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Amyloid-beta peptides and their impact on Alzheimer's disease pathophysiology

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder with the highest incidence of dementia. Despite the accumulation of knowledge about its etiology and pathophysiology, it is still unclear. The two main pathological features of AD, hyperphosphoric Tau and insoluble amyloid-beta (Aβ) peptide, include neurofibrillary tangles and senile plaques. Genes implicated in this disorder include the amyloid precursor protein (APP), presenilin 1, and presenilin 2 genes, which are inherited in an autosomal dominant manner with early onset, as well as the apolipoprotein E gene responsible for late-onset AD. The Aβ-42, Aβ-40, and Aβ-38 proteins, which are formed as a result of proteolysis of APP to Aβ, are important biomarkers in the diagnosis and detection of AD. However, the etiology and pathology of such biomarkers need to be further investigated and characterized. This review examines the relationship between Aβ peptides and AD.

Keywords: Alzheimer's disease, amyloid plaque, amyloid precursor protein, neurofibrillary tangle, PSEN1, PSEN2.

Dementia is a debilitating condition that affects daily activities, including household tasks and social interactions. When considering its prevalence across the population, it has been observed to increase significantly with age. The estimated prevalence rises to approximately 1.5% in individuals aged 65 and older, and it climbs to as high as 22% in those aged 85 and above.[1,2] According to other information, dementia causes a decrease in cognitive function in the patient due to memory loss.[3]

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In 1901, German psychiatrist Alois Alzheimer, fascinated by the complaints of memory impairment, paranoia, and progressive confusion in a 51-year-old patient named Auguste Deter, began to investigate and eventually elucidated the histopathological changes in the patient's brain called amyloid plaques and neurofibrillary tangles.[4]

The disorder can be classified into various categories, including Alzheimer's disease (AD), dementia with Lewy bodies, frontotemporal lobar degeneration, vascular dementia, Parkinson's disease, Huntington's disease, traumatic brain concussion, dementia due to substance and drug use, dementia due to HIV infection, dementia due to prion disease, dementia due to other medical conditions and dementia due to multiple etiologies.[5]

Among these types of dementia, it has been determined that AD is the most common with a rate of 50-70%.[1] When dementia is considered from a global perspective, it is determined that it doubles every 20 years and it is thought to affect 81 million people until 2040.[6]

A study based on the elderly population suggests that dementia in humans is not only AD but also mixed, i.e. AD and cerebrovascular ischemic disease (CVID). Other research strongly supports the idea that CVID seen under the age of 65 increases dementia and AD seen over the age of 65. Hobbies, physical activity, sports, etc. are thought to have protective effects on the development of AD. General population studies in the West suggest that the rate of spread of dementia may be decreasing.[7]

The clinical syndromes of AD include difficulty in learning, frequent recall of old and forgetting of new information, progressive language impairment, and deficits in functions such as planning, insight, and judgment. The patient is not aware of these symptoms and they worsen over time.[8]

It is a progressive neurodegenerative disorder that also includes confusion, sleep disturbances, fluctuations in emotions or states, and loss of bodily function in various parts.[9]

In other information, it is thought to involve excitotoxicity, neuronal oxidative stress, intracellular signaling pathway regulation, damage or loss of synapses, and neurodegeneration in different brain regions as well as the frontal cortex, hippocampus, and basal forebrain.[10] In the diagnosis of this disease, memory in combination with the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria, "Probable Alzheimer's" is diagnosed when at least two of the following areas are impaired: language, spatial perception, attention, executive functions, orientation, problem-solving skills, and functioning.[5]

The disease is characterized by the death of neurons in the cerebral cortex and hippocampus, and it has been found that such deaths occur in many other regions. As a result, brain shrinkage has been observed.[11] Two conditions are observed in AD according to the age of onset. These are sporadic, or late-onset AD (LOAD) and familial, or early-onset AD (EOAD). Although these two conditions differ in genetic and pathologic features, they are similar in terms of pathophysiologic symptoms.[12]

Although AD is predominantly seen in the elderly,[13] its pathophysiology is based on two hypotheses. The first hypothesis is called the amyloid cascade hypothesis and plays a very active role in environmentally and genetically influenced AD. Amyloid-beta (Aβ) forms a mass with its accumulation in the brain and this mass causes cell death and synapse loss in the brain. The second hypothesis is that tau, a microtubule-associated protein, becomes hyperphosphorylated, and neurofibrillary tangles (NFTs) accumulate. This results in loss of cellular and neuronal function and apoptosis.[14]

Although NFTs and extracellular Aβ plaques in the brain are distinct features of AD, many of the mechanisms involved in this disorder remain unclear. However, the amyloid cascade hypothesis has long been considered the dominant model for AD. In this model, Aβ peptides aggregate and accumulate, followed by rapid phosphorylation of tau proteins and neuronal degeneration. The hypothesis is supported by the recognition of mutations in genes encoding amyloid precursor protein (APP) and presenilin proteins. In addition, it has been determined that hyperphosphorylation of tau proteins in NFTs and Aβ are co-functioning in the pathogenesis of AD.[12]

The genes actively involved in EOAD are APP, presenilin 1 (PSEN1), presenilin 2 (PSEN2), and the apolipoprotein E (APOE) susceptibility gene, which is involved in LOAD.[4]

It was concluded that there were mutations in these three genes. The first of these genes is the APP gene which plays a role in the formation of Aβ peptide, the second is PSEN1 which is located on chromosome 14, and PSEN2 which is located on chromosome 1. In LOAD, it is the APOE locus on chromosome 19.[15,16]

The likelihood of mutations in the APP gene is low and has been observed to be less than 0.1% in AD patients. Based on the mutations seen, it has been observed that the APP gene is cleaved by β-secretase to form Aβ and then accumulates to form protofibrils, leading to an increase in the rate of amyloidogenic Aβ type 42 (Aβ-42) and thus AD.[16]

Among presenilins, PSEN1 mutations are known to be the most common hereditary cause of EOAD.[17] Functionally, it has been observed to be related to the activity of the gamma (γ) secretase enzyme. The mutations seen here are usually in the form of single nucleotide substitutions and cause accumulation in the hydrophilic region wrapped around the transmembrane region. Thus, it is concluded that mutations cause the pathogenesis of AD by decreasing the amount of Aβ-42 or decreasing the amount of Aβ-40.[18]

The APOE on chromosome 19 is a risk factor for LOAD and its alleles are ε2, ε3, and ε4.

Among them, only the ε4 allele has been found to pose a risk for the disease, but it is thought to be caught earlier. It was observed that the double ε4 allele increased the risk of the disease six times compared to the single allele. It has also been discovered that allele ε2 is protective against the disease.[15,19,20]

One of the hallmarks of AD is the formation of neuritic plaques by the accumulation of Aβ. The amyloid precursor protein is cleaved by ε and γ secretase[21] to form Aβ isoforms.[22] One of them is Aβ-42 found in cerebrospinal fluid (CSF) and is a good biomarker for AD. The Aβ-42 is frequently used as a biomarker in clinical trials and applications, and its use is increasing day by day.[23]

The most well-known of the other Aβ isoforms are Aβ-40 and Aβ-38.[24] As a result of the study conducted with a CSF sample, it is thought that Aβ-42/Aβ-40 and Aβ-42/Aβ-38 ratios are effective in differentiating AD from frontotemporal dementia and dementia with Lewy bodies and that Aβ-42 in CSF may have a great effect on the differentiation of AD in patients with mild cognitive impairment.[25]

ASSOCIATION OF AMYLOID-BETA-42, AMYLOID-BETA-40, AND AMYLOID-BETA-38 IN ALZHEIMER'S DISEASE

In 1984, Aβ was isolated from the meningeal vessels of AD and it was suggested that it may be the nucleus of senile plaques seen in the same patients. Amyloid-beta is a 40-42 amino acid protein encoded on chromosome 19 that is proteolytically formed from APP and whose function is not fully understood.[26,27]

Although it is not known exactly why Aβ-42 is most effective for amyloid plaque in AD, it has been discovered that it is more toxic inside the cell as an oligomer and that the formation of amyloid plaque with this peptide occurs in the outer part of the cell. However, it was also found in the data obtained that Aβ-42 accumulates in places such as lysosomes, mitochondria, endosomes, and cytoplasm.[28]

Amyloid-beta is expressed not only in brain cells but also in the adrenal gland, kidney, heart, liver, spleen, muscles, and various blood and peripheral organs.[29] It also affects neurodevelopment and neuronal growth. The APP gene is involved in synapse formation between neurons and cell adhesion.[30]

These peptides can easily aggregate due to the instability of the monomer and the inducing properties of environmental factors. The mechanism of Aβ self-assembly and aggregation has not been sufficiently investigated and elucidated. There are a series of transitions in Aβ, either by increasing the level of Aβ in the environment or by the influence of environmental factors. The secondary structure of our peptide has been discovered to change from the original alpha helix form to the transition form and finally to the β-sheet form.[31]

The amyloid precursor protein is thought to be processed in amyloidogenic and non-amyloidogenic pathways[32] and is cleaved by a series of proteolytic enzymes; alpha (α), β, and γ. Alpha-secretase cleaves APP from the central part of Aβ, forming the product as APP or secreted APP instead of Aβ. The other two enzymes cut APP at the amino end (β-secretase) or the carboxy end (γ-secretase) to form Aβs. The products formed are Aβ-40 and Aβ-42. These nomenclatures are given according to amino acid length. Since Aβ-42 is highly amyloidogenic, it is the first protein to collapse.[22]

Amyloid-beta deposition occurs at synapses, transported along the axons of APP to perisynaptic terminals.[33] These Aβs have been found to transform from diffuse plaques to dense neuritic plaques.[34]

In AD, the activity of the α-secretase enzyme is inhibited, leading to a shift in balance toward β-secretase and γ-secretase. The β-secretase gene is associated with β-secretase, while presenilin genes are associated with γ-secretase.[35]

Again, many studies on familial AD have investigated mutations encoding γ-secretase, for example, Xia et al.[36] showed that mutations in the PSEN1 gene abolished γ-secretase activity, resulting in a decrease in Aβ-40 and Aβ-42 formation. Another result obtained from this study is that a possible mechanism that loses its function with the onset of familial AD is an increase in the Aβ-42/Aβ-40 ratio with

the accumulation of Aβ. According to other information, mutations in PSEN genes are thought to increase the Aβ-42/Aβ-40 ratio.[36]

The Aβ-43 was discovered to be more toxic, amyloidogenic, and larger than Aβ-42 in 2011 as a result of extensive studies.[37]

In the study, it is thought that Aβ-42, Aβ-40, and Aβ-38 are formed by cutting the C-terminal and N-terminal ends of Aβs obtained from CSF and cell culture supernatant. In this information, it was discovered that Aβ-38 is a soluble peptide type that comes after Aβ-40, depending on where it is taken from. An immunosorbent assay was performed on the concentration of Aβ-42, Aβ-40 and Aβ-38 in CSF from Alzheimer's patients and control subjects.[38]

When the values of Aβ-42 levels in CSF were evaluated as Aβ-42/Aβ-40 and Aβ-42/Aβ-38 levels, it was observed that the values of the patients were lower than the values of the control subjects. On the other hand, Aβ-40 and Aβ-38 levels were the same. Aβ-42 accumulation was found to be higher than Aβ-40 and Aβ-38, and plaque maturation of Aβ-40 and Aβ-38 was found to be at later stages.[38]

According to another data, the formation of Aβ-40 was found to be higher than Aβ-42 and Aβ-42 is more prone to collapse and form amyloid plaques due to the hydrophobicity of its structure. When the relationship between genes and Aβ-42, Aβ-40, and Aβ-38 is compared, an increase in the level of Aβ-42 or both Aβ-40 and Aβ-42 may be observed as a result of a mutation that may occur in the APP gene function, or vice versa, the total level may decrease. In terms of presenilin genes, while the ratio of Aβ-42 and Aβ-40 increased for the PSEN1 gene, it was observed that the levels of Aβ-42 and Aβ-40 increased in the same way for the PSEN2 gene.[39,40]

Data for Aβ-40 and Aβ-42 show that while the amino acid sequences are similar, Aβ-42 differs from Aβ-40 in the excess of isoleucine and alanine at the C-terminal end of Aβ-42. This difference gives that region an important feature in terms of aggregation of Aβ-42.[30] Aβ-42 and Aβ-40 are similar in terms of energy profiles, but they follow a different pathway in the dimerization process. The Aβ-42 dimer is more hydrophobic than Aβ-40 and forms a β-sheet structure in the central core. The Aβ-42 is also amphipathic in aqueous media and has shown this amphipathicity by forming a nucleus in the C-terminal part.[30]

In addition, the amino acids Asp-23 and Lys-28 in Aβ-42 create an electrical attraction between them, which has been found to stabilize the nuclear aggression site.[31]

The reason why Aβ-42 is found more in plaques than Aβ-40 is its fibrillization and resistance to dissolution. In terms of its function, it is thought to cause oxidative damage and hyperphosphorylation of tau by forming polar on the cell membrane and disrupting intracellular balance.[29] There are biochemical and molecular simulation studies that prevent the aggregation of Aβ-40 and Aβ-42.[41-43]

Mutations in APP and secretase genes lead to an increase in the Aβ-42/Aβ-40 ratio and consequently to EOAD.[44-46] In this case, the Aβ-42/Aβ-40 ratio may be a diagnostic marker for AD.[47] Aβ-42s from CSF, brain, and blood have shown a direct correlation with the neurodegenerative level of AD.[48]

The most abundant Aβ alloforms in the cerebrospinal fluid sample are Aβ-38 with 15%, Aβ-42 with 10%, and Aβ-37 with 8%, according to their approximate percentage value.[42,49]

In conclusion, with the advancement of human life, dementia disorders such as AD are seen in a large part of the world population. Although it is a type of dementia that usually affects the older age group, when we look at its genetic origin, studies have focused more on APOE, APP, PSEN1, and PSEN2 genes. Among these genes, the APP gene attracts more attention and the formation of amyloid plaques due to mutations occurring here has increased the relationship with AD. These mutations affect the APP gene and cause it to be cleaved by different secretases named β and γ and lead to the formation of different types and numbers of Aβ plaques such as Aβ-42, Aβ-40, and Aβ-38. These isoforms in CSF are the best biomarkers for AD and are frequently used in diagnosis and treatment. Knowing the pathophysiology, history, and genetics of AD will guide diagnosis and treatment. The discovery of many undiscovered biomarkers used for diagnosis by scientists with the necessary studies will enable further research

to contribute to the literature and facilitate the diagnosis of the disease.

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