, reading, and math
5) Difficulty arranging ideas and applying logic
6) The incapacity to pick up new skills or deal with novel or unforeseen circumstances
7) Anxiety, restlessness, crying, and wandering, particularly in the late afternoon or at night

8) Repetitive motions or remarks, sporadic spasms in the muscles
9) Delusions, suspicion or paranoia, agitation, and hallucinations
10) A lack of impulse control, demonstrated by impolite behavior at meals, inappropriate clothing removal, or foul language
11) Perceptual-motor issues (e.g., difficulty getting up from a chair or clearing the table)

Delusions affect 20–40% of patients. Although auditory and olfactory hallucinations are less common, patients can still experience visual hallucinations. Almost half of the patients exhibit disruptive behaviors. Patients also experience fragmented sleep and lose their regular circadian sleep-wake pattern. These patients have higher rates of auto accidents.

Complex brain functions, all of which occur in a split second in a healthy brain, produce behavior. Many of these processes are disrupted in AD, which is the cause of a great deal of upsetting or inappropriate behavior. For instance, if someone does not understand what his caregiver is asking of him, he may angrily refuse to dress or take a bath. Even if he comprehends, he might not be able to recall the steps. His confusion and anxiety are hidden behind the anger. Alternatively, an AD sufferer might worry when her spouse or caregiver disappears and follow them around all the time. For someone who is incapable of looking ahead or recalling the past, The world she lives in can be frightening and strange. The only thing that makes sense and offers security might be to stay close to a dependable and well-known caregiver. A person with AD who feels hot and doesn't know or remember that it's improper to undress in public may find it reasonable to remove their clothes.
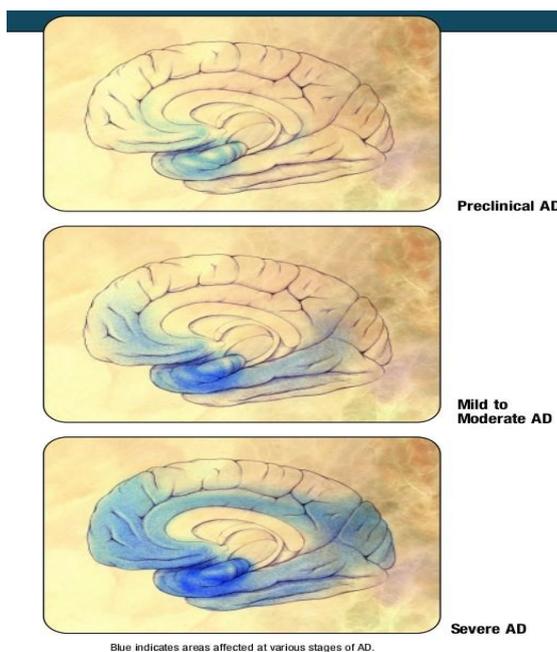

Fig. 9: Various stages of Alzheimer's disease in brain.

Severe AD

The brain is covered in plaques and tangles and has further atrophy in certain areas during the final stage of AD. Patients are unable to communicate in any way or recognize friends and family. They rely entirely on other people to take care of them. All self-awareness appears to disappear. Among the other symptoms are

1) Loss of weight
2) Convulsions, skin infections, trouble swallowing
3) Sighing, writhing, or sighing
4) Deeper sleep
5) Inability to control bowel and bladder

Patients may spend most or all of their time in bed by the end. The majority of AD patients pass away from other conditions, most commonly aspiration pneumonia. This kind of pneumonia develops when a person inhales food particles or liquids into their lungs due to improper swallowing.
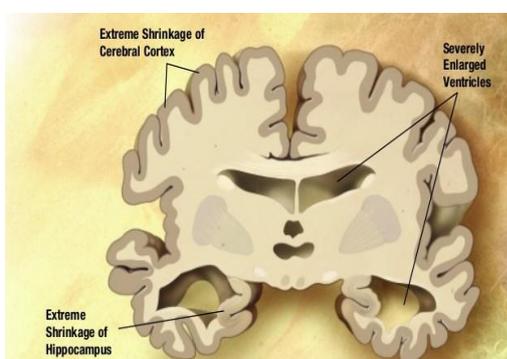

Fig. 10: Severe Alzheimer's disease symptoms.

Causes of the disease

Between 60% and 70% of cases of dementia are caused by Alzheimer's disease. It is a long-term neurodegenerative illness that often begins slowly and deteriorates with time. According to one theory, plaques prevent nerve cells in the brain from corresponding with one another. Tangles may complicate the cells' ability to absorb the necessary nutrients. It makes sense that as Alzheimer's progresses, more and more nerve cells—also referred to as neurons—die. This is how the disease progresses.

1. **Age:** The most important factor in the onset of Alzheimer's disease is age. After the age of 65, your chance of developing the condition doubles every five years.
2. **Down syndrome:** Alzheimer's disease is more likely to strike those who have Down syndrome illness. This is because the same genetic flaw that causes Down's syndrome can also accumulate amyloid plaques in the brain over time, which in certain cases can result in Alzheimer's disease.
3. **Genetics:** Based on analyses of twin and family studies, the genetic heritability of Alzheimer's disease (and its memory components) ranges from 49% to 79%. Familial forms of autosomal (not sex-linked) dominant inheritance that begin before the age of 65 account for about 0.1% of cases. Early

onset familial Alzheimer's disease is the term used to describe this type of the illness. Even though it's uncommon, only a tiny percentage of people get AD before turning 65. Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and amyloid precursor protein (APP) are the three genes that have been linked to the development of AD through mutation.[49]

Amyloid beta precursor protein, or APP: The gene in question codes for both a cell surface receptor and a transmembrane precursor protein. These proteins are broken down by secretases into a range of peptides, which attach to the acetyltransferase complex APBB1/TIP60 after being secreted. This process promotes transcriptional activation and provides the protein scaffolding for the amyloid plaques found in Alzheimer's disease patients' brains. This gene is located on chromosome 21. Amyloid plaque formation is a result of constitutive upregulation of soluble β-amyloids, which is linked to the pathophysiology of Alzheimer's disease. The monoclonal antibodies solanezumab, crenezumab, and gantenerumab, which target soluble and insoluble Aβ-aggregates, are part of the anti-amyloid therapy; however, because of their limitations and side effects, they were unable to improve the clinical outcomes of AD.[50,51]

Scientists have discovered what they believe to be the main causes of Alzheimer's disease: plaques and tangles, even though the precise cause of the illness is still unknown.

In the voids between nerve cells, amyloid beta deposits, or plaques, form. These deposits block signals and keep the substances that the nerve needs to survive from getting to it. In a healthy brain, amyloid beta helps to support neural growth and repair. However, there is an overabundance of this amyloid beta protein in Alzheimer's disease, which damages these cells and ultimately causes them to die. When old cells die, old memories and information are lost. The creation of new connections may be hindered by a temporary blockage of brain cells. Long-term memory is not being formed by the brain encoding memories correctly.

Twisted tau builds up in between tangles of cells to form. This gene codes for a protein that is necessary for the correct catabolism of triglyceride-rich lipoprotein components. It binds to specific receptors found in peripheral cells and the liver. This gene is found on chromosome 19, along with the genes for C1 and C2 apolipoproteins. Type III hyperlipoproteinemia (HLP III), which is caused by mutations in this gene, is characterized by elevated plasma cholesterol and triglycerides as a result of decreased clearance of chylomicron and VLDL remnants. Aβ42 is a small protein that is the main component of senile plaques and is produced more frequently when there is a mutation in the presenilin and APP genes. Some mutations only affect how much of Aβ42 there is compared to the other

main forms, particularly Aβ40, and do not cause an elevation of Aβ42 values. There are protective variations of the APP gene. When they are mutated, excessive amounts of the toxic protein fragment known as amyloid-beta peptide are produced. Tau protein malfunctions as these fragments clump together and build up as amyloid plaques in the brain. The brain cells die and the symptoms of Alzheimer's disease appear as the tau protein particles clump together to form neurofibrillary tangles.[49]

Treatment of Alzheimer's disease: Improving cognition and reducing behavioral disturbances (such as depression, psychosis, agitation, and insomnia) are the two main objectives of treatment.[52]

Pharmacotherapy: The medications used to treat behavioral disturbances include hypnotics, antipsychotics, mood stabilizers, and antidepressants.[53] Cognitive enhancers are among the current pharmacological options available to clinicians treating AD for the treatment of the cognitive deficit.[54]

Psychosocial treatment: It's critical to keep up proper hydration, diet, exercise, and hygiene. Family members are susceptible to depression, anxiety disorders, and sleeplessness, so support is vital. There should be little change in the patient's activities. A patient's surroundings should be adjusted in an effort to keep them in their homes for as long as possible if they have AD. Daily reminders that are written down can be useful in carrying out daily tasks. It is important to have prominent windows, clocks, and calendars. AD patients' functioning can be enhanced by controlling their environment, providing family support, preventing other medical comorbidities.

Treatment of cognitive disturbance
1. **Estrogen replacement therapy:** Currently under investigation for AD are compounds belonging to an intriguing class called selective estrogen-receptor modulators. These (raloxifene, droloxifene) function as antagonists in certain tissues and as agonists of estrogen in others. A substantial body of research has been conducted on the effects of estrogen on neuronal survival, regeneration, and plasticity in the brain. Many open-labeled clinical trials[38–40] and at least one double-blind placebo-controlled trial have demonstrated growing evidence that estrogen replacement therapy (ERT) in postmenopausal women may have a role in delaying AD by improving cognitive function and lowering the risk for both cognitive impairment and AD. It seems to work in the brain by improving nongenomic events' transcription and mediation. According to certain theories, postmenopausal women's sudden decrease in estrogen production raises their risk for Men, on the other hand, have an intrinsic supply of estrogen because their brains aromatize testosterone, which prevents these women from developing AD. The use of estrogen for primary prevention in AD patients is currently the subject of multiple ongoing studies (Women's Health Initiative- Memory Study; Women's International Study of Long Duration Oestrogen for Menopause, Preventing Postmenopausal Memory Loss and Alzheimer's with Replacement Estrogens Study).

2. **Cholinesterase inhibitors:** For AD patients, only cholinesterase inhibitors have demonstrated clinically significant improvements. By blocking the enzymes that cause acetylcholine to hydrolyze, these substances raise the concentration of acetylcholine that is available for synaptic transmission. These medications seem to be helpful at any stage of the illness, but especially in the intermediate phase.[55] Based on the severity of AD, the is seems to be a difference in the response to cholinesterase inhibition; patients with mild AD (MMSE scores 18–26) do not seem to respond as well as middle-stage AD patients (defined by MMSE scores 11–17). The idea that the cholinergic defect first becomes statistically significant at this stage of the disease is supported by these data.[56]

3. **Antioxidant agents:selegiline and vitamin E:** According to current theories, AD may experience an increase in free radical formation, which could have a direct harmful effect. The brain may be vulnerable to the damaging effects of oxidative stress because of an abundance of catecholamines and a relatively low concentration of antioxidative enzymes (superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase). Moreover, Aβ has been connected to a rise in the production of free radicals. Selegiline, a monoamine oxidase B inhibitor, should be taken orally in dose of 5 to 10 mg every morning, along with vitamin E in doses of 1000 IU twice daily.[57] A large, recent double-blind trial,[58] which examined the effects of selegiline alone, vitamin E alone, and selegiline and vitamin E with placebo in patients with AD, revealed that the loss of everyday activities and the delay in moving into a nursing home living. But when compared to a placebo, neither selegiline nor vitamin E enhanced cognition. When vitamin E and selegiline were combined, there was no additive effect.

4. **Anti-inflammatory agents:** Some retrospective epidemiologic studies have provided support for the hypothesis that anti-inflammatory therapy can slow the progression of AD. The rate of cognitive decline in 138 AD patients receiving prednisone for 16 months was not slowed down when compared to a placebo in a double-blind, low-dose, placebo-controlled study.[59] Long-term use of high-dose steroids can result in serious health issues, even though some previous high-dose prednisone studies showed improvement.

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