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Alzheimer's: A Degenerative Disease

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Abstract
Alzheimer's disease (AD) is a common, complex and challenging neurodegenerative disease. It is estimated to affect approximately 15 million people worldwide and the incidence increases from 0.5% per year at age 65 years to 8% per year at age 85 years. The neuropathological hallmarks of AD are the accumulation of extracellular amyloid plaque containing amyloid β-peptide (Aβ) and intracellular neurofibrillary tangles containing tau protein. Because the β-sheet formation and aggregation of Aβ are considered to be critical events that render these peptides neurotoxic, many researchers favor therapeutic approaches that target the formation, deposition and clearance of Aβ from nervous tissue. Experimental therapies and clinical trials using vaccination and non steroidal anti-inflammatory drugs have been reported.
Key words: Alzheimer's disease, amyloid plaque, cholinesterase inhibitors

Introduction
As a rule dead neurons in the adult central nervous system (CNS) are not replaced nor can their terminals regenerate when their axons are interrupted. Therefore any pathological process causing neuronal death generally has irreversible consequences. Alzheimer disease (AD) is a disabling senile dementia, the loss of reasoning and ability to care for oneself that afflicts about 11% of the population over age 65. Claiming over 100,000 lives a year, AD is the fourth leading cause of death among the elderly after heart disease, cancer and stroke. The cause of most AD cases is still unknown but evidence suggests it is due to a combination of genetic factors, environmental or lifestyle factors and the aging process. AD is first characterized by *Alois Alzheimer* in 1907, it is a gradually progressive dementia affecting cognition, behavior and functional status. The exact pathophysiologic mechanisms underlying AD are not entirely known and no cure exists.[1] Although drugs may reduce AD symptoms for a time, the disease is eventually fatal. AD profoundly affects the family as well as the patient. The need for supervision and assistance increases until the late stages of the disease, when AD patients become totally dependent on a family member, spouse or other caregiver for all of their basic needs.

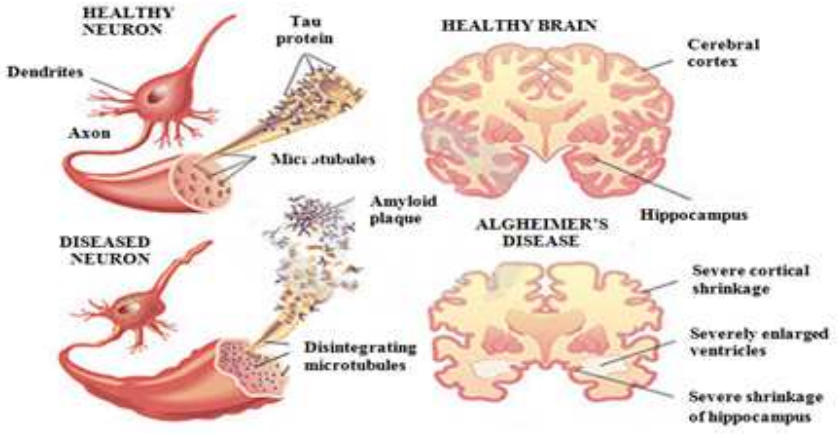


Fig: Difference between disease & healthy neurons and brain

Epidemiology

AD is the most common cause of dementia. The incidence increases to 80% if AD in conjunction with other pathologic lesions is considered.[2] Dementia in an individual can result from multiple etiologies. Approximately 4.5 million Americans have AD.[3] Most cases present in persons older than age 65 years but approximately 5% of cases occur in persons younger than age 65 years. Onset can be as early as age 40 years. Increasing age is the greatest risk factor for AD.[4] The prevalence of AD increases exponentially with age affecting approximately 7% of individuals ages 65 to 74 years, 53% of those ages 75 to 84 and 40% of persons ages 85 years and older. Individuals with AD survive approximately half as long from the time of diagnosis as those of similar age without AD. AD is the fifth leading cause of death as a consequence of disease in the United States. AD may not cause death directly but it predisposes patients to sepsis, pneumonia, choking, aspiration, nutritional deficiencies and trauma.[5]

Etiology

The exact etiology of AD is unknown however several genetic and environmental causes have been explored as potential causes of AD. Dominantly inherited forms of AD account for less than 1% of cases.[6] Almost all early onset cases of AD can be attributed to alterations on chromosomes 1, 14 or 21. The majority and most aggressive early onset cases are attributed to mutations of a gene located on chromosome 14, which produces a protein called presenilin 1. A structurally similar protein, presenilin 2, is produced by a gene on chromosome 1. Both presenilin 1 and presenilin 2 encode for membrane proteins that may be involved in amyloid precursor protein (APP) processing. Scientists have identified more than 160 mutations in presenilin genes and these mutations appear to result in reduced activity of γ-secretase, an enzyme important in β-amyloid peptide (βAP) formation. APP is encoded on chromosome 21. Only a small number of early onset familial AD cases have been associated with mutations in the APP gene.

Genetic susceptibility to sporadic, late-onset AD is thought to be primarily linked to the apolipoprotein E (Apo E) genotype. Thus far, the contribution of other candidate genes appears to be minor, although AD may be a heterogeneous disease resulting from complex interactions among multiple susceptibility genes and environmental factors. The gene responsible for the production of apo E is located on chromosome 19. There are three major subtypes or alleles of Apo E (e.g., Apo E2, Apo E3 and Apo E4). Humans inherit one copy of the Apo E gene from each parent. Inheritance of the Apo E4 allele is believed to account for much of the genetic risk in sporadic AD. The mechanism through which Apo E4 confers an increased risk is unknown, although Apo E4 is associated with other factors that may contribute to AD pathology, such as abnormalities in mitochondria, cytoskeletal dysfunction, and low glucose usage. The degree of risk depends on such factors as the number of Apo E4 copies, age, ethnicity and gender.[7] Overall, approximately 40% of patients with late-onset AD have at least one copy of Apo E4. Individuals homozygous for Apo E4 are at increased risk, and as many as 90% of persons inheriting two copies of Apo E4 will develop AD by age 80 years. Moreover, onset of symptoms occurs at a relatively younger age as compared to patients having none or only one copy of Apo E4 in their genotype. Inheriting a single copy of Apo E4 increases AD risk, whereas inheriting the Apo E2 allele may protect against AD.[8] Genetic variation at the angiotensin-converting enzyme locus may influence the risk for AD. Angiotensin-converting enzyme activity in the cerebrospinal fluid and in the brain differs significantly between individuals with AD and healthy controls. Angiotensin converting enzyme has also been demonstrated to inhibit βAP aggregation and plaque formation in vitro.[9,10] Genetic factors have been linked to both early and late-onset AD. Alterations to chromosomes 1, 14 and 21 are associated with early onset AD, whereas the presence of Apo E4 alleles increases risk of developing late-onset AD. Mutations in the tau gene on chromosome 17 are associated with an abnormality in tau protein and development of the rare frontotemporal dementia. A number of environmental factors are associated with an increased risk of AD, including age, head injury and risk factors for vascular disease (hypercholesterolemia, hypertension, atherosclerosis, coronary heart disease, smoking, obesity, and diabetes).

Pathophysiology

The lesions in AD are neuritic plaques and neurofibrillary tangles (NFTs) located in the cortical areas and medial temporal lobe structures of the brain. Along with these lesions degeneration of neurons and synapses as well as cortical atrophy occurs. Plaques and NFTs may also be present in other diseases even in normal aging but there is a much higher concentration of plaques and NFTs in patients with AD. The circumstances in which these lesions lead to the clinical picture of AD remain unclear. Several mechanisms have been proposed to explain these changes in the brain including βAP aggregation and deposition leading to the formation of plaques, hyperphosphorylation of tau protein leading to NFT development, inflammatory processes, dysfunction of the neurovasculature, oxidative stress and mitochondrial dysfunction.

Amyloid Cascade Hypothesis:

Neuritic plaques (also termed amyloid or senile plaques) are extracellular lesions found in the brain and cerebral vasculature. Amyloid precursor protein (APP) is the precursor to amyloid plaque. Plaques from AD brains largely

consist of a protein called βAP.[11] βAP is produced via processing of a larger protein, APP. Specific APP physiologic roles are not entirely clear but in a general sense it is felt to contribute to proper neuronal function and perhaps cerebral development altered APP processing drove βAP production, βAP gave rise to plaques and plaques induced neurodegeneration. It occurs in following three steps.

1. APP sticks through the neuron membrane.
2. Enzymes cut the APP into fragments of protein, including beta-amyloid.
3. Beta-amyloid fragments come together in clumps to form plaques.

In AD, these clumps disrupting the work of neurons and affects the hippocampus and other areas of the cerebral cortex.

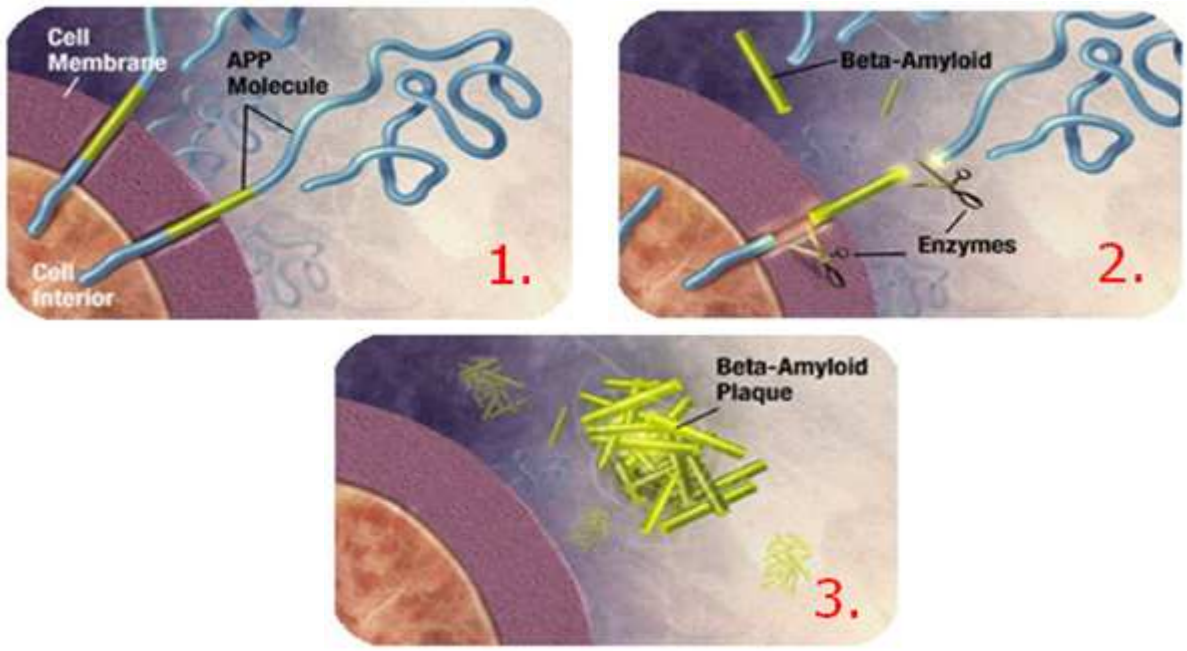
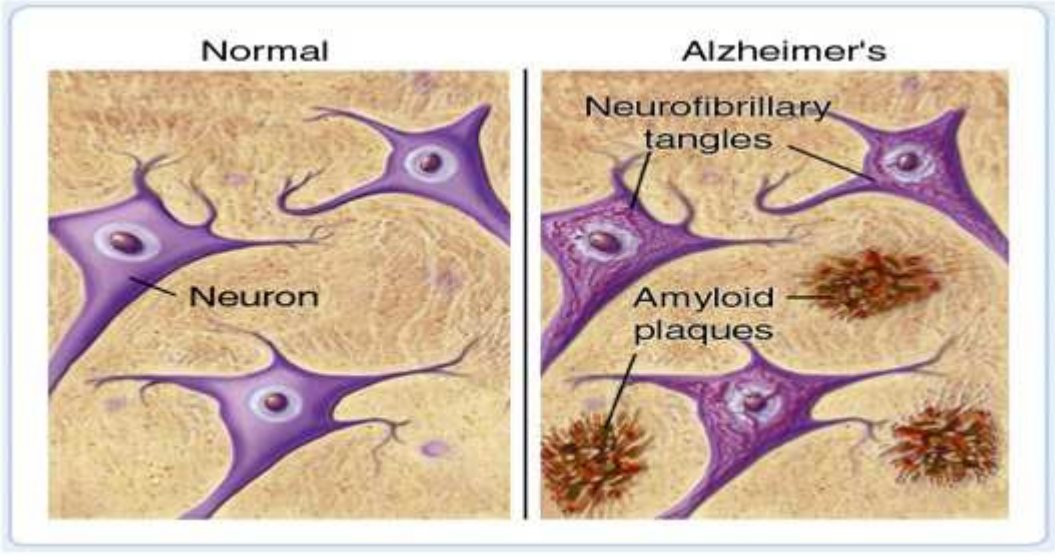


Fig: Amyloid Plaques

Neurofibrillary Tangles

NFTs are commonly found in the cells of the hippocampus and cerebral cortex in persons with AD and are composed of abnormally hyper phosphorylated tau protein. Tau protein provides structural support to microtubules, the cell's transportation and skeletal support system. When tau filaments undergo abnormal phosphorylation at a specific site, they cannot bind effectively to microtubules and the microtubules collapse. Without an intact system of microtubules, the cell cannot function properly and eventually dies.



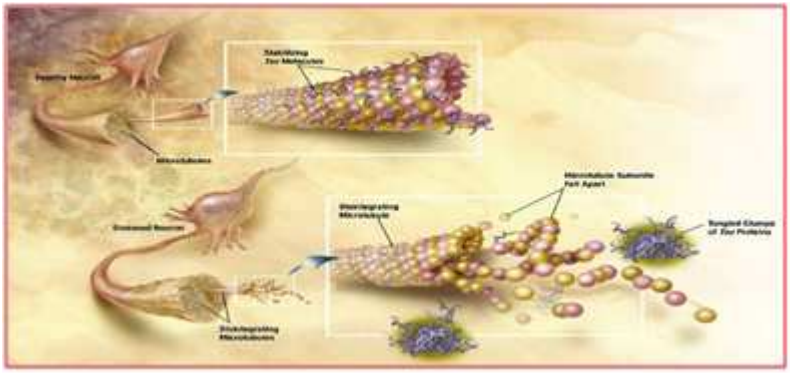


Fig: Neurofibrillary Tangles

Inflammatory Mediators

The inflammatory response may associated with release of cytokines, nitric oxide, and other radical species, and complement factors that can both injure neurons and promote ongoing inflammation.[12] Indeed, levels of multiple cytokines and chemokines are elevated in AD brains.

The Cholinergic Hypothesis

Multiple neuronal pathways are destroyed in AD. Loss of cholinergic activity correlates with AD severity. In late AD, the number of cholinergic neurons is reduced and there is loss of nicotinic receptors in the hippocampus and cortex. Presynaptic nicotinic receptors control the release of acetylcholine as well as other neurotransmitters important for memory and mood including glutamate, serotonin and nor epinephrine. The cholinergic hypothesis targeted cholinergic cell loss as the source of memory and cognitive impairment in AD. Consequently, it was presumed that increasing cholinergic function would improve symptoms of memory loss. This approach is flawed for two reasons. First, cholinergic cell loss appears to be a secondary consequence of Alzheimer's pathology, not the disease-producing event, seconds, cholinergic neurons are only one of many neuronal pathways destroyed in AD. It is increasingly clear that simple addition of acetylcholine cannot compensate for the loss of neurons, receptors, and other neurotransmitters lost during the course of the illness. Thus the goal is to minimize or improve symptoms through augmentation of neurotransmission at remaining synapses.

Mechanism of Neuronal Death

Exitotoxicity: Abnormalities appear in glutamate pathways of the cortex and limbic structures leads to a focus on excitotoxicity. Glutamate is the major excitatory neurotransmitter in the cortex and hippocampus. Many neuronal pathways (essential to learning and memory) use glutamate as a neurotransmitter including the pyramidal neurons (a layer of neurons with long axons carrying information out of the cortex), hippocampus and entorhinal cortex. Glutamate and other excitatory amino acid neurotransmitters have been implicated as potential neurotoxins in AD.[13] If glutamate is allowed to remain in the synapse for extended periods of time it can destroy nerve cells. Toxic effects are thought to be mediated through increased intracellular calcium and accumulation of intracellular free radicals. Dysregulated glutamate activity is thought to be one of the primary mediators of neuronal injury after stroke or acute brain injury. Calcium overload is the essential factor in excitotoxicity. The mechanisms by which this occurs and leads to cell death are as follows:

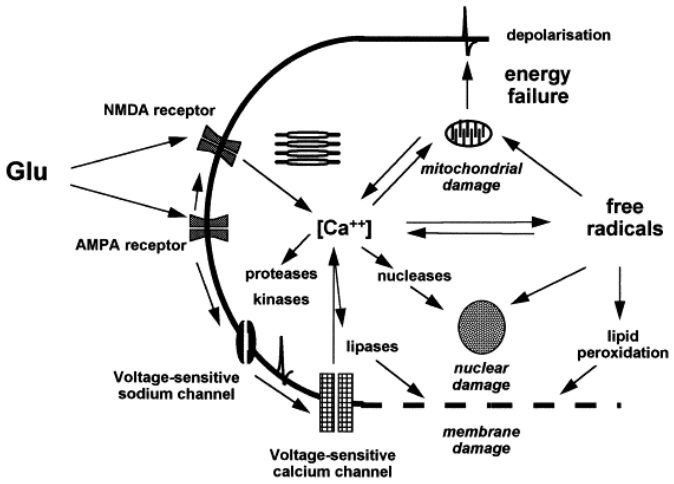


Fig: Excitotoxicity

- Glutamate activates NMDA, AMPA and metabotropic receptors. Activation of AMPA receptors depolarises the cell which unblocks the NMDA channels permitting Ca^{2+} entry. Depolarisation also opens voltage-activated calcium channels, releasing more glutamate. Metabotropic receptors cause the release of intracellular Ca^{2+} from the endoplasmic reticulum. Na^{+} entry further contributes to Ca^{2+} entry by stimulating Ca^{2+}/Na^{+} exchange. Depolarisation inhibits or reverses glutamate uptake thus increasing the extracellular glutamate concentration.
- The mitochondria and endoplasmic reticulum act as capacious sinks for Ca^{2+} and normally keep $[Ca^{2+}]_i$ under control. Loading of the mitochondrial stores beyond a certain point, however, disrupts mitochondrial function, reducing ATP synthesis, thus reducing the energy available for the membrane pumps and for Ca^{2+} accumulation by the endoplasmic reticulum. Formation of reactive oxygen species is also enhanced. This represents the danger point at which positive feedback exaggerates the process.
- Raised $[Ca^{2+}]_i$ affects many processes, the chief ones relevant to neurotoxicity being:
  - Increased glutamate release.
  - Activation of proteases (calpains) and lipases causing membrane damage.
  - Activation of nitric oxide synthase, while low concentrations of nitric oxide are neuroprotective high concentrations in the presence of reactive oxygen species generate peroxynitrite and hydroxyl free radicals which damage many important biomolecules including membrane lipids, proteins and DNA.
  - Increased arachidonic acid release which increases free radical production and also inhibits glutamate uptake.

Local injection of kainic acid is used experimentally to produce neurotoxic lesions. It acts by excitation of local glutamate-releasing neurons and the release of glutamate acting on NMDA and also metabotropic receptors leads to neuronal death. Domoic acid is a glutamate analogue produced by mussels which was identified as the cause of an epidemic of severe mental and neurological deterioration in a group of Newfoundlanders in 1987.

Oxidative stress:[14]

The brain has high energy needs which are met almost entirely by mitochondrial oxidative phosphorylation, generating ATP at the same time as reducing molecular O_2 to H_2O. Under certain conditions, highly reactive oxygen species for example oxygen and hydroxyl free radicals and H_2O_2 may be generated as side products of this process. Oxidative stress is the result of excessive production of these reactive species. They can also be produced as a by-product of other biochemical pathways including nitric oxide synthesis and arachidonic acid metabolism as well as the mixed function oxidase system. Unchecked, reactive oxygen radicals attack many key molecules, including enzymes, membrane lipids and DNA. Not surprisingly, defence mechanisms are provided in the form of enzymes such as *superoxide dismutase* (*SOD*) and *catalase* as well as antioxidants such as ascorbic acid *glutathione* and α;-*tocopherol* (vitaminE), which normally keep these reactive species in check. Some cytokines, especially tumour necrosis factor (TNF-α), which is produced in conditions of brain ischaemia or inflammation exert a protective effect partly by increasing the expression of SOD. Transgenic animals lacking TNF receptors show enhanced susceptibility to brain ischaemia. Accumulation of misfolded mutated SOD may contribute to neurodegeneration.

Apoptosis: Apoptosis can be initiated by various cell surface signals. The cell is systematically dismantled and the shrunken remnants are removed by macrophages without causing inflammation. Apoptotic cells can be identified by a staining technique that detects the characteristic DNA breaks. Many different signalling pathways can result in apoptosis but in all cases the final pathway resulting in cell death is the activation of a family of proteases (*caspases*) which inactivate various intracellular proteins. Neural apoptosis is normally prevented by neuronal growth factors including nerve growth factor and brain-derived neurotrophic factor, secreted proteins that are required for the survival of different populations of neurons in the CNS. These growth factors regulate the expression of the two gene products Bax and Bcl-2, Bax being proapoptotic and Bcl-2 being antiapoptotic.

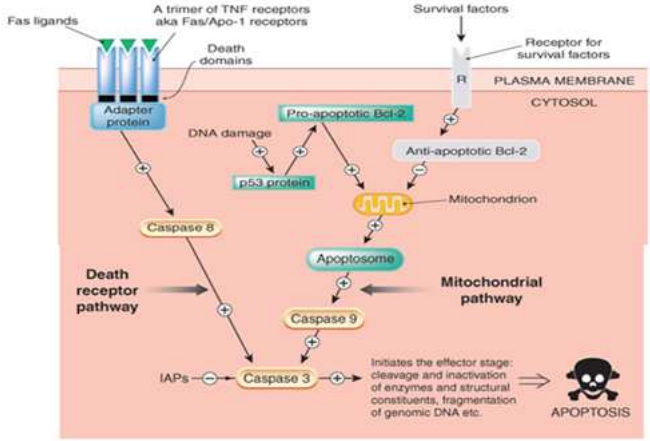


Fig: Apoptosis

Brain Vascular Disease and High Cholesterol

Cardiovascular risk factors that are also risk factors for dementia include hypertension, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol and particularly, diabetes.[15]

Brain vascular disease: Brain vascular disease may augment the cognitive impairment observed for a given amount of AD pathology in the brain. In addition, vascular disease may accelerate amyloid deposition and increase amyloid toxicity to neurons.[16]

Blood vessels: Dysfunctional blood vessels may impair nutrient delivery to neurons and reduce clearance of βAP from the brain.

Blood pressure: Controlling high blood pressure is associated with reduced rate of progression of dementia.[17]

Diabetes: Diabetes may increase the risk of dementia through factors related to "metabolic syndrome" (dyslipidemia and hypertension), effects of potentially toxic glucose metabolites on the brain and vasculature and through insulin itself.[18] Disturbances in insulin-signaling pathways both in the periphery and the brain have been linked to AD. Insulin may also regulate the metabolism of βAP and tau protein.

Cholesterol: There are multiple links between cholesterol and the occurrence of AD. Apo E is a lipoprotein that is synthesized in the liver, central nervous system, and cerebrospinal fluid. It is responsible for transporting cholesterol in the blood through the brain. The elevated cholesterol levels in brain neurons may alter membrane functioning and result in the cascade leading to plaque formation and AD.

Pathogenesis

Other hypotheses proposed to explain AD pathogenesis include oxidative stress, mitochondrial dysfunction and postmenopausal loss of estrogen in women. Each of these mechanisms may contribute to AD pathogenesis but the extent of the contribution is uncertain. There is a growing body of evidence of a role for oxidative stress and the accumulation of free radicals in the brain of AD patients [19]. Amyloid deposits consist of aggregates of Aβ containing 40 or 42 residues. Aβ40 is produced normally in small amounts whereas Aβ42 is overproduced as a result of the genetic mutations. Both proteins aggregate to form amyloid plaques but Aβ42 shows a stronger tendency than Aβ40 to do so and appears to be the main culprit in amyloid formation. Aβ40 and 42 are produced by proteolytic cleavage of a much larger (770 amino acid) APP, a membrane protein normally expressed by many cells, including CNS neurons. The proteases that cut out the Aβ sequence are known as *secretases*. It is uncertain exactly how Aβ accumulation causes neurodegeneration, and whether the damage is done by soluble Aβ monomers or oligomers, or by amyloid plaques. There is some evidence that the cells die by apoptosis, although an inflammatory response is also evident. Expression of Alzheimer mutations in transgenic animals causes plaque formation and neurodegeneration, and also increases the susceptibility of CNS neurons to other challenges, such as ischaemia, excitotoxicity and oxidative stress, and this increased vulnerability may be the cause of the progressive neurodegeneration in AD.

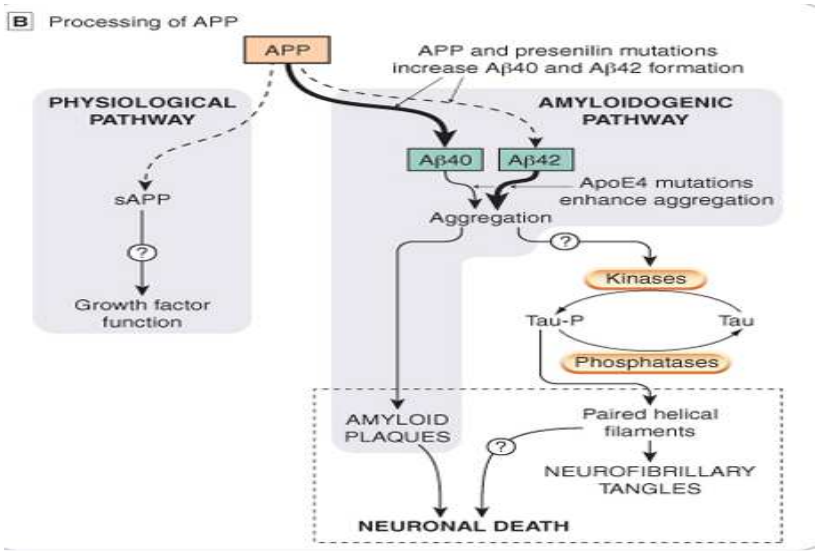


Fig: Pathogenesis of Alzheimer's

Clinical Presentation

It is helpful to divide Alzheimer's symptoms into two basic categories: cognitive symptoms and noncognitive (behavioral) symptoms.[20] Cognitive symptoms are present throughout the illness, whereas behavioral symptoms are less predictable.

Symptoms
Cognitive
Memory loss (poor recall and losing items) Aphasia (circumlocution and anomia) Apraxia Agnosia Disorientation (impaired perception of time and unable to recognize familiar people) Impaired executive function
Noncognitive
Depression, psychotic symptoms (hallucinations and delusions) Behavioral disturbances (physical and verbal aggression, motor hyperactivity, uncooperativeness, wandering, repetitive mannerisms and activities, and combativeness)
Functional
Inability to care for self (dressing, bathing, toileting, and eating)

Dignosis

At present the only way to definitively diagnose AD is through direct examination of brain tissue at autopsy or biopsy. AD is still primarily a clinical diagnosis.[21] Ideally, evidence of defective retention memory (amnesia) will implicate bimesiotemporal dysfunction. Evidence of parietal cortical dysfunction (visuospatial dysfunction), dorsolateral prefrontal dysfunction (executive dysfunction) or lateral temporal dysfunction (language dysfunction) should also be present. Almost any medication can contribute to cognitive impairment in vulnerable individuals but certain classes of medication are more commonly implicated. Benzodiazepines and other sedative hypnotics, anticholinergics, opioid analgesics, antipsychotics and anticonvulsants have been associated with cognitive impairment. NSAIDs, histamine (H2) receptor antagonists, digoxin, amiodarone, antihypertensives and corticosteroids have been implicated in cases of delirium.[22] Because medications are a reversible cause of cognitive symptoms, medication review and management are essential.

Several criteria have been developed for the detection and diagnosis of dementia, including the Diagnostic and Statistical Manual of Mental Disorders criteria,[23] the Agency for Healthcare Research and Quality (AHRQ) Guidelines,[24] the American Academy of Neurology Guidelines,[25] the National Institute of Neurological Disorders and Stroke (NINDS) criteria,[26] the National Institute of Neurological Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) Criteria. For patients who meet criteria for the dementia syndrome current recommendations from the American Academy of Neurology include a neuroimaging study (computed tomography or magnetic resonance imaging) as well as a serologic evaluation that includes blood cell counts, serum electrolytes, liver function tests, a test of thyroid function and a vitamin B12 level.

At autopsy, brains of AD victims show three distinct structural abnormalities:

1. **Loss of neurons that liberate acetylcholine:** A major center of neurons that liberate acetylcholine is the nucleus basalis which is below the globus pallidus. Axons of these neurons project widely throughout the cerebral cortex and limbic system. Their destruction is a hallmark of Alzheimer disease.
2. **Beta-amyloid plaques**: Clusters of abnormal proteins deposited outside neurons.
3. **Neurofibrillary tangles**: Abnormal bundles of filaments inside neurons in affected brain regions. These filaments consist of a protein called tau that has been hyperphosphorylated

Management[27]

Cholinesterase Inhibitors: A major approach to the treatment of AD has involved attempts to augment the cholinergic function of the brain. An early approach was the use of precursors of acetylcholine synthesis, such as *choline chloride* and *phosphatidyl choline (lecithin). Physostigmine*, a rapidly acting, reversible AChE inhibitor, produces improved responses in animal models of learning and some studies have demonstrated mild transitory improvement in memory following physostigmine treatment in patients with AD. The use of physostigmine has been limited because of its short half-life and tendency to produce symptoms of systemic cholinergic excess at therapeutic doses. Four inhibitors of AChE currently are approved by the FDA for treatment of Alzheimer's disease: *tacrine*, *donepezil*, *rivastigmine*, and *galantamine*. Tacrine is a potent centrally acting inhibitor of AChE. Studies of oral tacrine in combination with lecithin have confirmed that there is indeed an effect of tacrine on some measures

of memory performance, but the magnitude of improvement observed with the combination of lecithin and tacrine is modest at best. The side effects of tacrine often are significant and dose-limiting; abdominal cramping, anorexia, nausea, vomiting and diarrhea are observed in up to one-third of patients receiving therapeutic doses and elevations of serum transaminases are observed in up to 50% of those treated. Because of significant side effects, tacrine is not used widely clinically. Donepezil is a selective inhibitor of AChE in the CNS with little effect on AChE in peripheral tissues. It produces modest improvements in cognitive scores in Alzheimer's disease patients and has a long half-life, allowing once-daily dosing. Rivastigmine and galantamine are dosed twice daily and produce a similar degree of cognitive improvement. Adverse effects associated with donepezil, rivastigmine and galantamine are similar in character but generally less frequent and less severe than those observed with tacrine, they include nausea, diarrhea, vomiting, and insomnia. Donepezil, rivastigmine, and galantamine are not associated with the hepatotoxicity that limits the use of tacrine.

Table-1: Clinical Pharmacology of the Cholinesterase Inhibitors

	Donepezil	**Rivastigmine**	**Galantamine**
Brand name	Aricept	Exelon	Razadyne
Dosage form	Tablet & Orally disintegrating tablet	Capsule & Oral solution	Tablet, Oral solution & Extended-release (ER) capsule
Starting dose	5 mg daily at bedtime	1.5 mg twice a day	4 mg twice a day
Meals	No effect of food	Take with food	Take with food
Half-life	70 hours	1.5 hours	7 hours

Antiglutamatergic Therapy: An alternative strategy for the treatment of AD is the use of the NMDA glutamate receptor antagonist memantine (NAMENDA). Memantine is the only NMDAantagonist currently available. Memantine produces a use-dependent blockade of NMDA receptors. In patients with moderate to severe AD, use of memantine is associated with a reduced rate of clinical deterioration. Whether this is due to a true disease-modifying effect, possibly reduced excitotoxicity or is a symptomatic effect of the drug is unclear. Adverse effects of memantine usually are mild and reversible and may include headache or dizziness.

Estrogen: Estrogen replacement has been studied extensively for the treatment and prevention for AD. Most, but not all, epidemiologic studies show a lower incidence of AD in women who took estrogen replacement therapy postmenopausally. Recent clinical trials have not supported the use of estrogen as a treatment for cognitive decline.

Huperzine A Huperzine A is an alkaloid isolated from the Chinese club moss, *Huperzia serrata*. It reversibly inhibits acetylcholinesterase and is administered orally in doses of 50 to 200 mcg two to four times daily. Clinical studies suggest that huperzine A may be promising for symptomatic treatment of Alzheimer's disease, but more studies are needed to determine its particular place in therapy.

Antiinflammatory Agents: Epidemiologic studies suggest a protective effect against AD in patients who have taken NSAIDs.[28] Treatment for less than 2 years is associated with a lower relative risk of AD, however longer treatment duration lowered this risk further.[29]

Result & Conclusion

In conclusion, currently there is no drug which can cure Alzheimer's. The treatment of degenerated neurons usually not possible but there state can prevent by using polytherapy, therefore these patients are at increased risk of severe side effects. Hence, there is a need to emphasis and development of new drugs which can provide us a better cure with better efficacy and safety profiles than those of older drugs.

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