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Pathogenesis and treatment approaches of Alzheimer's disease

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Abstract

One of the most common neurodegenerative diseases can be listed as Alzheimer's disease. The physiopathology of the disease includes senile-amyloid plaques and neurofibrillary tangles that accumulate in certain regions of the brain. Therapeutic treatments developed for the disease are limited and aim to reduce specific clinical symptoms and slow the course of the disease.

Introduction

Alzheimer's disease is a fatal neurodegenerative disease that becomes more common with age, resulting in loss of cognitive functions, which is considered the most common cause of dementia. The disease progresses slowly and starts with the death of neurons in the brain and spreads to all neurons, causing brain damage. These damages are seen in the hippocampus entorhinal cortex and cerebral cortex of the brain. Damages in this area result in the loss of glial cells, which help neurons and neurons, and play a major role in their functioning. These cell losses are also associated with disruption of cognitive functions [1-4].

Although there are short-term memory loss and difficulty in remembering recent events at the beginning of the symptoms seen in the first stage of the disease, towards the last stages it results in cognitive forgetfulness where even daily personal care needs are not remembered in the individual. There are 7 stages of Alzheimer's disease that are clinically recorded and followed. The first stage is also defined as the early stage. At this stage, the disease is the stage in which mutated genes in the central nervous system begin to show their effects. The patient has very mild cognitive symptoms at the initial level. In the second stage, the symptoms of the disease are very similar to the first stage, and the patient begins to experience cognitive loss even if it is very mild. The effects of cognitive loss in the patient's communication with his environment are not yet seen. In the third stage, the patient's mild cognitive loss is noticed and it affects his daily life, albeit slightly. In this stage, patients have difficulty in remembering situations such as planning, organization, the location of their belongings and names. The fourth stage can also be described as the stage of moderate cognitive weakness. At this stage, patients experience losses in short-term memory and in remembering information such as personal background information, which can affect their lives and distance themselves from social life. The fifth stage is the stage in which moderate-to-severe cognitive weakness is seen and is described as early dementia. At this stage, symptomatic conditions called agnosia and apraxia occur in patients. Agnosia is the experience of recognizing sounds, smells, names, objects, shapes and entities that are known/recognized before, without any loss of sense, due to Alzheimer's disease. Apraxia, on the other hand, includes defects in acquired/learned motor movements and speech without any muscle loss. Patients with apraxia and agnosia disrupt their daily routine and need the help of a second person for these tasks, including personal care. In the sixth stage, severe cognitive losses and moderate dementia are seen. In addition to agnosia and apaxia, patients also have aphasia. Aphrasia is characterized as the inability to remember in the speech order of the person without any loss of sense in speaking skills, and as a result, the disruption in speaking ability. In this

stage, which is accepted as the seventh and clinical final stage of the disease, severe cognitive deficits and late dementia are seen in patients. This stage includes all the symptoms seen in the previous stages, but indicates the most severe and last degree of the symptoms of these stages. At this stage, patients experience losses in basic needs such as speaking, swallowing, and going to the toilet, and they need surveillance all day [5].

Discussion

The pathogenesis of Alzheimer's disease can be elucidated by the evaluation of autopsy results. In addition to genetic approaches, *in vitro* or *in vivo* studies also play a role in determining the pathogenesis of the disease. In the light of these studies, senile beta-amyloid plaques that accumulate excessively outside the cell and neurofibrillary tangles that accumulate inside the cell are counted among the molecular differences in the formation of Alzheimer's disease [6,7].

Neurofibrillary tangles consist of double-strand breaks as a result of the accumulation of neurons in the cell body and dendrite regions by hyperphosphorylation as a result of differences in kinase and phosphatase levels responsible for the phosphorylation of tau proteins within the cell. In addition to kinases and phosphatases, which are responsible for the hyperphosphorylation of tau proteins, some proteins also play a role. CDK5 serine threonine kinase protein is involved in the phosphorylation of tau protein. In addition, proteins such as GSK-3β protein, protein phosphatase 2A, and proyl isomerase pin1 cause hyperphosphorylation of tau proteins, resulting in the formation of neurofibrillary tangles. Neurofibrillary tangles accumulating in the cell induce apoptosis, disrupt the functional structure of microtubules that make up the cytoskeleton, create toxic effects within the cell, and impair transmission between neurons. The formation and course of neurofibrillary tangles progress in direct proportion to the clinical course of the disease [6].

In addition, cellular events such as oxidative stress, Down syndrome, insulin resistance, neuronal glucose metabolism and neuroinflammation are effective in the pathophysiology of the disease [6,7].

The most obvious and most important symptom of the disease is the formation and accumulation of senile-amyloid plaques in certain regions of the brain. It forms/accumulates in the amygdala, hippocampus and neocortex regions of the brain. Amyloid β consists of 40-45 amino acids and consists of APP protein. Amyloid plaques are based on the intracellular proteolytic formation of the amyloid precursor protein, APP. Amyloid beta consists of the part of the transmembrane APP protein in the extracellular membrane [7-9].

There are some genes responsible for Alzheimer's disease. These genes are; There are 4 amyloid precursor protein (APP), presenilin 1 (PS1), presenilin 2 (PS2) and apolipoprotein E (ApoE). It is known that Alzheimer's disease occurs as a result of mutations in these genes. As a result of the mutation in the APP gene, an increase in the level of amyloid beta plaques has been observed. It is known that Alzheimer's disease occurs when any mutation in the PS1 gene causes changes in tau proteins, forming neurofibrillary tangles associated with these proteins and accumulating in the cell. While the e4 allele of the ApoE gene has an enhancing effect on the emergence of Alzheimer's disease, the e2 allele has a reducing or protective effect [7,8,10].

Conclusion

The drugs used for the treatment of Alzheimer's disease aim to eliminate the specific clinical manifestations of the disease. Tacrine was the first drug used and approved for Alzheimer's disease. This drug significantly reduces the symptoms of people with Alzheimer's disease. In addition, it greatly increases the expression level of liver enzymes. However, the hepatotoxic effect of this drug limits its use in the disease. It is thought that developing and suggesting drugs that reduce the effects of Alzheimer's disease in its holistic and basic form, instead of nonspecific drug treatment approaches, may reduce the disease [10,11].

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