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Review Article

GENETIC DISORDER ALZHEIMER

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ABSTRACT

Alzheimer's disease (AD), slowly continuous neurological disorder, mostly appears in older >65 age that deals with the memory loss due to death or damage of brain cells and cognitive functions (thinking, reasoning, and behavior abnormalities) due to the accumulation of the specific protein (beta-amyloid protein) which form plaque and fibers (tau tangles) in the brain. Not only the genetic factors are responsible but also most of the non-genetic factors are responsible for AD. Several mutations in the gene (*APP, APOE, PENS1, PENS2* on chromosome no. 21, 19, 14, 1) are responsible for causing four types of AD. Memory loss is most common sign of AD. Predisposing factors of AD are hereditary, severe brain injury or traumatic, and metabolic diseases such as diabetes mellitus, hypercholesteremia, and obesity. Although treatment can manage some symptoms in few people, but there is no current mechanism to cure AD or stop its progression. Beta-secretase inhibitor molecule prevents the first step in a chain accumulation which leads to the formation of amyloid plaque in the brain. However, the scientist or researchers have established a compound NIC5-15 they have been found NIC5-15 has safe and effectual treatment which has been used to stabilize cognitive performance in patients with mild to moderate AD.

Keywords: Alzheimer's disease, Beta-amyloid protein, Memory loss, Hypercholesteremia.

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INTRODUCTION

Alzheimer's disease (AD) is a slowly progressive neurological disorder which is deals with the death of brain cells causes' memory loss and by disturbances in reasoning, planning, and languages, perception, and ultimately patient's premature death [1]. AD is one of the basic causes of dementia that affects the 1 of 8 persons older than 65 years of age [2]. The prevalence of AD noted that out of 1000 persons which lying between age 65 and 69 have been increased around 2.8%, similarly out of 1000 persons age about 90 years have 56.1% incidence (49). World widely, more than 11 million people are goes though Alzheimer disease. At present, it is still not cure [2-3]. If the condition remains incurable, the expected estimation become doubled, and around 80 million people will be affected in the upcoming years [4]. A postmortem performed on AD patient's brains revealed as neuropathological appearance, the existence of senile plaques and neurofibrillary tangles, described by beta-amyloid peptides and hugely phosphorylated tau protein [5]. Aggregation and deposition of beta-amyloid protein and abnormally phosphorylated tau protein (neurofibrillary tangles) in the brain lead the development of AD. Three major enzymes (α-, β-, and-γ secretases) are responsible for degradation in amyloid precursor peptide (APP) and a shortcoming between the clearance and production of Aβ40-42 fragments by the enzymes β- and γ-secretases margins to the accretion of Aβ peptide monomers, oligomers and finally the Aβ plaques that botch or bungle the parenchymal space between neurons in the brain [6]. Till exact cause of these various changes is undiscovered, but the progress age, and genetic factors and non-genetic factors perform an important role. Mutations in the gene APP gene on chromosome No. 21, ApoE on chromosome No. 19, presenilin 1 on chromosome No. 14, and presenilin 2 on chromosome No. 1 are associated with AD [7].

EPIDEMIOLOGY

According to the study conducted in Baston, Framingham, Rochester, and Baltimore the age-specific incidence rate of AD is doubled in every 5 years after the age of 60 and increased from about 0.17% per year at age 65, to 0.7% per year at age 75, 1.0% per year at age 80 %, and 2.92% per year at age 85 [8]. The epidemiology of the disease estimated in 2001 was around 24 million globally and predict that if condition remains incurable, the estimation becomes double in every 20 years, and around 80 million people will be affected by 2040. The percentage of patients will rise from 80% to 190% from 2001 to 2014 in Europe and the advanced western Pacific region. However, more than 300% were seen in Latin America, India, China, and the Middle Eastern crescent. The rate of incidence is approximately 2% in 65-69 years of age, 25% in people aged over 90 years. According to the study, it is more estimated in females than males because of the greater life expectation of female. At present, 5.3 million people are estimated in the United State and 5.1 million of people aged over 65 years [9].

PATHOPHYSIOLOGY

The pathophysiology of the AD is associated with brain injury and death of neurons in the brain region which leads to the effects on memory and learning, and then alter the whole brain. In the past several years, Abeta plaques and neurofibrilly tangles are the two identified hallmarks in the brain of this disorder. Abeta plaque is accumulated in the extracellular space in the brain and its initiating lesion formation in the brain and that ultimately leads to AD while the neurofibrillary tangles accumulated intracellular part and presence of tangles appears essential to dementia. Synapse loss, neuron loss, and cerebral atrophy are other pathological features. In AD, there is abnormally deposition of tau protein (t-protein), components of the cytoskeleton microtubule system becomes hyperphosphorylated and aggregates as paired helical filament leads to deposition of neurofibrillary tangles in the nerve cells. According to the current information, changes in cerebrospinal fluid (CSF) levels of abeta, tau, and phosphorylated tau (P-tau). The exact mechanism of the formation of plaque and neurofibrillary tangles are still unknown. The neuron death and injury are prompted by the neurofibrillary tangles and senile plaque, which lead to the behavioral symptomatic changes and memory loss. Senile plaques are not alone neurotoxic, but the α-β-oligomers which are circulating potentially neurotoxic. The uncontrolled release of glutamate (neurotransmitter) contributes to inflammation and neuronal death. Neuroinflammation is also involved in the pathology of the AD as well the symptoms [10].

CLINICAL MANIFESTATION

The clinical manifestation of AD is divided into three groups [11].

a. Contemporary lack of ability to remember, depression, clement coordination problems, and apathy.
b. Because of memory loss that disrupts daily life activity, such as person is unable to perform a regular task and also problems with language, disorientation to time and places.
c. Executive dysfunction such as poor judgment, mood swing and behavior, problems with abstruse thinking, misplacement in things, slowly changes in personality, and severe loss of ability to remember [12].

RISK FACTORS

Age-related changes in the brain; mostly in people who are older than 65 years of age develop AD [13]. The main risk factor is increasing the age. On the basis of the population of ages the frequency of the AD is continuously increasing after 65 years of age [14].

On other hand some risk factors for AD include persistent high blood pressure (hypertension), heart disease (coronary artery disease), diabetes, smoking, obesity, dyslipidemia, body weight, and traumatic brain injury also have an increased prospects for AD [15].

Genetics of AD - mutation in APP gene on chromosome No. 21, presenilin-1 on chromosome No. 14, presenilin-2 on chromosome No. 1, ApoE -ε4 gene is the dominant risk factor that conceals a protein which is involved for the metabolism of cholesterol. ApoE exists three alleles: ε2, ε3, and ε4. ApoE-ε3 allele is mostly rich in the population, and ApoE-ε4 is responsible for increasing the risk of AD [16,17], and it is also responsible for deposition of Aβ plaque in the brain a majority of patients with Down syndrome will have high chances to develop the brain changes of AD [18,19].

The other risk factors for the AD are aluminum. Aluminum (Al) is a routinely type of metal are found in the environment, and in the terrestrial crust most abundantly it is also used. By natural process such as soil erosion and volcanic eruptions it is liberated in the environment [20]. Nowadays, developing countries are widely using aluminum utensils [21]. The foodstuff particularly salty, acidic and alkaline may have been observed with a high level of aluminum content [22]. Aluminum (Al) is also used in food additives and toothpaste [23]. Intake of excess Al leads to memory impairments [24], amyloid protein deposition in central nerve cells (CNS) and overexpression of APP [25]. Researchers and scientist showed that excess intake of Al cause neurotoxicity which is associated with apoptosis [26-27] and oxidative stress [28-29].

BIOCHEMICAL BIOMARKER

Amyloid beta

Amyloid precursor protein is abundantly used for the production of 36-43 amino acid, which comprises the amyloid beta. 1, 14, 15, 16 and 37, 38, 34, 40, 42 are the isoforms of amyloid beta. The discovered function of amyloid beta is protection against oxidative stress [30], enzymes such as JNK and MAPK are activated [31], and also seen effect in improvement of synaptic plasticity and memory [32] and it has functions to show the activity against microorganism [33]. Neurotoxicity causes when oligomers (ligand binding complexes) attacked at specific synapses [34]. In AD patient the levels of Aβ-42 in the CSF are decreased. The calculated ratio of Aβ-42/Aβ-40 is useful for the untimely and clinical phases of (AD) ,and other isoforms ratio also calculated and found 14, 15, 16, 37, 38 and 39 isoforms are useful [35]. During the determination, the difference in an AD from non-AD showed that Aβ1-42 IS 79% and specificity is 61% [36]. On familial AD the Aβ-42 levels are increased in plasma. Aβ42-Aβ40 ratio is less present in the CSF of the non-demented mutation carriers (MCs) [37].

CSF-Tau

Tau protein is necessary to the study of factors that promotes the microtubule formation. In the middle of 1970s, it was discovered first by Weingarten *et al*. [38]. CSF tau protein, components of the cytoskeleton microtubules system and is concealed by a single gene based on chromosome no. 17q21 [39]. Microtubule-associated protein that is CSF-tau suggest acute injury successively development of plaque, but in case of vascular dementia more amount of CSF-tau is found that arise in a lower specificity. During the full course of AD, high CSF-tau is present which results in dementia [40]. For segregating the AD patient with Frontotemporal dementia, tau is also found helpful [41]. Two isoforms of tau protein, total tau, and P-tau, elevation of these two consider sensitive indications of presymptomatic disease [42].

IMAGING AND RADIOLOGICAL MARKER

Investigation of the AD can be possible alone through autopsy after death, and examine the brain tissue. Accumulation of Aβ plaque in the brain is the useful biomarker for the estimation of the AD and such kind of clinical changes in brain are estimated by various tools such as positron emission computed tomography (PET) or single photon emission computed tomography. Two other tools are magnetic resonance imaging (MRI), and computer aided tomography is also useful for visualization of the brain tissue which helps for the diagnosis of AD. In AD patients, extensive contraction of the brain region is observed which is involved in memory process. These observations are helpful for discriminating the progress from normal to MCI and from MCI to AD [43]. The metabolic activity of the brain is another diagnostic parameter consistent in AD. In the early stage of AD patient determine the decreased level of brain metabolism due to the brain atrophy and neuronal loss [44]. PET scans with fluorodeoxyglucose (FDGPET) and functional MRI (FMRI) are useful for the demonstration of metabolic activity of the brain [45,46]. FMRI is helpful for measuring the difference in oxygen concentration associated to cortical blood flow, and FDGPET is responsible for measuring glucose metabolism in the brain region populations. 11C-PIB (Pittsburgh compound B) is the advanced diagnostic tool for the AD. According to the study 11C-PIB load is the indicator of the progression of the disease in the next 2 years [47,48].

INFLAMMATORY MARKERS

Due to the deposition of amyloid plaque in the brain cytokine interleukin (IL)-6, C-reactive protein, interleukin IL-1-beta, tumor necrosis factor-α, IL-6, IL-6 receptor complex, α-antichymotrypsin, and transforming growth factor-β, these inflammatory markers have been express in the CSF of AD patient and these CSF components are not able to differentiate the AD patients and non-AD demented patient [49]. These inflammatory mediators are released in AD. Due to the inflammation, several proteins are detected using enzyme-linked immunosorbent assay in previous studies. During inflammation in the AD the cytokine study are produced, and it shows various results such as CSF interleukin-6 levels are elevated, decreased, or unchanged in AD [50].

GENETIC MARKERS

There are five main genes responsible for causing AD; these are APP, PSEN 1, PSEN 2, APOE, and TOMM40.

Mutation in the gene APP, PSEN 1, and PSEN 2 are responsible for early onset of AD and APOE is the only gene which is responsible for early-onset disease [51].

Molecular diagnostic test: Mutation screening is surely theoretically achievable, mostly by focusing with decreasing cost of genomic DNA analysis. Although there is no way to determine that which children have AD because currently, predictive screening is not present due to on phenotyping it show sporadic nature [52].

APP

APP gene located on chromosome No. 21 concealed a transmembrane protein named APP, consists of 39-43 amino acids arrangement comparable to the Aβ peptide. The degradation of Aβ peptide produced from APP by β and λ secretases. Aβ peptide being the major component of amyloid plaque accumulation in the brain region. Single nucleotide mutation of 24 APP is reported as causes AD, and these mutations are gathered with 54 amino acid sections, bounded close to the Aβ peptides. The Swedish mutation leads to the interchange of 2 amino acids lysine - methionine to asparagine - leucine before the initiation of Aβ peptide sequence. Production of Aβ peptide is much higher than that it was produced from the non-mutated APP, thus declining the efficacy of β-secretase cleavage. Besides another, APP mutation occurs after the C-terminal amino acids of Aβ peptides, thus changing the activity of λ- secretase cleavage. Normal APP proteolysis occurred by λ- secretase leads the formation Aβ40 with smaller amounts of Aβ that are Aβ42 [53].

PSEN1 and PSEN2

Mutation of the Presenilin 1 on chromosome No. 14 and Presenilin 2 on chromosome No. 1. these two genes concealed the two firmly linked proteins which are a part of λ-secretase complex. When the mutation occurs on these two genes, it leads the alteration in the λ-secretase [54].

APOE gene

ApoE gene being the only prominent genetic biomarker for the late onset of the AD has been found to be situated on chromosome No. 19. It encodes for ApoE which is one of the components of lipoprotein. ApoE is in turn divided into three allelic forms, namely, ε2, ε3, and ε4. All the three ApoE polymorphs ε2, ε3, and ε4 are strongly bound with the AD. ApoE has a vital role in lipid metabolism along with CNS. Since ApoE, is the major cholesterol lipoprotein transporter, thus possess a magnanimous role in cholesterol transportation and brain integrity maintenance because lipids are important for axons myelinations. But it has been found that ε4 ApoE allele suppresses the cholesterol delivery and therefore depressing the lipid homeostasis in the CNS and leading to Aβ accumulation [55].

Treatment

AD is an incurable disease. The aim of treatment is to control the sign and symptoms such as loss of memory, behavior problems, and cognition, and sleep problems.

Drug treatment

The Food and Drug Administration permitted that five drugs for AD cure such as donepezil, rivastigmine, galantamine, tacrine, and memantine, these drugs are used to slow down the rate of symptoms before they become worsen.

Treatment of behavioral symptoms

For depression, antidepressant drugs such as clomipramine and placebo are given to the patient for 6 weeks [56,57].

As the AD progresses, there is a constant decrease in the stages of rapid eye movement and non-rapid eye movement causing the patient to remain awake for too long [58], tacrine and metrifonate and the cholinergic agonist xanomeline these drugs are helpful for reducing the hallucinations than those persons who take a placebo [59].

CONCLUSION

AD is a progressive neurological disorder that leads the death of brain cells causes' memory loss and disturbance in reasoning, listening, planning, and learning. Mostly older peoples are affected (>65 age). Not only the genetic factors are responsible for causing, but also environmental factors are also responsible. The exact cause is still not known, but the sign and symptoms can control by drug treatment. The diagnosis of AD can be possible particularly through autopsy after death, by combining clinical measures with an examination of brain tissue. Some diagnostic tools are helpful for the diagnosis such as computerized scan, MRI, and positron emission tomography. These tools distinguish the AD from other causes of memory loss. Patients should be in undertaken with strictly care.

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