# Dementia, A General Medical Practitioner's Concern: A Review

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## Abstract

The senile population is often ignored by society without heeding to their actual complaints; their medical management is carried superficially. It is inevitable for the growing population and increased lifespan to pose the threats of psychosomatic discomforts of advancing age, where early clinical recognition of conditions like dementia will play an important role. Dementia requires keen scrutiny by the general practitioners, they need to give utmost importance and attention. The medical practitioner will play an important role in identifying the clinical condition like dementia during its initial stage itself. From the point of general practice, it will become important to convince the patient and his family members to handle the situation by referring to a psychiatrist or psychologist or a rehabilitation center for the needful. Hence this article will review some basics of Alzheimer's disease (AD) especially form the point of the fraternity of general medical practitioners in the society.

***Keywords****: Alzheimer's disease, Dementia, Psychiatrist, Psychologist, Psychosomatic.*

## Introduction

Dementia and depression are two major problems among the senile population in society. **Dementia** is a syndrome presented with deterioration in memory, thinking, behavior, and the ability to perform day-to-day activities. **Depression** is a severe feeling of despondency and dejection[1]. Alzheimer's disease stands as one of the leading causes of death due to dementia, especially in western countries. Dementia increases with age; it is invariably associated with some degree of cognitive decline. There is a lot of similarity between these two conditions. Dementia starts with mild cognitive impairment (MCI); it is a progressive declining change in cognitive function with an increased disability of self-management by an individual. It will progress from mild to moderate, and then to advanced stages; it may be difficult to identify during its initial stages. Alzheimer's disease (AD) is a leading cause of dementia among elderly citizens in the world. Dr. Alois Alzheimer has first recognized this condition of irreversible neurodegenerative disorder in the year 1907 in a female patient aged 51 years old; hence fourth it was known as Alzheimer's Disease[2]. Its etiology is multifactorial showing dominance of gene and sporadic nature of the disease. Subtle pathophysiological changes in AD sets in 10-15 years before its insidious clinical manifestations; hence one should be keen while dealing with the complaints of senior citizens.

**Types of Dementia:** Alzheimer's Dementia, Vascular dementia, Lewy body dementia (LBD), Frontotemporal Dementia (FTD).

**Alzheimer's Disease (AD)**: is a syndrome with degenerative changes in the brain, manifested with insidious onset with a progressive decline in cognitive, emotional, and motor functions.

**Vascular Dementia:** it is seen as a result of a deformity in blood vessels due to various underlying factors like diabetes, hypertension, dyslipidemia, etc. affecting brain perfusion which is gradually leading to brain parenchymal changes at the different regions[3].

**Lewy Body Dementia (LBD)**: it is due to abnormal deposits of an alpha-synuclein protein called "Lewy Bodies" inside the neuron; which is manifested with inconsistent cognitive dysfunction[4].

**Frontotemporal dementia (FTD):** it is due to the involvement of the frontal and temporal lobes of the

brain associated with neurocognitive behavior changes[5].

**Role of Neurotransmitters**: The neurotransmitters will play an important role in cognitive function. The activity of the brain is driven through several neurotransmitter chemicals like cholinergic, glutaminergic, adrenergic, serotonergic, dopaminergic fibers, they play an important role in individuals' psychosomatic excellence. With the advancing age, low-profile neuronal activity is seen in the cerebral cortex of the brain, it results in cognitive dysfunction with gradual synaptic functional impairment followed by loss of neurons in the patients with AD[6].

Neurotransmitters will play an important role in motor function; it maintains one's alertness and wakefulness. Declining cognitive ability is an important sign of AD, associated with dysfunction in neurotransmitter secretion. Acetylcholine (Ach) has a crucial role in both the central and peripheral nervous system; it is used in the neuromuscular junction to activate skeletal muscles. The cholinergic hypothesis underscores the events of reduced Ach uptake, Ach release, uptake of choline acetyltransferase. Due to impaired secretion of Ach causing synaptic loss of cholinergic neurons is an important event leading to progressive motor and cognitive impairment. The drugs which are enhancing the activity of the cholinergic system has therapeutic implications to treat AD patients[7,8]. Glutamate is another excitatory neurotransmitter of the nervous system, transmitted through glutaminergic fibers. If there is over activation of N-Methyl-d-Aspartate (NMDT) receptors by glutamate leading to the reduced neuronal activity which results in excitotoxicity and neuronal loss in AD[9]. Serotonin is another neurotransmitter; which contributes to the sense of wellbeing and happiness in an individual. Excessive serotonergic(5-Hydroxytryptamine) denervation is observed in AD. These patients may experience severe sleep and circadian rhythm disturbances with emotional behavior. Serotonin reuptake inhibitors are playing an important role; hence reinstating serotonergic neurotransmission has an important therapeutic value[10].

**Pathophysiology of Alzheimer's**

EOAD (Early onset of Alzheimer's disease)

EOAD is seen in families with autosomal dominant genetic inheritance; its early-onset age ranges from 30-65 years. The dominant genes which are linked with the familial autosomal inheritance of EOAD are including amyloid precursor protein (APP) on chromosome 21q, PSEL1(presenilin) on chromosome14 and PSEL 2(presenilin) on chromosome1. APP is functionally involved in neuronal plasticity and synapse formation. Recently through genome-wide association studies, a greater number of genes identified, which are showing high penetrability in EOAD[11,12].

APP is a substrate of the ɣ-secretase enzyme complex which is involved in its cleavage process. The amyloid cascade hypothesis proposes that there is a progressive accumulation of β-amyloid protein in the brain. APP cleavage occurs by the process of proteolysis through amyloidogenic and nonamyloidogenic pathways by the action of gamma-secretase complex; it contains individual proteins presenilin-1, presenilin-2, nicastrin, and APH-1(anterior pharynx defective-1). APP cleavage by α-secretase and ɣ-secretase enzymes results in the formation of nonharmful fragments that are undergoing easy degradation hence called the nonamyloidogenic pathway. APP cleavage by ɣ-secretase and β-secretase occurs through the amyloidogenic pathway results in the formation of β-amyloid formation which is not undergoing degradation easily; it results in β-amyloid stagnation and decreased clearance. This results in amyloid senile plaques accumulation in the brain parenchyma; this extracellular debris deposited outside the neuron, which initiates the inflammatory reactions. There is an association between a mutation in the APP gene or any one component of ɣ-secretase complex expression that can cause excess formation and aggregation of β-amyloid, leading to its undue deposition in the brain[13,14.15].

PSEN 1 protein is a component of the ɣ-secretase complex which deals with the APP cleavage process, its mutation in the complex deals with the EOAD by causing the disproportion in the formation of amyloid- β (Ab) ratio Ab42/Ab40. Three proteases enzymes cleavage the APP is alpha, beta, and gamma-secretase enzymes play a role in the etiology of AD. Beta-amyloid peptides are created in two forms, one is made up of 40 amino acids and another by 42 amino acid peptides. There is a selectively increased production of Ab42 monomer levels in the brain. The elevated ratio of beta-amyloid 40

and 42 is an important event in early pathological changes seen in the AD. Curbing the β-amyloid 42 productions and maintaining its concentration is having therapeutic value. PSEN2 gene functionally resembles the PSEN1 is also one the main component in the gamma secretory complex having relatively rare and less influence on EOAD [16,17,18,19].

Down Syndrome (DS) is an autosomal genetic disorder having an extra copy (trisomy) of chromosome 21. It is interesting to note this extra copy of chromosome 21 (trisomy) is the housing APP gene. Due to this extra copy of APP leads to excess formation of β-amyloid peptide formation[20]. This condition is also associated with deranged microglial cells with neurofibrillary tangle formation. DS patients are also having high-level production of Reactive Oxygen Species (ROS) causing overall oxidative stress in the body; it affects the improper scavenging of β-amyloid which accelerates the pathophysiological changes in the brain; hence Down syndrome patients are prone for early onset of AD [21,22].

**LOAD (Late-onset of Alzheimer's disease)**

LOAD is sporadic, can be seen in the prone elderly population usually after 65 years of age. There is growing evidence of heterogenicity of LOAD involving both genetic and environmental risk factors. Apolipoprotein E (ApoE) is a type of protein involved in lipid homeostasis; it is a major cholesterol transporter that plays an important role. It helps in repairing the neuronal injury, maintain synaptic integrity, neuronal plasticity, neurogenesis, synaptic transport, cholesterol metabolism, etc. ApoE gene quotes for apolipoprotein is located on chromosome 19, it helps in the clearance of accumulated beta-amyloid. It has three different isoforms ApoE ε2, ApoE ε3, and ApoE ε4. ApoE ε2 has a protective effect against AD; in contrast, ApoE ε 4 quantity will increase the risk of AD, hence taming ApoE ε4 is having high therapeutic importance. Much association of dementia in a family is seen in an Individual who carries two APOE ε4 alleles; gender-wise the females are relatively more prone to AD when compared with males. APOE also influences the susceptibility of the body towards bacterial or viral infections. APOE ε4 causes the subtle brain changes posing the lifelong risk associated with late risk of AD[23,24,25]**.** Inherent ApoE ε4 allele of the APOE gene from parents is a greater risk factor for AD, it was the first clinically correlated gene involved in late-onset of AD. Later it was also found its correlation with early onset of AD. ApoE is also expressed in different tissues of our body; found abundantly in the brain tissue. Altered APOE gene expression in glial cells may be one of the factors influencing the pathophysiological changes in the brain[26,27]. ApoE ε4 is mediating the Alzheimer's risk, which affects the astrocytes and microglial cells supporting proinflammatory influence, and decreased phagocytic capacity leading to neurodegeneration[28].

**Role of Genetics in Twins:** Studies showing improper disease concordance in monozygotic (MZ) and dizygotic (DZ) twins. It is showing discrimination in age onset of disease and clinical manifestation. Discordance depends on environmental risk exposure, and influence by lifestyle factors; hence there is no such similarity exists among these two comparable groups. The inter pair differences in the age of onset of disease were significantly greater among dizygotic pairs when compared with monozygotic pairs. These findings are showing the difference in individual gene expressions probably associated with the host and environmental interactions[29].

**Tauopathies:** Tau is a microtubule-associated protein (MAP) found in the cytosol and axon of the neuron. Tau protein is doing the function of building the integration of microtubule inside the cell, they help in axonal transport. Tauopathies are a group of disorders where there is an abnormal filamentous protein formation in the neurons, oligodendrocytes, astrocytes, etc. Its gene represented on chromosome 17 q21; gene mutations affecting the formation of normal tau proteins results in the disorganization of structural microtubules of the cytoskeleton, gradually leading to reduced neuronal plasticity, nerve conduction, synaptic transmission, etc. Hyperphosphorylation of tau is causing disorganization and self assembles of microtubules resulting in the formation of neurofibrillary tangles (NFT) in the brain, it is toxic to the neurons. Higher levels of tau in the CSF are showing detrimental effects in an individual when it is associated particularly with the ApoE ε4 genotype. Hence hyperphosphorylated tau is one of the important biomarkers seen in the CSF having a high diagnostic value in Alzheimer's disease. Similar metabolic changes are also seen in frontotemporal dementia in Parkinson's disease (FTDP). Tauopathies are not only

restricted to dementia, but aberrant tau proteins are also seen in several neurological diseases with cognitive dysfunctions including patients with Type 1 Diabetes Mellitus. Amyloid plaques and Neurofibrillary tangles in the brain are considered as the "**Hallmarks**" of the Alzheimer's disease[30,31,32].

**Dealing with Alzheimer's disease**

History of illness and family history of dementia patients plays an important role in diagnosis at the early stage. Primary prevention includes reducing the incidence of dementia. Secondary prevention includes early detection of the condition before its explicit manifestations. Tertiary prevention includes early diagnosis and treatment initiation[33]. It is also important to convince the family members and caregivers to handle the worst scenarios. Even counseling the patient and patient family members play an important role.

**Clinical Examination in Dementia:** The physician will play an important role in making use of an appropriate tool to examine the patients clinically. The mental status examination is mainly intended to probe the cognitive domain. Mini-mental state examination (MMSE) is a widely used clinical psychometric evaluation method intended to assess the cognitive levels; used for diagnostic, prognostic, and severity confirmation of dementia disorders. MMSE assesses the domains like attention, language, memory, orientation, visual and spatial proficiency. This test with the maximum assigned score is 30. The lower score indicates increased severity of the cognitive disability; score 24 is an indication of normal cognitive ability. The mental examination is useful to elucidate the difference between neurological and psychiatric disorders of the variable range[34,35].

**Structural changes in Brain:** Being the most susceptible organ, the brain shows senile degenerative changes in its different regions. Hippocampus, amygdala, entorhinal cortex, parahippocampal regions of the brain showing architectural changes in individuals with AD. The hippocampus is a site of memory, showing more significant degenerative changes. On gross anatomical examination of the brain was showing cortical thinning, narrow gyri; sulci which are a space between the adjacent gyrus will be increased considerably. Undergoing brain degeneration can be correlated with an increase in the size of the ventricles of the brain. Microscopic examination is revealing the neuronal loss which is seen along with gross degenerative brain changes of Alzheimer's disease[36,37].

**Radiology investigations:** Advances in neuroimaging biomarkers will play an important role in early recognition of clinicopathological stage progression in dementia. It also helps to exclude the etiology of the nondegenerative neurological deficits, these investigational findings should be always used in conjugation with clinical findings. The prime goal of biomedical research is to establish an affordable and non-invasive biomarker at the preclinical stage of AD. These biomarkers are used as surrogates for the disease progress at different ages through neuroimaging techniques. It helps in understanding the alteration in the structure and volume of the brain. There is several advanced non-invasive neuro-imaging clinical equipment, like Amyloid PET (Positron Emission Tomography), Tau PET, activated fMRI, resting-state fMRI, diffusion MRI, structural MRI, etc. These radiological procedures are specific to find changes like an amyloid deposition, hyperphosphorylated tau protein; and also to find changes in white matter, cortical grey thickness, hippocampus, etc. MRI images are fair to show some early structural and volumetric changes in different parts of the brain in AD patients. These biomarkers are having diagnostic and prognostic importance[38,39].

**Laboratory findings:** Though our knowledge of genomics and proteomics has created large opportunities to explore into the disease-specific molecular marker identification; however**,** the common circulatory biomarkers like beta-amyloid, tau proteins, phosphorylated tau in CSF are considered as most appropriate and important in disease staging and confirmation of Alzheimer's dementia[40].

**Treatment and future scope:** The neurodegenerative changes in Alzheimer's disease are irreversible, hence as such, there is no cure for this ailment. Presently existing modern treatment of Alzheimer's dementia can't stop the disease progress. The basic pharmacological line of treatment includes drugs like cholinesterase inhibitors and memantine, they can reduce the symptomatic cognitive and functional decline[41]. The non-pharmacological treatment includes psychological support by caregivers, and the enriched

sociocultural environment will help. There is a lot of scope for the holistic treatment approach for this ailment. There are large opportunities for research especially in the field of application of nootropic herbal agents in dementia syndrome. Among several modifying factors, a healthy diet, exercise, lifestyle modification, and practicing yoga may be having an advantage in delaying the disease onset.

## Conclusion

Alzheimer's dementia is the most important medical and social problem of age advanced senior citizens, hence its prevalence is estimated to rise in society. Early identification of clinical symptoms of dementia before its explicit manifestation is crucial. The fraternity of general medical practitioners are playing an important role, they act as bonding between patients, family members, and caretakers. The dementia is recognized as a public priority; increasing awareness, and establishing dementia-friendly initiatives in the society and early initiation of treatment can lessen the socioeconomic burden on the country.

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