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Review Article

Current Developments in Alzheimer's Disease and Treatment

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ABSTRACT: Alzheimer's Disease is a progressive and irreversible disease with a high incidence in older people both in our country and the world, and its pathophysiology is not fully understood. There is no definitive treatment for the disease, but some hypotheses that are thought to be effective in treatment have been determined; the most effective of these is the cholinergic hypothesis, which suggests that acetylcholine levels are low in the brains of patients. Other hypotheses are the tau and amyloid hypothesis, oxidative stress and neuroinflammation. Current treatments are mostly symptomatic, and the first drugs approved for use are the acetylcholinesterase inhibitor rivastigmine, galantamine, donepezil, and the N-methyl-D-aspartate receptor antagonist memantine. In developing new treatments, pathological causes have been targeted, new methods have been tried to reduce amyloid accumulation and tau phosphorylation, and effective drugs have been found. Still, they have not been put into clinical use. Antioxidant compounds have been studied to suppress oxidative stress. Other treatment methods include stem cell therapy, vaccination and the use of estrogen.

Keywords: *Alzheimer's disease, current treatment, pathophysiology.*

1 INTRODUCTION

Dementia is known as a chronic, progressive, and irreversible disease that is common after the age of 65. A diagnosis of dementia requires problems with at least two cognitive functions, such as memory impairment, speech abnormalities, and orientation problems. Additionally, patients have difficulty fulfilling their ordinary daily needs [1,2]. There is no definitive treatment for Alzheimer's Disease (AD) and the treatments applied are aimed at relieving the symptoms [3]. Several hypotheses have been proposed regarding the pathology of AD, including decreased cholinergic activity, amyloid deposition, excessive tau protein phosphorylation, and increased levels of inflammation and oxidative stress in brain tissue. Drugs commonly used in treatment include acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, galantamine) and memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist [4]. In current treatment studies, in addition to pathology-oriented studies, anti-inflammatories, antioxidants, and stem cell therapy have been

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tried. Studies have been conducted on compounds aimed at reducing tau protein and amyloid accumulation, but suitable methods for clinical use have not been found [5]. Since the classical methods used in treatment today are inadequate and are symptom-oriented, this review study investigates whether there are new developments in treatment and at what stage these developments are [5].

Dementia is a chronic and progressive disease characterized by problems in at least two of the cognitive functions such as speech, memory loss, judgment, and problem solving. Dementia can develop due to trauma, inflammation, infection, vascular, brain degeneration, and toxic causes. It is classified according to its etiology, findings, and brain regions, and is divided into two groups according to its etiology [1].

A-Primary dementia; AD, Lewy body dementia, pediatric dementias, and rare dementias [1],

B-Secondary dementia; vascular dementia, toxic metabolic dementia, and normal pressure hydrocephalus [1].

AD is a neurodegenerative disease and is usually seen in advanced ages. The brain's behavioral and cognitive functions are impaired and it is a progressive disease [2]. When the brain tissue is examined microscopically, tangles and plaques are seen in the neurons. The first symptom is memory loss, and the patient has problems in fulfilling their daily needs (shopping, personal hygiene, eating, and using devices), in addition, the patient also has psychiatric disorders [3]. Pathological causes include senile plaque (SP) formation, neurofibrillary tangle (NFT) formation containing phosphorylated tau proteins in the hippocampus, and a decrease in acetylcholine (ACh) levels [4].

1.1 History

Dr. Alois Alzheimer is the first person to describe the clinical and anatomopathological findings of the disease. The first symptom of a 51 year-old patient named Auguste Deter, who caught Dr. Alzheimer's attention in 1901 at the institution where he worked in Frankfurt, was paranoid jealousy of her husband, which was soon followed by memory impairment, disorientation in time and space, paranoia, and auditory hallucinations. Later, the patient became bedridden with incontinence and died within 4.5 years. After the death of his patient, Dr. Alzheimer presented the histopathological findings that he had identified in the cerebral cortex at a scientific meeting in Tübingen, Germany, in 1906. However, since he did not receive the expected recognition, he published his

findings in 1907 as an article in the journal "*Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medicin*", titled "A Peculiar Disease of the Cerebral Cortex" [3].

1.2 Epidemiology

The number of elderly individuals who died from AD was 13,859 (4.6%) in 2018 and 11,880 (3.2%) in 2022. When deaths from AD are analyzed by gender, the rate for men was 2.3%, and the rate for women was 4.1% in 2022 [6]. The incidence of AD by age is 0.4% in the 65-69 age group and increases to 10% by the age of 90, while the prevalence is 2% in the 65-69 age group and exceeds 25% in individuals over 90. The prevalence doubles every 5 years over the age of 65. In developed countries, it is reported that AD symptoms occur in one in every 10 people aged 65 and over, and in one in three cases aged 85 and above [7].

1.3 Risk factors

1.3.1 Genetics

Three gene disorders responsible for Early Onset Alzheimer's Disease have been proven. These genes are Amyloid precursor protein (APP) on chromosome 21, Presenilin 1 (PSEN1) on chromosome 14, and Presenilin 2 (PSEN2) on chromosome 1. The only gene known to have an effect on Late Onset Alzheimer's Disease is Apolipoprotein E4 (ApoE4) [8].

APP gene: Although its exact function is not fully understood, it is thought to be involved in synaptic formation and neuron migration. The pathology of the disease is caused by the accumulation of amyloid β (Aβ) resulting from the cleavage by β and γ secretase enzymes. Similar findings to AD are also observed in patients with Down syndrome after the age of 40. Because Down syndrome and AD are associated with overexpression of APP on the q arm of chromosome 21 and Aβ accumulation [9].
PSEN1 gene: It is the gene with the highest risk in the development of the disease. It is a part of γ secretase, which is responsible for the degradation of APP. It is responsible for the catalytic activity of the enzyme. When PSEN1 is mutated, changes occur in γ secretase. As a result of the change in the enzyme, the formation and accumulation of Aβ40 and Aβ42 increases [9]. The PSEN2 gene is highly similar to the PSEN1 gene. The age of onset of the disease is higher. Mutations in the PSEN2 gene cause different clinical pictures compared to the PSEN1 gene. The mutated PSEN2 gene binds to kinases that regulate signaling and increases β secretase activity. Mutations in the PSEN2 gene are not as frequent as mutations in the PSEN1 gene [9].

ApoE4 gene: It is a serum protein involved in functions such as the transport and

storage of cholesterol. It has three alleles, ApoE 2, 3 and 4, and the ApoE4 allele increases amyloid accumulation (8). The ApoE2 allele has a protective effect against the disease [3].

1.3.2 Age

After the age of 65, the risk of AD doubles every five years. Those under the age of 65 are classified as Early Onset Alzheimer's Disease, and those over the age of 65 are classified as Late Onset Alzheimer's Disease Early and late-onset AD differ in terms of clinical, pathological, and imaging as well as age of onset [10].

1.3.3 Gender

Since women have a longer lifespan than men, their risk of developing the disease is higher. Although the disease is associated with low education levels in women, it is more meaningful to associate it with estrogen levels that fall, especially after menopause, because estrogen has a regulatory effect in the brain and increases the formation of new synapses in hippocampal cells [11]. Estrogen regulates brain functions by adjusting the levels of neurotransmitters, slows down the production of ApoE and increases its destruction, and reduces the formation of SP by reducing Aβ production. It also has an antioxidant effect by reducing the neurotoxic effects of Aβ and reduces inflammation by affecting interleukin-6 (IL-6), which is effective in the formation of SP. Although most epidemiological studies show that the risk of developing AD is significantly reduced in women who receive estrogen replacement therapy after menopause compared to women who do not, this result could not be confirmed in some studies, and it has been suggested that factors such as patient selection, the route of administration of the treatment, the dose, and the duration of the drug are different [12].

1.3.4 Depression

It has been suggested that depression doubles the risk of AD, but another hypothesis is that depression may actually be an early symptom of AD. Depression increases the risk of developing vascular dementia and AD in older individuals [13, 14]. Long-term use of selective serotonin reuptake inhibitors (SSRIs) has been found to delay the progression from mild cognitive impairment to AD, and it is thought that it shows its effect by reducing Aβ production [15].

1.3.5 Diabetes

Patients with diabetes are at risk for cognitive impairment and dementia. Toxicity and increased oxidative stress caused by the accumulation of glycation products damage the structure of the vessels, resulting in increased neuronal loss,

and as a result, long-term hyperglycemia leads to worsening of cognitive impairment. Hypoglycemia is also effective in cognitive impairment. In severe hypoglycemia, cognitive impairment accelerates with neuronal loss and fibrinogen formation. Hyperinsulinemia reduces the number of insulin receptors, disrupts insulin response, and thus inhibits insulin passage to the cerebrospinal fluid (CSF) and brain tissues, resulting in problems in learning and memory formation. Insulin sensitivity in the brain is impaired in Alzheimer's patients, and the enzymes responsible for the destruction of insulin also destroy amyloid. When insulin levels are high, enzymes compete to destroy insulin, and Aβ destruction decreases and amyloid accumulation increases in the brain [16]. Diabetes is also effective in tau protein accumulation; antidiabetics used in the treatment of diabetes have been found to reduce Aβ and tau protein accumulation and provide cognitive improvement [17]. The most effective are metformin, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 analogs, and sodium glucose transporter-2 inhibitors [18].

1.3.6 Hypertension

High blood pressure is considered a risk factor for AD, but the relationship between them has not been fully determined. Hypertension is thought to cause poor cognitive performance and cognitive decline [19]. A postmortem study in humans found that hypertension in middle age causes a decrease in brain volume, increased Aβ accumulation, and NFT formation [20].

1.3.7 Dyslipidemia

Hypercholesterolemia seen in middle age is a risk factor for AD, and the information supporting this is the decrease in Aβ40 and Aβ42 levels in patients using statins [8]. Increased cholesterol levels in the brain increase oxidative stress, neuronal loss and phosphorylation of tau proteins. Another negative result of an increase in cholesterol level is that it affects APP degradation, leading to an imbalance and amyloid accumulation. [21]. In some studies, there is no relationship between hypercholesterolemia and AD [8]. The reason for the different results may be due to the subjects used in the studies or changes in the protocol [21].

1.3.8 Family History

Family history is a more important factor in Early Onset Alzheimer's Disease, and most cases that start before the age of 60 have a family history. The risk of developing the disease in children of people with AD is 6 times higher than in healthy people [22].

1.3.9 Smoking and alcohol

Smoking increases the risk of AD. Smoking and alcohol disrupt the balance between the formation and reduction of oxidants and free radicals, and due to the disrupted balance, the level of oxidants and free radicals in the body increases, ultimately causing oxidative stress. Increased oxidative stress is effective in the accumulation of SP and NFTs and plays a role in the pathology of the disease with this mechanism of action [23]. Long-term alcohol use negatively affects the motor and cognitive functions of the brain, causes cholinergic neuron loss and atrophy in brain tissue. In a study conducted in mice, it was observed that it caused an increase in the phosphorylation of tau protein and memory impairment. Acetaldehyde, which is formed as a result of alcohol metabolism, has a neurotoxic effect on the brain, thus causing permanent damage to the brain. Although alcohol has an immunomodulatory effect depending on the dose and frequency of consumption, the effect of alcohol on AD is not fully understood [24].

1.3.10 Nutrition and Obesity

Obesity in middle age is a risk for AD, but there is no definitive data on obesity in advanced age. In fact, some studies have shown that obesity is protective against AD [25]. Obese elderly individuals have less Aβ accumulation and larger hippocampus volumes [26]. There is no specific diet for AD, but the Mediterranean diet is recommended. This diet includes more vegetable and fruit consumption. It limits the consumption of saturated fat, meat, and dairy products. It reduces oxidative stress in AD due to its antioxidant content. Many studies have shown that microbiota is important in brain functions. Disruption of the microbiota can cause degeneration in the brain, and exercise and probiotic use reduce inflammation, oxidative stress and Aβ accumulation. Aluminum accumulation in the brain has been observed in AD, and long-term exposure is risky because aluminum causes neuropathy, oxidative stress, and inflammation. High copper intake leads to learning deficits, lead increases neurodegeneration, and cobalt accumulation negatively affects neurotransmission. Mercury accumulates in neurons and increases the accumulation of Aβ and tau protein. Even small amounts of arsenic can cause neurological disorders. High calcium levels can affect AD pathology by increasing Aβ accumulation and phosphorylation of tau protein [27].

Vitamin B_{12}: Neurological problems are experienced in vitamin B_{12} deficiency. In vitamin B_{12} deficiency, the homocysteine cycle is disrupted, and its level in the blood increases [28]. High homocysteine levels

increase neurotoxicity and hydrogen peroxide formation [8]. Homocysteine shows its neurotoxic effect by activating the NMDA receptor or by converting to homocysteine acid. Another negative result of high homocysteine levels is that it causes Aβ accumulation and phosphorylation of tau protein. Methylation reaction is also disrupted in vitamin B_{12} deficiency. Methylation reaction is important in neurotransmitter, phospholipid, and nucleotide production in the brain. Therefore, vitamin B_{12} deficiency is a risk factor for AD [29].

Vitamin D: In vitamin D deficiency, individuals may experience decreased cognitive functions, intermittent memory loss, and executive dysfunction [22]. Vitamin D is important in neurotransmission, protection, and synaptic plasticity in the brain. Its active form, 1.25 $(OH)_2D$, is effective in the phagocytosis of amyloids. In this case, $A\beta_{42}$ accumulation decreases and plays a role in the differentiation and maturation of neurons. Since it regulates the genetic expression of neurotransmitters in the hippocampus, vitamin D intake may be beneficial for Alzheimer's patients [30].

Vitamin A: Vitamin A plays a role in the differentiation and protection of neurons in the brain and in the release of neurotransmitters. Vitamin A and beta-carotene levels are decreased in AD. In a study conducted in mice, it was observed that low vitamin A levels resulted in Aβ accumulation, and Aβ inhibits retinoic acid synthesis, which worsens the pathology of AD. The importance of vitamin A is explained by the retinoid-dependent transcriptional regulation of genes such as APP, $PSEN_1$, and $PSEN_2$, which are effective at the amyloid level. All-trans-retinoic acid regulates the transcription and activation of these genes in an antiamyloidogenic manner. Giving vitamin A supplementation to patients improves cognitive impairment [30].

Vitamin E: The most abundant form of vitamin E in human tissue is α-tocopherol. As a result of low levels of vitamin E in the body, $ApoE_4$ transport in the brain increases and causes cognitive damage. In addition, vitamin E has antioxidant properties for the brain [22].

Vitamin C: It is found in very small amounts in neurons. It cleans superoxide, a product of mitochondria in neurons. Vitamin C protects synaptic activity and helps detoxification. It suppresses genes that cause inflammation and prevents Aβ accumulation. Taking vitamin C supplements improves memory performance and memory problems [30].

Vitamin K: Cognitive performance disorders are observed in vitamin K deficiency. It protects brain cells from inflammation and oxidative stress. Therefore, the use of vitamin K may be beneficial in AD [30].

1.4 Pathology and physiopathology

Despite extensive studies, the pathology and physiopathology of AD are not fully understood. Macroscopic findings show atrophy in the cortex and hippocampus regions, while histological findings show NFT, amyloid plaques, synaptic loss, and cholinergic neuron loss [31].

1.4.1 Amyloid hypothesis

The enzymes responsible for APP metabolism are α, β, and γ secretase. In the first step, it is metabolized by being cleaved by α and β secretase enzymes. When cleaved by the α-secretase enzyme, SAPPα and C_{83} fragments are formed. These fragments are not toxic to the brain. Then, the SAPPα fragment is secreted out of the cell, while the C_{83} fragment remains in the cell membrane. As a result of the cleavage by β secretase, sAPPβ and C_{99} fragments are formed. The sAPPβ fragment is secreted out of the cell, while the C_{99} fragment remains in the cell membrane. In the second step, the C_{99} fragment is cleaved by γ-secretase and Aβ and APP intracellular domain fragments are formed. The fragments formed as a result of the cleavage are neurotoxic. This cleavage is heterogeneous, and $A\beta_{40}$ formation is more than $A\beta_{42}$ formation. Amyloid plaque accumulation is caused by $A\beta_{42}$. Because it is more prone to turning into fibrillar form and has a hydrophobic structure [9]. Amyloid accumulation is seen in the meningeal vessels of the brain. This accumulation leads to cerebral hemorrhages and cognitive impairments [32].

1.4.2 Tau hypothesis

Tau protein is mostly found in mature neurons but can also be found in the nucleus, mitochondria, dendrites, synapses, and membrane. Tau protein maintains the stability of microtubules, which are important for the transport of products in neurons and cell structure [33]. Therefore, tau protein is responsible for maintaining cell shape and axonal transport. After tau protein is synthesized, it differentiates with reactions such as phosphorylation and nitration, and with the increase in phosphorylation reaction, the structure of tau protein is disrupted, and it cannot bind to microtubules. When tau protein cannot bind to microtubules, it binds to each other and forms double or single helices. The mechanism that causes increased phosphorylation is not fully known. However, cyclin-dependent kinase 5 (CDK5), a serine-threonine kinase,

phosphorylates cytoskeletal proteins, synaptic proteins, and transcription factors, including tau protein. It is suggested that phosphorylation of tau protein increases as a result of high activation of CDK5, and the increased activity of CDK5 is caused by Aβ accumulation [34]. The resulting helical structures lead to the formation of NFTs [35]. NFTs facilitate the aggregation of tau proteins and disrupt cell integrity by preventing the stability of microtubules, causing neuronal death [36].

1.4.3 Cholinergic hypothesis

ACh has activity throughout the cortex, basal ganglia, and basal forebrain. It is effective in physiological processes such as memory, attention, sleep, and sleep disorders. ACh is synthesized with the help of choline and acetyl coenzyme A by choline acetyltransferase (ChAT). After synthesis, it is released into the synaptic cleft and shows its effect by binding to the postsynaptic receptor. Unbound excess ACh is broken down into choline and acetic acid by AChE. These are taken back to the presynaptic neuron by a mechanism for recycling to acetyl coenzyme A. According to the hypothesis, ACh level is reduced in AD pathology, and the reasons for this decrease are decreased ChAT level, increased AChE activation, and insufficient choline reuptake. In short, insufficient ACh production leads to cognitive impairment [37].

1.4.4 Oxidative stress

Free radicals can form in both physiological and pathological conditions. Reactive oxygen species (ROS) play a role in cellular metabolism and signal transduction pathways. Due to excessive production, lipids, intracellular proteins, and DNA are damaged. ROS are retained or transformed by antioxidants. Aβ causes neuronal loss by inducing oxidative stress in the brain. As an indicator of this, 4-hydroxynonenal and malondialdehyde levels, which are markers of lipid damage, are increased. When the antioxidant system becomes inadequate, mitochondrial function is impaired and cell death occurs [38]. As a result of lipoperoxidation, phospholipids decrease, and plaque formation can be observed in the brain due to lipid formation and antioxidant depletion. Oxidative stress markers have been detected in brain tissue and CSF in AD [39].

1.4.5 Neuroinflammation

Pro-inflammatory mediators are found in high amounts in the brain tissue and CSF of Alzheimer's patients. Neuroinflammation occurs due to the excessive secretion of pro-inflammatory cytokines and chemokines, which activates macrophages in the brain and increases the levels of tumor necrosis factor-alpha,

interleukin-8, transforming growth factor-β, and macrophage inflammatory protein-1α and Aβ plaques [32].

1.5 Clinical findings

The disease usually starts at the age of 40 in Early Onset Alzheimer's Disease, and after the age of 65 in Late Onset Alzheimer's Disease. The first complaint of most patients is memory problems, and the symptoms can be divided into cognitive disorders and non-cognitive, i.e., psychiatric symptoms [40].

Cognitive disorders;

• Dysphasia: Speech disorder,

• Anomia: Forgetting the names of objects or people,

• Inability to do calculations,

• Difficulty solving problems,

• Disorientation: Decreased sense of direction and time perception, inability to recognize people,

• Agnosia: Inability to process sensory information,

• Difficulty in remembering,

• Dyspraxia: Inability to perform tasks that require skill [40].

Non-cognitive (psychiatric) symptoms;

• Depression,

• Psychotic behaviors: Seeing hallucinations and paranoia,

• Non-psychotic behaviors: anxiety, exhibiting repetitive behaviors, and hyperactivity [40].

Disease stages; Early stage: Patients begin to experience memory problems. They have difficulty learning new information, repeating their questions and conversations. They forget names and the location of objects. They have difficulty using devices and doing their hobbies. Although they have problems with reasoning skills in the first stage, they do not have much trouble in terms of behavior [41].

Middle stage: Patients now have difficulty performing their daily activities. Despite receiving help, they are unable to recognize people, have difficulty eating, and have decreased motor functions such as incontinence and walking. They can go out with their relatives, but they cannot find their way when they are alone, i.e., behavioral problems begin to emerge [42].

Advanced stage: The patient's personality traits have completely changed. They have difficulty speaking and understanding what is said, and have difficulty chewing and swallowing. They cannot express their

feelings [43]. They can no longer take care of themselves and need an assistant. They cannot perform behaviors such as eating, cleaning and dressing on their own. The disease progresses and results in death, and the cause of death is due to bed sore infections, lung infections, and nutritional deficiencies [44].

1.6 Diagnosis

For the definitive diagnosis of AD, a biopsy or an autopsy can be performed to examine brain tissue. In the clinic, a diagnosis can be made with high accuracy using patient history, laboratory results, imaging techniques, psychological tests, and neurological examination. There are criteria used in the diagnosis of the disease. These are established by NINCDS-ADRA and DSM-V [45].

Alzheimer's type dementia according to DSM-V criteria is diagnosed as follows [45].

A. Diagnostic criteria for severe or mild neurocognitive impairment must be met.

B. There is a slowly progressive, insidious, and silent deterioration in one or more cognitive domains.

C. Diagnostic criteria for probable or possible AD are met as follows:

• C1. For severe neurocognitive impairment:

If 1 of the following is present, the diagnosis of possible/probable AD should be made; if not, possible AD should be made.

1. Evidence of a causative AD heritable mutation (genetic mutation) from family history or genetic measurements

2. All three of the following:

a. Clear evidence of decline in memory and learning and at least one other cognitive domain (by detailed history or a battery of neuropsychological measurements)

b. Steady, progressive decline in cognitive function without long-term cessation.

c. No evidence of other confounding factors that could cause cognitive impairment. (Other neurogenerative or cerebrovascular disease or other neurological, mental or systemic disease or condition that may contribute to cognitive decline)

• C2. For mild neurocognitive disorder:

A diagnosis of probable AD is made if there is evidence from family history or genetic measurements of a causative AD hereditary change (genetic mutation). In the absence of this evidence, a diagnosis of probable AD is made if all three of the following are present:

1. Clear evidence of memory and learning decline

2. Steady, progressive decline in cognitive functions without long-term cessation.

3. No evidence of other confounding factors that could cause cognitive impairment. (Another neurodegenerative or cerebrovascular disease, or another neurological, mental, or systemic disease, or a condition that may contribute to cognitive decline)

D. The disorder is not explained by the effects of cerebrovascular disease, another neurodegenerative disease, a substance, or another mental, nervous, or systemic disorder [45].

1.6.1 Taking patient history

Since sufficient information cannot be obtained from the patient if the disease is advanced while taking the history, information should be obtained from the patient as well as from the relative. The patient's relative can see the differences between the patient's past and current state. The patient should be asked about the functions that have been affected, and questions such as eating, remembering recent events, driving, calculating, finding one's way, repeating the same conversations and questions, solving problems and changes in personality traits can be used to get an idea about the stage of the disease. The patient's general medical, psychological, toxicological and neurological history should be asked, and family history should be taken and the presence of people with AD in their relatives should be questioned [46].

1.6.2 Neuropsychological evaluation

An examination should be performed initially to understand the changes in functions such as memory impairment, language, attention, visual skills, problem solving and perception in the patient. It also helps to understand the cause of the patient's cognitive impairment [47].

1.6.3 Imaging methods

Magnetic resonance imaging (MRI) of the patient's brain is used for diagnosis. The findings seen are regional or general atrophy and white matter lesions [47]. Distinguishing AD from other types of dementia becomes easier with computerized tomography or MRI, and atrophy in the temporal lobe and hippocampal formation in volumetric studies strengthens the diagnosis. Among other methods, cerebral blood flow with single photon beam computed tomography and decreased glucose metabolism in the temporo-parietal region with positron emission tomography (PET) are helpful in diagnosis [31]. Fluorodeoxyglucose-positron emission tomography is used to differentiate AD from frontotemporal dementia [47].

1.6.4 Laboratory findings

There is no laboratory test with proven validity for AD. There are recommended tests for the differential diagnosis of the disease. These tests help in the diagnosis of metabolic and systemic diseases that may lead to AD [31].

1.6.5 Recommended Laboratory Parameters

Complete blood count, sedimentation, serum electrolytes, glucose, BUN, creatinine, B12 and folate levels, liver, kidney and thyroid function tests [47].

1.7 Treatment

Although there is no drug that completely stops AD, there are FDA-approved AChE inhibitors (Rivastigmine, Galantamine and Donepezil) and Memantine, an NMDA receptor antagonist [48]. Treatments available for AD are used to slow the progression of cognitive, behavioral and psychological symptoms. The treatment applied is symptomatic and improves the quality of life for patients and their relatives. If the drugs are started before degeneration begins, i.e., before symptoms appear, their effectiveness may increase, in other words, early diagnosis provides significant benefits in treatment. Theeffectiveness of the drugs is also affected by their degree of penetration into the brain [49]. The primary treatment of the disease aims to improve cognitive symptoms, while the secondary treatment aims to improve psychological symptoms [31].

1.7.1 Classical treatment approaches

AChE inhibitors: According to the cholinergic hypothesis, the source of cognitive functions, especially memory impairment, is seen as a decrease in cholinergic activity. The fact that AChE activity is low in the disease and that neuronal loss is mostly seen in cholinergic neurons supports the hypothesis [50]. These drugs inhibit the AChE enzyme, reducing ACh destruction in the synaptic cleft, and after the destruction decreases, ACh levels increase in the synaptic cleft, which results in ACh binding to muscarinic and nicotinic receptors and increased stimulation intensity [51]. AChE inhibitors increase ACh levels, provide neuroprotective effects via nicotinic receptors, and regulate APP and Aβ formation by enabling neuron regeneration via muscarinic receptors [52].

AChE inhibitors:

a-Pseudo-reversible; Carbamates (Rivastigmine) [51].

Rivastigmine: It is approved by the FDA for use in the early and middle stages of AD. In the MR and PET results of patients who used rivastigmine for 6 months, great improvements were seen in the hippocampal metabolism of the brain. Side

effects include diarrhea, vomiting, anorexia, and weight loss [36]. Like ACh, it binds to the esteratic part of the enzyme, but its dissociation from the enzyme is slow. Although its plasma half-life is short due to its pseudo-reversible inhibition, the enzyme inhibition in the brain lasts 10 hours. It is highly selective for the hippocampus and cortex regions, and high doses are more effective in treatment [52]. It does not have a toxic effect on the liver, and since it binds to plasma proteins less and liver enzymes do not take part in its metabolism, it has very few interactions with other drugs [50].

b-Reversible; Tacrine, Donepezil, Galantamine [51].

Tacrine: It is the first drug approved for treatment. Its most obvious side effect is the increase in serum alanine transferase (ALT) enzyme levels. If the increase reaches three times the normal level, no change in treatment is made, and the use of the drug is stopped at higher values. After the drug is stopped, the ALT value returns to normal. In this case, the drug can be started again. However, when jaundice occurs, the drug is stopped and not restarted. Other side effects include headache, nausea and diarrhea [50]. It has central and peripheral effects and inhibits the enzyme reversibly. Its effect is not selective, meaning that it inhibits other choline esterases as well as the AChE enzyme. Drugs it interacts with include theophylline, warfarin and cimetidine [51].

Donepezil: Side effects are less common than other AChE inhibitors. It has no hepatotoxic effect [31]. It can be used in the early, middle and advanced stages of the disease. In addition to its cholinergic effect, it suppresses the production of inflammatory cytokines, oxidative stress and glutamate-induced toxicity. When taken in high doses, hypotension, respiratory distress, vomiting and muscle weakness are observed [36]. It has a more selective effect than other inhibitors. It binds to the AChE enzyme at a high rate. It has a lower affinity for butyrylcholinesterases and a higher central effect. It improves cognitive and behavioral symptoms. Sleep problems, anorexia, fatigue and cold symptoms are observed among its side effects [51].

Galantamine: In addition to enzyme inhibition, it is suggested that it stimulates nicotinic receptors and increases ACh release [50]. It is thought to provide improvement in cognitive disorders in Alzheimer's treatment. In mouse experiments, it is seen that it reduces inflammation and Aβ accumulation. Side effects include watery eyes, muscle weakness and nausea [36].

Metrifonate: It irreversibly inhibits the AChE enzyme. It has a higher affinity for the AChE enzyme than other enzymes. According to research, it has no hepatotoxic effects. Its side effects mostly affect the digestive system, and it is reported to have an effect on behavioral symptoms as well as cognitive symptoms [52].

c-Irreversible; Organo phosphorus compounds (metrifonate) [51].

NMDA receptor antagonists: This group includes memantine. Moderate improvement is observed when used alone or together with AChE inhibitors in the middle and advanced stages [53]. It has low selectivity for the NMDA receptor. It prevents toxicity in neurons, but there is no definitive information that it prevents degeneration [48]. It prevents toxicity because it reduces excessive glutaminergic activity in the nervous system [32].

1.7.2 Current treatment approaches

A-Muscarinic and nicotinic agonists: Another option to increase the activation of the cholinergic system is to stimulate the receptors. It has been observed that despite the decrease in cholinergic activity in AD, muscarinic receptors in the cortical and hippocampal regions remain intact. Therefore, muscarinic agonists are thought to be effective [31]. Muscarinic and nicotinic agonists are thought to be a good option for treatment because of the bradyarrhythmia, gastric acid secretion and bronchial secretion caused by AChE inhibitors, the increase in the effects of cholinergic drugs and the decrease in the effects of anticholinergic drugs. Their use is advantageous because they do not stimulate the inhibition of M_2 muscarinic autoreceptors. However, research on these drugs is ongoing [51]. Nicotinic receptor agonists play a role in memory and learning [50].

Xanomoline; It shows high selectivity for the M_1 muscarinic receptor. Aβ production decreases by stimulating the M_1 receptor. It has been tried in patients in the early and middle stages. According to the results, it has been found to be good for psychiatric symptoms such as hallucination, delusion and agitation. However, its use is limited due to fainting and digestive system side effects observed during the use of the drug. It is thought that the cause of its side effects may be due to the product formed as a result of its metabolism and its transdermal formulation is being developed [50].

ABT-418; It binds to the α4 and β_2 subtypes of nicotinic receptors with high selectivity. The structure of ABT-418 is similar to the structure of nicotine. It is seen to increase cognitive performance in studies conducted in animal models. It improves memory,

attention and executive function. Research is ongoing for its use in treatment [54].

B-Drugs based on the amyloid hypothesis:

The aim of this group of drugs is to prevent amyloid formation or reduce Aβ accumulation. Therefore, it is thought that their use in the early and middle stages of AD may be more beneficial [53].

BACE inhibitors; BACE enzymes cut APP and form the C99 fragment that causes Aβ to form. The cutting of APP by the BACE enzyme is the rate-limiting step. In the treatment, this enzyme is inhibited and the formation of Aβ is reduced. Therefore, it is important for the treatment [5]. The first examples were unsuccessful due to low bioavailability, inability to cross the brain barrier and liver toxicity [48].

γ secretase inhibitors; γ secretase enzyme does not only cut APP. The most important member of this enzyme family is the notch protein. Because it has important functions in the immune and digestive systems. In the treatment of Alzheimer's, selective inhibition is desired to prevent only APP from being cut by γ secretase. Non-selective inhibitors have serious side effects. For this reason, failure is observed in studies [32]. The most undesirable side effect among the observed side effects is learning disability. This situation is an undesirable side effect in the treatment [48].

α-secretase modulators; When the α-secretase enzyme cleaves APP, APPα and C_{83} fragments are formed. Since the cleavage is between the 16th and 17th amino acids of the Aβ sequence, Aβ production is prevented. The fragments formed are retained in the membrane and p3 is formed as a result of cleavage by γ-secretase. p3 is a non-amyloidogenic peptide [32]. Therefore, increasing the activation of the α-secretase enzyme reduces amyloid accumulation. There are many proteases that help in the activity of the enzyme. However, since it is not known which protease will increase the activity of α-secretase, this causes slow progress in drug development. Another problem is that there is no evidence as to whether it is indicated in AD [53].

RAGE inhibitors; By activating the receptor, it activates inflammatory responses and oxidative stress by increasing the activities of β and γ-secretase enzymes and helps Aβ formation [32]. RAGE is a receptor that binds many ligands. Among these ligands are Aβ peptides. Therefore, inhibitory agents may be useful. This inhibition reduces Aβ accumulation [48].

C-Drugs based on the tau hypothesis:

The aim of this group is to inhibit excessive phosphorylation and aggregation of tau protein. Another aim is to dissolve

previously found aggregates [5]. Prevention of tau hyperphosphorylation: Hyperphosphorylation prevents proteins from performing their functions. Hyperphosphorylation is a prerequisite for aggregation. The normal progression of phosphorylation depends on the balance between tau protein kinases and phosphatases. In Alzheimer's, the aim is to inhibit kinases and activate phosphatases. Therefore, kinase inhibitors are being developed. Glycogen synthase kinase 3 (GSK3β), CDK5 and extracellular signal-regulated kinase 1/2 are more focused on inhibition of these kinases. Tideglusib is a GSK3β inhibitor. Hyperphosphorylation is also observed by inhibiting enzymes such as protein phosphatase 1, protein phosphatase 2A (PP2A) and protein phosphatase 2B. PP2A is the enzyme most closely associated with the tau protein. Sodium selenate is an agonist that stabilizes the tau complex with PP2A [5].

Tau aggregation inhibitors; Tau aggregation leads to neuronal loss. For this reason, studies are being conducted to develop tau aggregate inhibitors. PE859, which is similar to the structure of curcumin, has been shown in experiments to prevent tau aggregation and prevent nerve dysfunction. Small molecules such as rhodanines, traquinones, and quinoxalines have also been found to prevent tau aggregation [5].

A study was conducted with methylthioninium and its oxidized form was found to be more stable. The chloride salt of the oxide form is called methylene blue. TRx0237 was developed based on methylene blue. However, studies have found that it is not effective in early and mid-stage Alzheimer's [48].

Microtubule stabilizing agents; As a result of increased phosphorylation or mutations of tau protein, tau protein cannot bind to microtubules. Thus, stability and axonal transport are impaired. Therefore, it has been thought that stabilizing agents can be used in treatment. Paclitaxel has been used and it has been observed that it increases the number of microtubules and axonal transport. This situation shows that it is suitable for treatment. However, it is unclear whether it helps treatment since it cannot pass the blood-brain barrier (BBB). Epitilons can pass the BBB. It has been observed that it improves cognitive functions by stabilizing microtubules in mice without causing a toxic effect. Davunetide has been reported to reduce tau pathology and cognitive function decline in mice and increase microtubule formation [5].

D-Antioxidant treatment:

Oxidative stress causes DNA fragmentation, cell membrane damage and

neuron death in the brain. When the activity of glutamine synthetase, which is sensitive to oxidation, decreases, free radicals are formed and antioxidant activity decreases. This pathological condition is seen in Alzheimer's patients. Antioxidants with neuroprotective effects are thought to be MAO inhibitors, vitamin E, ginkgo biloba and coenzyme Q10 [52].

Monoamine oxidase (MAO) inhibitors; The focus has been on developing MAO-B inhibitors for AD. Inhibition should be selective and reversible. Being reversible is important in preventing side effects. The amount and activation of MAO-B in the brain increases in advanced ages. This abnormal increase both reduces the level of neurotransmitter substances and increases the accumulation of radicals resulting from the oxidation of neurotransmitters. The increase in radicals causes an increase in oxidative stress. These can be prevented by using MAO-B inhibitors. Selegiline is in this group [55].

Vitamin E; There is evidence that free radicals may contribute to cognitive impairment in AD. Therefore, it has been thought that vitamin E can be used as an antioxidant. However, there is no evidence that vitamin E improves cognitive functions [56].

Coenzyme Q10; It is found in the membranes of many cells in the body and is fat-soluble. It is found in reduced form near unsaturated lipids to collect free radicals. The amount of coenzyme Q10 in the body decreases with age. Studies have found that its use may be beneficial because it reduces amyloid accumulation, degeneration and neuron loss in AD [58].

Ginkgo Biloba: It has an antioxidant effect due to the flavonoids it contains and an anti-inflammatory effect due to the terpenoids. It is also effective on memory and cognition [58]. Ginkgo biloba reduces the level of intracellular reactive oxygen species by inhibiting vanilloid type 1 channels. It also reduces the death of neurons. In this way, it is thought to have a protective effect on AD [59].

E-Anti-inflammatory treatment:

In epidemiological studies, anti-inflammatory drugs have been tried because AD is less common in patients with rheumatoid arthritis and inflammation is effective in Alzheimer's pathology. Indomethacin has been observed to slow the progression of AD [31]. There are active microglial cells and cytokines around the SP and astrocytes. Interleukin-1 and IL-6 cytokines contribute to the formation of Aβ by increasing APP production. Therefore, it has been thought that anti-inflammatory

drugs may be effective [51]. It is thought that they show their effects by inhibiting the cyclooxygenase enzyme or by affecting the γ-secretase enzyme. Based on the studies, it is understood that anti-inflammatory drugs are effective when taken in middle age and have no effect after the disease occurs [58].

F-Estrogen treatment: Estrogen receptors are found in the hippocampus and cholinergic neurons. Estrogen stimulates the release of nerve growth factor (NGF) and has an antioxidant effect. It increases Ach formation by increasing ChAT activity. In the study, it was found that estrogen is beneficial for verbal memory. Estrogen studies are ongoing in Alzheimer's. However, it is not recommended to use it as a primary treatment method [50].

G-Vitamin B_{12} and Folate; Vitamin B_{12} deficiency causes homocysteine balance to be disrupted and homocysteine levels in the blood increase. Therefore, it is thought that vitamin B12 and folate supplements may be useful to reduce homocysteine levels. However, in the study, no significant effect of vitamin B_{12} supplementation was found against the deterioration seen in cognitive functions [53].

H-Statins; Statin use disrupts the production of Aβ proteins and ApoE4. It reduces the hyperphosphorylation of tau proteins with its anti-inflammatory effect. In other words, tau aggregation also decreases. Thus, it is thought that they have a positive effect in AD. Studies have shown that statin use reduces the risk of developing AD [60].

I-Rosiglitazone; Insulin is effective on memory. Since the enzyme responsible for Aβ destruction is from the same group as the enzyme that breaks down insulin, it is thought that insulin may be effective in the formation of APP and Aβ. Therefore, eliminating insulin resistance has the potential to be beneficial for AD. Studies on the potential of rosiglitazone as a treatment for AD are ongoing. [53].

J-Stem cell therapy: The aim of the treatment is to use stem cells to replace neurons lost in Alzheimer's. There are four types of stem cells that can be produced from the body. These are neural stem cells (NSCs), mesenchymal stem cells (MSCs), embryonic stem cells and induced pluripotent stem cells. MSCs differentiate into neural cell types, increase ACh levels and improve cognitive functions. They reduce Aβ formation. They prevent tau phosphorylation and Aβ-related cell death. Studies have been conducted on MSCs and no serious side effects have been observed. However, studies are still ongoing. NSCs differentiate into mature cell types in the

brain and improve learning and memory [5]. In the study, NKH was injected into the brains of mice, and the stem cells in the injection area differentiated into brain cells, 3resulting in improvements in brain functions. In this way, damaged cells were repaired, memory loss was prevented, and positive results were obtained in learning [61].

K-Treatment with vaccination; It was aimed to benefit from the immune system to reduce Aβ accumulation in the brains of Alzheimer's patients, and for this purpose, vaccines containing different fragments of Aβ were administered to the patients subcutaneously or intravenously. However, since infection developed in the brains of the patients after the vaccination, studies on vaccination are continuing [62].

L-Treatment with neurotrophic factors; Studies have been conducted on neurotrophic factors such as NGF, neurotrophin-3 and insulin-like growth factor (IGF-1). NGF receptors have been found in cholinergic neurons in the basal forebrain, and it has been shown that the life span of cholinergic neurons is extended with NGF treatment. It has been found to be effective in cognitive recovery in animal experiments. Since it cannot pass to the central nervous system when given systemically, different administration methods have been tried. When given intrathecally, it caused meningeal thickening, and when used nasally, it caused extremity pain. Gene therapies are being studied for continuous NGF release. As another way, agents that will increase the effect of NGF are being tried. These agents include AIT-082, idebenone and propentofilin. Another neurotrophic factor is IGF-1. Its effect is to protect hippocampal neurons from Aβ-induced toxicity. Experimental studies on IGF-1 are ongoing [50].

2 CONCLUSION

AD is a neurodegenerative disease seen in older individuals and its incidence is increasing worldwide due to the increasing human lifespan. The lack of a definitive treatment method is a major problem. Existing drugs improve the patient's quality of life by reducing symptoms and slowing down the progression of the disease. The basis of the disease is targeted in the development of new treatment methods. AD does not occur due to a single cause. In other words, its development is influenced by multiple factors, making it difficult to find an appropriate treatment. Another reason for the failure of the studies conducted is that it is difficult for drugs to pass through the blood-brain barrier. The lack of clinical application for hypothesis-based drugs raises questions about their

accuracy. Therefore, understanding the causes of the disease is essential for developing definitive treatments. Because for a definitive treatment, those problems must be eliminated. Therefore, the development of new treatments will be facilitated by increasing the research on the causes and mechanisms of the disease.

3 CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

4 AUTHOR CONTRIBUTIONS

Literature review: S.K., İ.Y.; Manuscript writing: S.K., İ.Y.

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