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Genetic Insight into Familial and Sporadic Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder and common form of dementia in elderly patients accounting for 60 to 80 percent of cases worldwide. The hallmark of AD is deposition of neurofibrillary tangles and amyloid plaques in the brain that lead to neurotoxicity and irreversible loss of neurons in the hippocampus and cortex. Based on the onset of age, AD can be classified into early onset (<65 years) and late-onset (≥ 65 years) groups. Genetic factors such as gene mutation as well as environmental factors both can trigger the disease pathogenesis. The preliminary diagnosis can be performed based on the specific clinical symptoms and genetic analysis can help in establishing the familial cases. Treatments are suggested according to the stages of AD, such as mild, moderate, and severe, based on the clinical symptoms and the diagnosis of the patients.This review focuses on overall AD.

Keywords: Early onset; Late onset; Neurofibrillary tangles; Tau protein.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease and a common form of dementia in old age, which arises due to irreversible loss of neurons, particularly in the hippocampus and cortex.[1] Dementia is a clinical disorder that involves the progressive deterioration of intellectual ability. Irreversible dementia (primary) is the most common cause of AD accounting for 70% of the population.[2]

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AD is also referred to as a "family disease" due to the tremendous impact on the immediate social support system that befalls the patients.[3] AD can be classified into two types based on the onset age of the disease symptoms such as early onset and late onset of disease (Fig. 1).

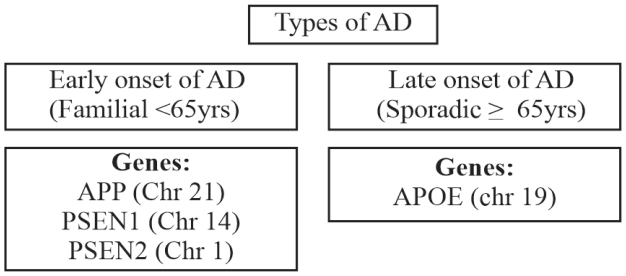

Fig. 1: Classification of AD

The pathogenesis and progression of AD vary due to environmental factors, gene interaction, and genetic causes. Familial early onset Alzheimer's disease (EOAD) can be caused by mutations in one of several genes.[4] Late onset Alzheimer's disease

(LOAD) which commonly represents its sporadic form also exhibits a strong genetic component. LOAD is inheritable up to 60%–80%, but genetic and environmental factors play a pivotal role in the onset, progression and severity of the disease.[5]

The early onset form of AD is also called "familial AD" (FAD) that accounts for about 5-10% of all the reported case of AD. It is an autosomal dominant, inherited due to mutation in PSEN1, PSEN 2 and APP gene.[6] The early onset form of AD develops between the ages of 30 to 60 years. On the contrary, late-onset AD is mostly driven by sporadic factors and generally manifests beyond the age of ≥ 65years. It is a complex genetic disorder and inherited about 60% to 80% of the population.[7] The duration of disease is usually 8 to 10 years vary from 2 to 25 years after diagnosis.[8]

History:

At the age of 51, a woman 'Auguste' presented with peculiar dementia, behavioral and cognitive features that are correlated with those of Alzheimer's. The histopathological analysis revealed the presence of extracellular senile plaques and neurofibrillary tangles (NFTs) in her cerebral cortex.[1] These findings were reported by the German psychiatrist and neuropathologist Alois Alzheimer in 1906.[2]

Pathophysiology of AD

The hallmark of AD is the presence of extracellular plaques composed of the β-amyloid peptide (Aβ) in neuronal cytoplasm and intraneuronal neurofibrillary tangles are rich in abnormally phosphorylated tau in the brain leads to AD.[9] Amyloid plaques are extracellular deposits of Aβ within the brain parenchyma and within the cerebral blood vessels it's referred to as congophilic angiopathy also called as cerebral amyloid angiopathy (CAA).[10] The presence of extracellular neuritic plaques mainly due to aggregated Aβ. The changes in the AD brains arise due to the extracellular accumulation of beta amyloid plaques and the intracellular presence of tau tangles in the neuronal cells. Neurodegeneration is a result of the compromised neuron to neuron communication at synapses due to the accumulation of beta-amyloid plaques in the brain, while tau tangles block the transport of other essential molecules and nutrients inside the neuronal cells. Atrophy occurs due to the degeneration of neuronal cells in the brain. Microglia cells which are present along with the neuronal cells attempt to remove the damaged cells. The presence of toxic tau tangles and beta-amyloid plaques also activate microglia- mediated immune response in the brain. Even though, the chronic inflammation clears the toxic protein in the brain. However, prolonged activation of microglia is associated with neuroinflammation and inflammaging that aggravates the neurodegenerative condition.[11]

Amyloid-beta (Aβ):

Amyloid-beta is a peptide (Aβ) consists of 37–43 amino acids with high resistance to proteolytic degradation. The most common isoforms are 1–40 and 1–42. The β-pleated sheet configuration often aggregates and forms the core of the amyloid plaque and it is the main component of amyloid neuritic plaques. Diffuse plaques and dense core plaques are types of amyloid plaques. A dense core plaque has senile plaques (neuritic plaques) and these cored neuritic plaques are associated with dystrophic neurites. Diffuse plaques are observed in advanced AD and lack neuritic components. The maturation of neuritic Aβ plaques in the early stage is a part of pathological aging. The extracellular nonvascular accumulation of Aβ40 and Aβ42 peptides are formed by amyloid plaques.[12] Aβ42 oligomers are produced by both neurons and associated astrocytes by cooperative activities. Aβ42 oligomers induce tau hyperphosphorylation, oxidative stress, results in toxic effects on synapses and mitochondria.[10] Aβ42 are abundantly found in plaques, more insoluble, and have a higher chance of polymerization. In cerebral amyloid angiopathy the primary constituent of amyloid plaques is Aβ40.[12]

Neurofibrillary Tangles

Neurofibrillary tangles (NFT's) composed of tau protein in affected individuals. In healthy individual, the tau is a vital interacting component of microtubules that stabilize the growing axons and play an important role in the development and growth of neurites. Microtubules are the inner structural supports for the transportation of nutrients, vesicles, mitochondria, and chromosomes within the cell.[13] In AD, tau protein dysfunction occurs due to its pathogenic hyperphosphorylation. Hyperphosphorylation of tau causes its detachment from the microtubule and their subsequent aggregation with the other cytoskeletal proteins. It has a reduced degree of communication with microtubules which favours an increase in free tau protein, which subsequently increases aggregation and fibrillization of itself, arising in axonal transport malfunction.[14] Abnormal tau spreads throughout the brain as the amount of beta-amyloid increases that eventually leads to atrophy and inflammation

in the brain of AD patients.[11] Furthermore, the development of NFT's near the cell surface forms thick bundles of affected neuronsthat leads to neuronal death in AD.[12]

FAMILIAL ALZHEIMER'S DISEASE

A high penetrance of mutation carriers is closely related to the early-onset of the disease.[6] Understanding the pathogenesis of EOAD will lead to the development of effective diagnosis, and treatment strategy.[15] In the early onset of diseases, there is a family history of dementia and are thus designated as familial AD (FAD).[16] The PSEN1 (78%), APP(18%), and PSEN2 (4%) genes have been identified as having the majority of mutations that cause early onset familial AD (EOFAD) (Fig. 2).

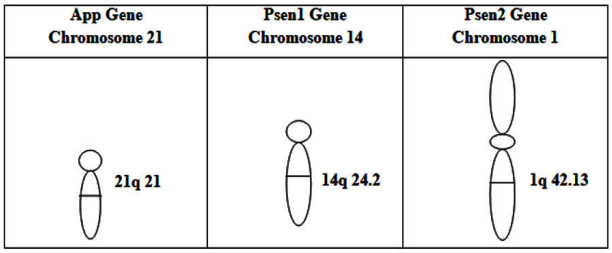

Fig. 2: Represents the gene location present on chromosome 21, 14 and 1 in early-onset of disease.

Early-onset disease is caused by a mutation in these three genes, which account for 30–50% of autosomal dominant AD cases.[1]

Amyloid Precursor Protein (APP Gene)

Amyloid precursor protein (APP) resembles a signal-transduction receptor and is a type I integral membrane glycoprotein.[6] APP is essential for physiological processes such as differentiation, neural proliferation, plasticity, migration, and synaptogenesis.[15] The disease is evaluated as a series of abnormalities in the process and secretion of the APP in the amyloid cascade hypothesis of AD, where an imbalance between amyloid production and clearance is the triggering event and the most important factor; responsible for other abnormalities observed in AD.[14]

Gene Location and Expression

The APP gene is located at chromosome 21q21 position.[6] It is secreted by the endoplasmic reticulum, post-transcriptionally modified in the Golgi, and is transported to the cell surface through the secretory pathway.[8]

Splice Variant

APP consists of 18 exons.[6] The different splicing isoforms of APP proteins range from 365 to 770 amino acids.[15] The exons 16 and 17 are encodes the Abeta peptide.[4] About 8 different isoforms exists and the three main isoforms are APP695 (695 amino acids), APP751 (751 amino acids), and APP770 (770 amino acids). APP695 is primarily expressed in neurons and it is the dominant isoform.[17]

Mutation

Mutations in APP are located near the cleavage sites of alpha, beta, and gamma-secretase enzymes that alter the proteolysis of the Abeta peptide involved in the onset of AD.[4] 26 missense mutations have been identified in the APP gene. For instance the mutation of codon 670 results in lysine to asparagine substitution and that of codon 671 results in methionine to leucine substitution in the APP protein.[18]

In the C-terminal end, α-secretases cleave APP from its carboxyl terminus. The α-secretase enzyme activity includes the ADAM protease family and the β-secretase enzyme consists of two different complexes namely BACE1 and BACE2. The BACE enzymes cut APP from the carboxyl terminus. The ɣ-secretase enzyme complex is rendered by the APP cut. The catalytic function of ɣ-secretase is mediated by either PSEN1 or PSEN2 and this α-secretase cuts APP twice.[19] Amyloid plaques composed of Aβ40 and Aβ42 (extracellular accumulation) are generated after cleavage APP by β- and γ-secretases.[17] The extracellular domains of APP mutations are located at the N-terminus of Aβ at the β-secretase cleavage site.[18]

The increased levels of Aβ due to the presence of APP mutations result in augmented ROS levels and mitochondrial dysfunction, thus increasing oxidative damage in EOAD.[6] The proteolytic cleavage of APP by α-, β-and γ-secretases can lead to activation of either non-amyloidogenic or amyloidogenic pathways. In the non-amyloidogenic pathway, the APP protein is cleaved by α-secretase in the middle of the Aβ sequence that results in the release of sAPPα. In the amyloidogenic pathway, the APP protein is cleaved by β-secretase at the 1st residue or at the 11th residue of Aβ sequence that results in the release of soluble β-cleaved soluble APP (sAPPβ). The β- and γ-secretases amyloid precursor protein result in abnormal processing, imbalance in the production, and clearance pathways.[12]

Alzheimer Disease in Down Syndrome

Down syndrome (DS) arises due to trisomy of chromosome 21 and the most common genetic cause of AD. In most adults, the DS develops AD-like neuropathology at the age of 40.[16] The increasing risk of AD develops clinical symptoms in adults with DS. Individuals with DS are more prone to developing AD, which is thought to be due to amyloid precursor protein over expression.[20] Aβ accumulation has been found in 8-12 years old children suffering from DS with an increased risk of AD in later life.[21] Some behavioural changes observed in AD-DS individual are social withdrawal, less psychotic, emotional instability, apathy, and reduced empathy. Fewer delusions and hallucinations are some additional symptoms.[22]

Presenilins-1 and Presenilins-2 Gene

Presenilins

Presenilins are expressed mainly in neurons, brain andin several other tissues. Presenilins localize in the lysosomes, golgi apparatus, endoplasmic reticulum, endosomes, plasma membranes, phagosomes, and mitochondria. PSEN1 and PSEN2 are expressed at similar levels andexhibit similar distribution.[1] Presenilin is a subunit of γ-secretase with aspartyl protease activity. ɣ-secretase can produce different lengths of the β-amyloid peptide (Aβ) upon cleavage of APP.[23] Mutations in PSEN1 and PSEN2 thus impairs the ɣ secretase mediated cleavage of APP in Aβ fragments and results in an increased ratio of Aβ1–42 to Aβ1–40 and either increase result in Aβ1–42 production or decreased Aβ1–40 production or a combination of both.[24]

Presenilins1 (PSEN1Gene)

The complete penetrating of mutation in the PSEN1 gene leads to a severe form of AD at the early stage of 25-65 years of age.[24] Studies in mice models have shown that presenilins-1 play an importantrole in promoting, maintaining memory and neuronal survival in the CNS.[25] PSEN1 is an autosomal dominant inheritance and associated with neurogenerative disorders such as dementia, Parkinson's, Notch signaling modulation and Aß intracellular domain generation.[8]

Gene Location and Expression:

Gene for Presenilins-1 is located at chromosome 14q24.2 position and comprises of 12 exons.[25] The polytopic membrane protein forms the catalytic core of the γ-secretase complex in the PSEN 1 gene. γ-secretase is an integral membrane protein found in the cell surface, mitochondria, Golgi, endoplasmic reticulum.[8]

Splice Variant

Presenilins-1has 12 exons. It encodes 467 amino-acids which localizes in the lumen/extracellular space. It has 9 C-terminal transmembrane domains.[25] PSEN1 mutations have been identified in over 300 people, and they are the most common cause of early onset AD.[26] Most of these mutations are found throughout the protein and located in the transmembrane region.[6]

Mutation

200 pathogenic mutations have been identified in the PSEN1 gene and approximately 70% mutations occurs in exons 5, 6, 7, and 8.[25] Missense mutations in presenilin-1 cause amino acid substitutions that render the protein with changed function of γ-secretase activity resulting in an increase in Aβ42 to Aβ40 ratio result in changes in function.[8] In most of the cases, the γ-cleavage produces Aβ40 which generates a more toxic variant, Aβ42. In 390 families over 176 different mutations in PSEN1 has been identified.[8]

Presenilins-2 (PSEN2 Gene)

Presenilins-2 gene was initially reported as the causative gene for AD. It is rare cause of early onset of familial AD with lower penetrance due to missense mutation.[8] The onset of disease can occur in older age of 39-83 years and highly variable among PSEN2 affected family members.[24] It plays an important role in Notch signaling, intracellular signaling, and APP processing.[23]

Gene Location and Expression

Presenilins-2 is located on chromosome 1q42.13.[25] It has a molecular weight of 55Da and spans nine times the lipid bilayer. PSEN2 has two isoforms (Isoform 1 and 2). Isoform 1 is found in the skeletal muscle, heart, and placenta. Isoform 2 is found in the brain, skeletal muscle, placenta, brain, heart, liver, and kidney and lacks 263–296 amino acids.[23]

Splice Variant

Presenilins-2 has 12 exons. It encodes a 448-amino-acid protein and consists of 9 transmembrane domains.[26] It lacks exon 5 and aberrant splice

variant and results in the insertion of five amino acids. SSMAG is a protein variant that introduces exon 6 a premature stop codon. In the adjacent transmembrane regions two aspartyl residues–D263 and D366 are found.[23]

Mutation

In PSEN2 gene 19 different mutations have been identified.[26] 38 mutations were reported and have two frameshift mutations Glu126fs and Lys306fs and the others are non-synonymous substitutions.[23] PSEN2 mutations are associated with other disorders, such as frontotemporal dementia, dementia with Lewy bodies, dilated cardiomyopathy, breast cancer, and Parkinson's disease with dementia (PDD).[25]

SPORADIC ALZHEIMER'S DISEASE

LOAD has a strong genetic predisposition, complex with genetic components, heterogeneous, and considered to be multifactorial.[24] LOAD common among the population and accumulation of p-tau and toxic Aβ may not be the initial cause of neural degeneration.[27]

Apolipoprotein E (APOE Gene)

Apolipoprotein E (APOE) is the strongest genetic risk factor for late-onset AD.[7] The apolipoprotein is associated with both familial and sporadic late-onset of AD.[8] It is involved in neuronal maintenance, repair, and transport of cholesterol carrier in the brain. APOE binds to several receptors on the cell surface, which are involved in neuronal signaling, lipid delivery and transport, glucose metabolism, and mitochondrial function. The APOE gene has three main alleles, called "ε2," "ε3," and "ε4".[4] The female carriers of APOE ε4 between the age of 65 and 75 has increased risk compared to male carriers.[7] The decreased risk of AD associated with APOE is the ε2 allele as well as later onset of age.[12]

Gene Location and Expression

The APOE gene is located on chromosome 19q13.32 (Fig 3). It has 299 aminoacid glycoprotein with varying levels of posttranslational sialylation due to O-linked glycosylation at threonine 194.[8] APOE is expressed in several organs with the highest expression of this geneinthe liver and brain. Astrocytes and microglia are the major cell types of non-neuronal cells that express APOE in the brain. ApoE plays a vital role in maintaining lipid homeostasis in the CNS, repairing damaged neurons, maintaining synaptic connections, and scavenging toxins. ApoE2, ApoE3, and ApoE4 are the three alleles encoded by the ApoE gene. The three common SNPs cause changes in the coding sequence, resulting in three different apoE isoforms: apoE2 (cys112, cys158), apoE3 (cys112, arg158), and apoE4 (arg112, arg158).[28] ApoE4 is the most common genetic risk factor for sporadic AD. ApoE4 is linked to cognitive impairment, and its impact is tempered by cholesterol levels. In contrast to ApoE2 and ApoE3, ApoE4 is more sensitive to stress which forms bioactive toxic C-terminal fragment and causes neuron-specific proteolysis.[29]

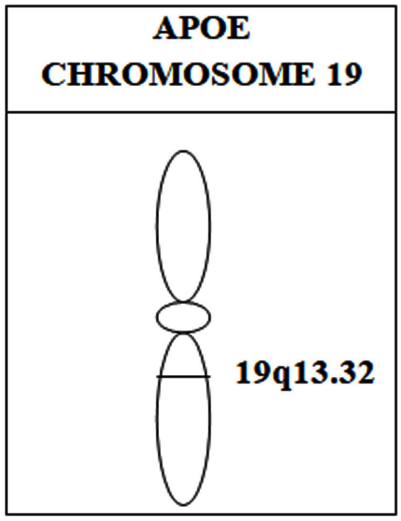

Fig. 3: Represents the gene location present on chromosome 19 in late onset of disease.

Splice Variant

APOE encodes 299 amino acid glycoproteins with a molecular weight of 34,200 and containsseveral single nucleotide polymorphisms distributed across the gene. Two single nucleotide polymorphisms, rs429358, and rs7412, which encode three protein isoforms E2, E3, and E4, define the three APOE ε4 alleles (ε2, ε3, and ε4). The ε4 allele is largely linked to clinical symptoms of AD due to an association with pathologic hallmarks of the disease rather than any other mechanism. The distribution of ApoEε4 alleles in some ethnic minority populations contradicts the claim that ApoEε4 is the single most important genetic factor linked to AD in all populations.[30] ApoE is involved in the distribution and metabolism of cholesterol and triglycerides in human organs and cell types.[8]

The development of the familial and sporadic forms of late onset AD has susceptibility factors of the ε4

allele of ApoE.[30] The several apolipoproteins are found in the brain, namely apoA-I, apoA-II, apoA-IV, apoD, apoE, apoH, and apoJ. The apoA-I and apoJ have potential roles in Aβ fibrillogenesis and clearance. ApoJ is known as clusterin is expressed in astrocytes and neurons.[28] Clusterin is a chaperon molecule that involves in membrane recycling and apoptosis. Clusterin is found in amyloid plaques, like the apolipoprotein E.[31] The metals such as iron, zinc, and copper bind to ApoE isoforms and affect the cortex in the brain. In AD patients the serum or plasma metals are traced for homeostasis.[32] The development and progression of AD contribute to ApoE receptors and plays a role in the cholesterol metabolism, neurogenesis, control of inflammation, and trafficking of APP and Aβ.[33]

CLINICAL FEATURES

The signs such as change in the mood and decline in memory are often observed in the affected individuals.[8] The early-onset AD clinical features include visuospatial, hypertonia, dysexecutive phenotypes, language problem, headaches, early myoclonus, seizures, dysarthria, gait abnormalities, pseudobulbar palsy, deterioration is faster, incontinence, mutism, more extensive atypical amyloid plaque morphology and distribution and amyloid angiopathy. The patients with early-onset AD are at a greater risk for mortality compared to those with late-onset AD and early-onset AD accounts for an oversized number of premature deaths among those 40 to 64 years aged due to aggressive symptoms. The early onset clinical features differ from that of late onset AD.[34]

The late onset of AD clinical features includes daily life activities disrupt due to memory loss, familiar tasks become difficult to complete, difficulty in solving the problems. Social withdrawal, depression, paranoia, and mood swings are indications of these symptoms. Anxiety, irritability, and agitation become much more prominent as the disease progresses.[35] Delusions and hallucinations can present at any time during the course of illness but are not typically presenting signs. Death occurs due to general inanition, malnutrition, and pneumonia.[8]

RISK FACTORS

There are several physiological factors that increase the chance of AD.[6] The history of traumatic brain injury is more likely to have AD and also have a risk factor of dementia.[34] For instance factors such as hyperhomocysteinemia, hypercholesterolemia, hypertension, diabetes mellitus, and smoking are report to elevate the chances of AD (Table 1).[36] Other AD risk factor includes family history, age, obesity, hypertension, diabetes, hypercholesterolemia, and apolipoprotein APOE4 genotype.[3]

Table 1: Represents the risk factors for AD

S. No.	Acquired risk factor	Effects	References
1	Cerebrovascular diseases	The hemorrhagic infarcts, vasculopathy, small and large ischemic cortical infarcts, and cerebral white matter change increase the risk of dementia.	(6; 36)
2	Hypertension	The development of AD due to changes in the vascular walls that trigger and lead to hypoperfusion, ischemia and cerebral hypoxia.	
3	Type 2 diabetes	The development of AD due to insulin deficiency, impaired insulin receptor, the toxicity of hyperglycemia and insulin resistance. The adverse effects lead to cerebrovascular damage, vascular inflammation and glycation end products.	
4	Obesity	The higher risk of developing AD in late life due to obesity and underweight in middle age.	
5	Dyslipidemia	The effects on the blood-brain barrier increase hypercholesterolemia that leads to the risk of AD.	
6	Smoking	The risk of AD increase by smoking which leads to cerebrovascular diseases.	

DIAGNOSIS

Family History

The first degree relatives of at least three generations should be diagnosed with the early onset of the disease and should obtain the history of individuals with dementia.[26] Medical records and the reports such as neuroimaging studies and autopsy examinations of affected family members should be obtained. The diagnostic evaluation of AD patients an in depth investigation should be done like history includes general medical, neurological, neuropsychiatric, family, and psychiatric and history of medicines used and side effects, alcohol, depression, and delirium.[38] The patient history involves family members to determine whether the onset and course of cognitive decline are gradual and progressive as in AD or sudden occurrence.[3]

Genetic Counseling

AD is genetically heterogeneous; counsel of persons with AD and their family members must be tailored to the knowledge available for that family. Genetic counseling for people with non-familial AD and their members of the family must be empiric and comparatively non-specific. Early Onset FAD depends upon the status of the proband's parents that determines the risk status for other family members.[39]

Prenatal Testing

Prenatal diagnoses are performed to determine disease causing mutation. Presenilin1 can be analyzed by DNA extracted from foetal cells obtained via amniocentesis. Amniocentesis was generally performed during 15-18 weeks' of gestation or otherwise gestation chorionic villus sampling is performed during 10 to 12 weeks'. These prenatal testing is done to ascertain the presence of mutation in the foetus.[39]

Neurological Testing

The physical examination and neurological examination should be performed for acute and chronic illness.[38] In the early stages of AD, the neuropsychological tests of memory should be performed.[40] The Montreal Cognitive Assessment (MoCA) was developed recently to detect deficits associated with mild cognitive impairment. The Mini-Mental State Examination (MMSE) screens cognitive impairment and is the most widely researched instrument.[41] The routine laboratories examinations such as complete blood count, thyroid function tests, vitamin B12, folate, and rapid plasma regain are often performed. Neuropathological examination looks for the presence of neurofibrillary tangles and senile plaques to detect AD. It is done by using standardized criteria such as the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM TV).[42]

Neuroimaging

Neuroimaging techniques such as computed tomography or magnetic resonance imaging can be performed to evaluate the morphology of the brain.[42] The MRI scan assesses the patient's cognitive impairment and evaluates cerebral atrophy in the posterior parieto-temporal, frontal and medial temporal regions.[43] The other advanced structural and functional neuroimaging used for the detection of pathological changes associated with AD includes diffusion tensor imaging and resting-state functional MRI that creates algorithms for classifying AD and mild cognitive impairment (MCI).[44] The PET scan evaluates AD features in vivo and radiotracers bind to amyloid plaque.[43]

MANAGEMENT

The first cholinesterase inhibiting that drug was approved for AD is tacrine in 1993.[45] Tacrine imposes serious side effects, thus this drug prescribed rarely.[15] The tacrine has eclipsed due to troubling adverse effects, complicated dosage schedule, and risk of hepatotoxicity.[37]

Cholinesterase inhibitors (ChEIs) are recommended for patients with mild to moderate AD for symptomatic treatment.[46] Some of the second generation of cholinesterase inhibitors that are available are donepezil, rivastigmine, and galantamine.[28] Acetylcholinesterase inhibitors are shown to improve memory function and attention in AD patients. It interferes with the breakdown of acetylcholine and increases the level of the neurotransmitter at the synapse.[2] Choline acetyltransferase is an enzyme that synthesizes acetylcholine and its catalytic activity require these substrates: choline, acetyl-CoA, and adenosine triphosphate (ATP).[47]

Memantine, an FDA-approved medication is used to treat moderate to severe AD patients.[2] Memantine is an antagonist that protects the neurons from excitotoxicity and consists of N-methyl-D-aspartate (NMDA).[45] It protects vulnerable neurons from morbidity and mortality from glutamate induced

excitotoxic.[28] Both classes of drugs are well tolerated with common adverse effects such as dizziness, gastrointestinal upset, and headache.[2] This drug has shown effective for the later stages of AD.[10]

In patients with uncontrolled airway obstruction, medication like rivastigmine tends to increase gastrointestinal bleeding, gastric ulcer disease, pulmonary and gastric secretions, and should be used with caution.[7] The major advance in the treatment of AD is neuroleptics and serotonin-modulating antidepressants.[28]

CONCLUSION

AD is a major health problem in the worldwide population. There is no cure for the disease but we can prevent the severity of the disease state. The mutation within the early onset of the disease is rare and can be diagnosed earlier. APOE genes are the foremost common mutations within the population that cause severity within the patient when remain untreated. The main risk factor is the age that is positively correlated with progression of AD. The interactions of metals can also increase the risk of AD. The disease is often diagnosed and medications are prescribed to scale back the severity and to manage the disease within the individuals.

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