The Genetic and environmental risk Factors of Alzheimer's disease

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ABSTRACT

Alzheimer is one of the most common neurodegenerative disease generally found in the form of dementia in old age population. Advanced age is still considered as most influencing risk factors for this disease. WHO reported that dementia is the seventh leading cause of death in 2018 and affecting about fifty million people worldwide. Aging led to impair protein metabolism in the Alzheimer's disease. A number of molecular events has been implicated behind this disease. As AD is a chronic neurodegenerative disease and etiology is still unclear, familial AD accounts only 5% of the disease. Then it is important to know about some other hidden risk factors that may play crucial role in the onset of the disease. Thus, this paper focused on the role of genetics, different environmental, oxidative stress factors and its association with the pathogenesis of Alzheimer's disease.

Keywords: Alzheimer's disease, Amyloid, Beta, Neurodegenerative and Oxidative stress etc.

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Introduction:

Alzheimer affects over 34 million people worldwide. AD is the most common neurodegenerative disease found in the form of dementia in the elderly population and accounts to 60–70% of cases. It is a progressive and irreversible loss of memory and cognition impairment. [1] Advanced age is most vulnerable to this disease. Disease onset is classified into two types: early-onset (<60 years of age) EOAD and late-onset LOAD (> years of age). A very less percentage of the disease is genetically mutated is called familiar onset of Alzheimer's disease (FAD), and it is usually early-onset. When no family history is present, the form is called sporadic. [2] Genes that are responsible for the EOAD are amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). After the action of various secretase enzymes on APP produces Aβ is a natural product that helps in neuronal growth and repair. Altered production of amyloid beta (Abeta) both Abeta 40 and Abeta 42) is found due to mutation in these genes. Abeta is supposed to lead apoptosis of the neurons results in dementia. [3-6] One of the important gene is considered a genetic risk factor for LOAD and that has been validated from different population based studies is APOE located on chromosome 19. [7] The pathological hallmark of AD is the presence extracellular deposits of protein called amyloid beta or senile plaques and intracellular neurofibrillary tangles (NFT). [8] Now it is considered that environmental and genetic risk factors may play a positive role in disease onset. No specific treatment is available.

Pathogenesis of Alzheimer disease:

The action of proteases, the α-, β-, and γ secretases on larger protein, i.e. amyloid precursor protein leads to the production of amyloid beta in senile plaque. [9] The γ-secretase may be responsible for production of one particular β- amyloid peptide Aβ42 that is 42 amino acids in length that has pathogenetic importance, because it is form insoluble toxic fibrils and accumulates in the senile plaques isolated from the brains of Alzheimer's patients. [10,11] Production of β-amyloid in the brain is normal process, but excess production and impaired clearance by the central nervous system in AD patients, further accelerating the accumulation of plaques. [12] **Genetic role in Alzheimer's disease:**

More than 90% of patients with AD are late onset of disease (LOAD) have no family history and sporadic in nature. [13] No causative gene has been identified yet, but twin study supported the role of a genetic component in LOAD. Moreover, the only one gene that has been consistently found to be associated with sporadic LOAD in multiple genetic studies, is the apolipoprotein E (APOE) gene. [14-18] ApoE gene produces the apolipoprotein in the brain where it is synthesized and secreted primarily by astrocytes in high-density lipoprotein (HDL) -like particle. [19] A primary function of ApoE is the transportation of cholesterol to neurons. That is essential for axonal growth, synaptic formation, memory formation and neuronal repair. [20, 21] The synaptic remodeling impairment and synaptic loss occur due to the decreased level of ApoE in the cortex and hippocampus region of the brain. [22, 23] Three common polymorphic allele of ApoE protein is found as APOE2, APOE3 and APOE4. The APOE4 form of the gene is supposed to be the reliable genetic biomarker for the late onset of Alzheimer's disease (LOAD), it has possibly increased the level of risk three times in heterozygous individuals and by twelve times in homozygous individuals. [24] The least frequent allele APOE2 is found only in 5–10% of individuals are considered to have a more protective effect against the AD onset, while the APOE3 gene has been shown intermediate risk possibilities in about 70- 80 % of the individuals. [25, 26] So many studies have revealed that in mild cognitive impairment (MCI) prevalence of E4 allele is higher than in control individuals. [27] Recent evidences are suggesting the

overwhelming role of the microglial molecular network in the AD pathophysiology. [28] Microglia cells have protective function against the accumulation of Aβ and TREM 2 gene mutation (R62H, R47H, and D87N) in the brain are the important risk factor of AD. Moreover, cultured cells of TREM2 mutation show expression in disrupting translocation of cell membrane and impaired ligand binding property. [29- 31]
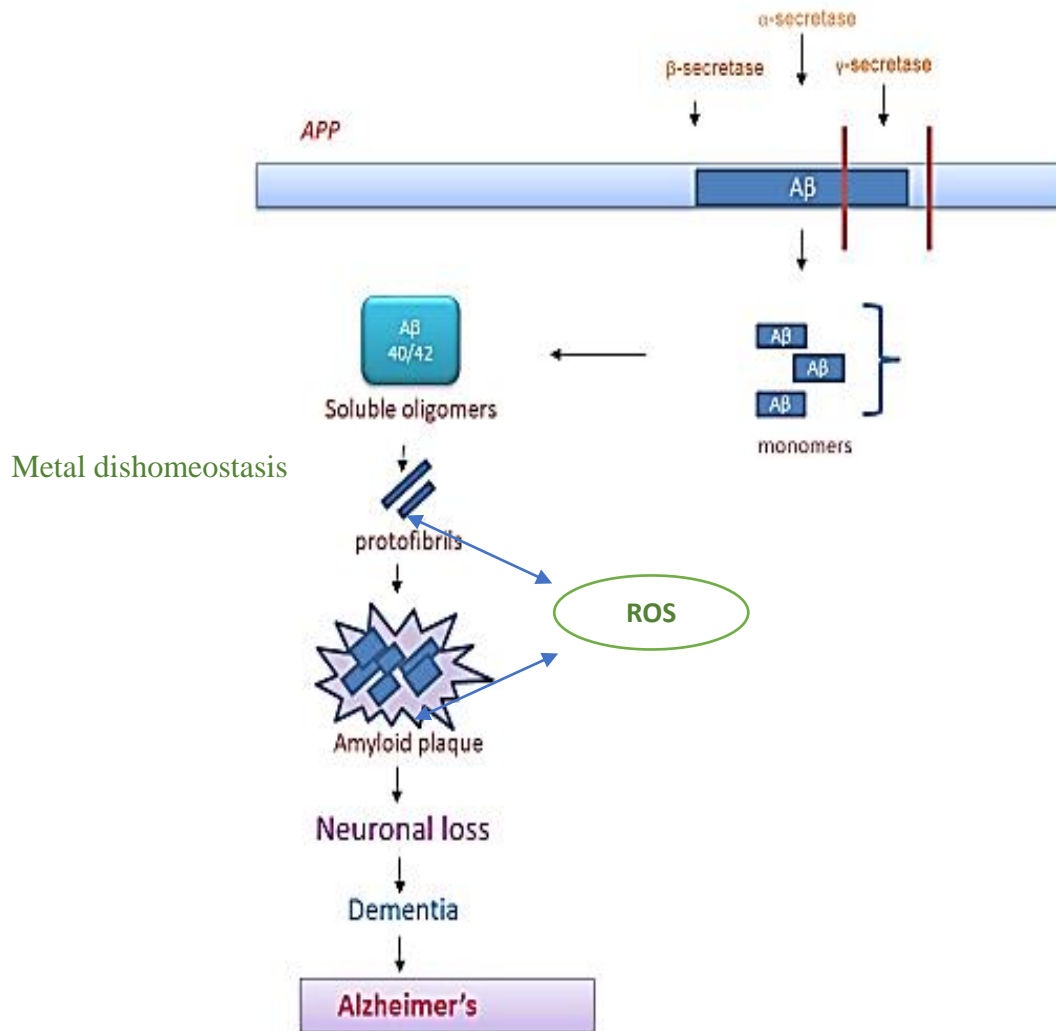

Figure 1. This diagram depicting the action of protease enzymes on APP and production of amyloid beta that finally leading to Alzheimer's disease.

Environmental role in Alzheimer's disease:

Previous studies are providing the evidence that environmental factors may play crucial role in the pathogenesis Alzheimer's disease as the prevalence and incidence of late onset of disease, indicating towards the age is the most common known risk factor. The prevalence of AD increases significantly with age and incidence increases from 2.8 per 1000 person years for people between 65 to 69 years and 56.1 per 1000 person years for people who are older than 90 years. [28] It is well established that several essential transition metals, such as zinc, iron, copper, selenium, cobalt and manganese play vital role in the control of different metabolic and signaling pathways. Patients have been found with altered metal homeostasis in the brain and plasma/ serum,

level compared with age-matched controls, AD patients show elevated zinc and copper in cerebro-spinal fluid (CSF). [29] Senile plaques and NFTs were found to enriched with this metal. [30] Some metals have been found to facilitate Aβ aggregation. In presence of zinc and copper Aβ tends to form fibrils, oligomers respectively. [31] In AD patients, the presence of transition metals within amyloid plaques indicates the possible interaction with abeta. [32-34]

Oxidative stress:

Oxidative stress is state that leads the overproduction of free radicals. In AD oxidative stress is found as a result of amyloid beta misfolding. [35] In AD amyloid beta peptide shows a direct source of free radical production in which methionine, at the position of 35, is supposed to be responsible. [36] Abeta directly disrupts mitochondrial function due to less energy metabolism neuronal death occur. [37] Reactive oxygen species (ROS) may play a role in many chronic diseases and neurodegenerative diseases. [38-40] Mitochondrial dysfunction involves changes in mitochondrial enzymes, structure, impaired mitochondrial fission and fusion was found altered in AD. [41]

The relation between oxidative stress and tau pathology has been less studied. The cells overexpressing tau protein had increased susceptibility against oxidative stress [42] Moreover, oxidative stress is able to damage DNA strand and large deletions that can change different enzymatic and mitogenic pathways. DNA methylation may influence by oxidative stress, which helps in the regulation of gene expression. [43] Interestingly, oxidative stress has been shown to decrease neurogenesis in the adult brain, thus limiting its neurodegenerative capacity. [44,45] One study found a direct relation between oxidative stress and brain cognition severity. [46] Recent studies are showing that altered metal homeostasis may play role in oxidative stress. Evidence supporting that metal dependent enzymatic process of the brain is disrupted in AD. [47, 48] Aging process is itself an important reason to increase oxidative stress. [49]

Conclusion:

As the AD is multifactorial in nature due to this specific biomarker is not available currently. [50] Progressive brain atrophy and cognition impairment lead the patient to face trouble in performing daily routine activities. [51] Increased apoptosis have been seen in AD person caused by oxidative stress results in lipid oxidation, protein oxidation and damage of the DNA strand. [52] Metal ions may also contribute to AD by accelerating protein aggregation. Copper, zinc and iron are found in high micromolar concentrations in amyloid plaques because Aβ is able to bind these metals with different affinities. [53,56] There are growing evidence that are suggesting a role of heavy metals in AD. Genetic mutations accounts only about 5% of the disease, remaining other factors may play hidden positive role in the disease onset.

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