Alzheimer’s Disease and Role of Apolipoprotein E in Alzheimer’s Disease

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ABSTRACT

Alzheimer’s disease (AD) is progressive, irreversible, neurodegenerative memory disorder linked with somehow aging and comes under the umbrella of dementia. It may be rare Familial AD or randomly occurring Sporadic AD. Some preventable acquired risk factors and non-preventable e.g., age and genetics are the main risk factors for Alzheimer’s. The most essential genetic risks factor for (LOAD) late onset of Alzheimer’s disease is APOE genes present on chromosome 19, has three major alleles (e2, e3, and e4). We can slow Alzheimer’s but cannot prevent or stop it till now. Some non-drug treatments, like physical activity, social engagement, nutritious supplemented food, and FDA approved drugs i.e., Donepezil, Galantamine, cholinesterase inhibitors, Mementine, Antidepressants, Antipsychotics and mood stabilizing medication helps to reduce AD.

Keywords: Amyloid beta (AB), Apolipoprotein (APO), Tangle formation, Cerebrovascular (CBV), Late onset of Alzheimer’s disease (LOAD), APOE isoforms, Ligand activated receptors (LXRs).

Introduction

Alzheimer’s disease was first noticed by Dr. Alois Alzheimer, so it is named as Alzheimer’s disease (AD). Dr. Alzheimer observed some changes in tissues of brain of a woman, who died with unusual mental disability [1],[2]. Alzheimer’s is a major public health problem in which brain cells degradation occurs, when neurofibrillary tangles (which are abnormal particles) and neurotic plaques formed in brain [3].

There is a loss of connection between nerve cells in brain. This is irreversible, degenerative, neurological disorder [4]. There are two main categories of Alzheimer’s disease (AD). One is Familial AD, and second is Sporadic AD [5]. AD spread globally and affects more than 35 million people. It is sixth leading cause of death. In future, it will be third leading cause of death after cancer and heart disease [6].

Symptoms of AD vary in person to person. It includes problem with language, difficulty in performing similar tasks, problems with language, disorientation of time and place, poor and impaired judgement, problem with abstract thinking, displacing things, personality changes, loss of initiative, change in mood and behavior [4],[7].

Genetic, environmental and life style of person are some main causes of AD. Risks of developing Alzheimer’s disease are of two types. One is called as preventable risk factors, and other is non-preventable risk factors. Preventable risk factors include, smoking, alcohol, sedentary life style, obesity, head injury, hypertension, type 2 diabetes, cardiovascular, and cerebrovascular diseases. Others are some non-preventable risk factors which include; person’s age, person’s genetics [6],[8].

Apolipoprotein E

It is estimated that more than thirty-eight genetic loci have been associated with Alzheimer’s disease risks [9],[10]. E4 allele is considered as main factor of AD, which actually produces Apolipoprotein (ApoE) [11]. One E4 allele triples the risks of AD. In case of homozygous individual for e4 allele, risk of Alzheimer’s disease becomes seven folds. It is observed that AD patients contain about 60% Apolipoprotein E upon diagnosis [12],[13]. First ApoE, to
be determined and sequenced was human ApoE. It is polymeric protein, major carrier of cholesterol in human brains and involved in glucose metabolism, neuronal signaling pathway and inflammation of neurons.

The most essential genetic risks factor for (LOAD) late onset of Alzheimer’s disease is APOE genes present on chromosome 19, has three major alleles (e2, e3, and e4). APOE protein in human is a lipoprotein of 299 amino acids (AAs) with two structural domains. First is N-terminal domain hold the receptor-binding region. Second is the C-terminal domain which holds the lipid-binding region as shown in fig.1.

There are three APOE isoforms and difference among them is amino acid residues in APO protein structure. The main difference between these isoforms differs in 1 amino acid at active site position that is between 112 and 158 amino acid residues.

![Fig.1. Linear structure of Human Apolipoprotein E (APOE)](image)

Apolipoprotein E is protein type which is explained well in term of function and structure. It regulates the metabolism of apolipoprotein. Mainly apolipoprotein perform three functions. Firstly, due to its ability to bind lipids, they stabilize the pseudo micellar structure of lipoproteins. Secondly, they act as cofactors for various enzymes activation. Thirdly, they serve as ligands for many receptors.

Apolipoprotein is expressing in many tissues especially in liver and brain. Neurons and microgliia also synthesized this protein. This protein modulates receptor function of glutamate and synaptic plasticity by regulating APOE receptors. Modern studies states that APOE maintain cerebrovascular (CBV) integrity by cyclophilin A.

APOE4 is identified as major risk factor during genetic analysis in 1993, for AD. It means two copies of this allele increase the progression of AD in 80s. APOE2 is identified as protective allele which means two copies of this allele decrease the progression of this disease. It means one copy of allele APOE4 shifts the disease risk factor 5 years earlier and one copy of APOE2 make the disease risk five year later. So, decreasing APOE4 and increasing APOE2 helps to decrease the risk of AD. APOE2 being protective in nature also have some negative impacts on human health. It increases cholesterol plasma level, triglyceride level and also has some role in coronary artery disease. On the contrary side, APOE4 is also associated with elevating the risk atherosclerosis.
Graph 1. Graphical representation of unaffected individual with different APOE alleles

Fig. 2. Role of Apolipoprotein E4 in Alzheimer’s disease
Apolipoprotein E4 (APOE4) in Alzheimer’s disease confers toxic gain of function e.g. increase in brain atrophy, neuronal toxicity, AB aggregation, tangle formation and aberrant brain activity. APOE4 also confers loss of neuroprotective functions e.g. decrease in synaptic function, glucose function, neurogenesis, AB clearance, vascular function, mitochondrial function and lipid or cholesterol metabolism.

All the loci of Alzheimer’s disease identified till now relates to the pathways of immunity, cholesterol metabolism, inflammation and endosomal vesicle recycling. This means, these pathways somehow relate to APOE in AD. Instead of isoforms of APOE, amount of this protein also matters a lot in AD. Expression of this protein is maintained and regulated by ligand activated receptors (LXRs).

Till now there is no absolute cure for Alzheimer’s disease. Some therapies can be used for curing AD patients. APOE4 binding with amyloid beta is central point in diseases progression. We can decrease the level of APOE4 by knockout therapy. We can also use therapy which helps us to block binding between amyloid beta and APOE4. In this way we can inhibit the toxic interaction easily. On the same side, we can also use anti-amyloid beta antibodies-based therapies. Antisense knockdown approach is first line of treatment in which therapeutic agents such as antisense oligonucleotides (ASOs) are used to damage the formation of specific protein. We can use this therapy. Moreover, genes involved in progression of Alzheimer’s Disease, can also be silenced by gene silencing method. We can also use protein-protein interaction inhibitors to inhibit the amyloid beta and APOE4 interaction. Modern CRISPR/Cas9 mediated gene editing can also be used to cure AD. Different medicines are used to reduce the progression of AD. Donepezil (Aricept), Rivastigmine (Exelon), Galantamine (Razydyne) [14]. Beside these, some other group of medicines e.g., antidepressants, antipsychotics, and mood stabilizing medicines are also used. All above medicines have some side effects e.g., Nausea, diarrhea, dizziness, headache, confusion [15]. Nutritious diet, physical activity, social engagement and mental pursuits helps to reduce risk of AD. These are some non-drug treatment methods [16],[8],[17]. Exercise plays important role for the betterment of functionality and performance in daily life activities. It improves the cognitive functions e.g., visual memory, attention etc. in patients of Alzheimer disease [16].

Conclusion

AD is a degenerative, incurable and terminal disease of neuron degeneration. In AD the connection of neurons is lost. Some preventable and non-preventable risk factors cause AD. About 20 genetic loci are involved to cause risks of Alzheimer. Means, one copy of allele APOE4 shifts the disease risk factor 5 years earlier and one copy of APOE2 make the disease risk five year later. Despite of continuous research, we still don’t have any diagnostic as well as treatment method. All methods that we have till now are symptomatic. Early detection of AD is big challenge that must need to be coping up.

Declarations

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Consent for publication

Authors declare that they consented for the publication of this research work.
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