Black Sea Journal of Health Science
doi: 10.19127/bshealthscience.1064168

Open Access Journal
e-ISSN: 2619 – 90410

Review
Volume 5 - Issue 2: 322-327 / May 2022

ETIOLOGY AND HISTOPATHOLOGY OF ALZHEIMER'S DISEASE AND CURRENT APPROACHES

Fikri ERDEMCİ[1], Fırat AŞIR[1], Fatih TAŞ[2]*

[1]*Dicle University, Faculty of Medicine, Department of Histology and Embryology, 21200, Diyarbakır, Turkey*
[2]*Siirt University, Faculty of Medicine, Department of Histology and Embryology, 56100, Siirt, Turkey*

Abstract: Alzheimer's disease (AD) is a widespread kind of dementia and is one of progressive neurodegenerative diseases that leads to permanent damage to neurons. It has known that genetic and non-genetic factors play a role in the etiopathogenesis of AD. The accepted genetic factors are mutations on genetic codes especially on PSEN1, PSEN2, and APP genes. However, non-genetic factors include advanced age, exposure to occupational factors, current disorders, and lifestyle characteristics of the person. The final AD diagnosis can establish by histopathological examination of the brain after death. Pathologically, AD has two distinguishing features. Of these, beta-amyloid (Aβ) neurotic plaques are protein aggregates outside of nerve cells in the brain, whereas neurofibrillary tangles are structures found inside cells. The main component of amyloid plaques is Aβ, and the main component of neurofibrillary tangles is tau protein. Despite current therapies for Alzheimer's disease, no definitive treatment is available. Today, preventive and curative treatment approaches for the disease include cholinesterase inhibitors, neurotrophic factors, NMDA-receptor antagonists, HMG-CoA reductase inhibitors, non-steroidal anti-inflammatory drugs, estrogen replacement therapies, antioxidants, and regular sleep. Despite all these approaches for the disease, further multidisciplinary studies are needed for the definitive treatment of the disease.

Keywords: Alzheimer's disease, Dementia, Beta-amyloid, Tau protein

***Corresponding author:** Siirt University, Faculty of Medicine, Department of Histology and Embryology, 56100, Siirt, Turkey
E mail: ftas85@yahoo.com (F. TAŞ)
Fikri ERDEMCİ https://orcid.org/0000-0001-8083-0183
Fırat AŞIR https://orcid.org/0000-0002-6384-9146
Fatih TAŞ https://orcid.org/0000-0001-9817-4241

Received: January 27, 2022
Accepted: February 26, 2022
Published: May 01, 2022

Cite as: Erdemci F, Aşır F, Taş F. 2022. Etiology and histopathology of Alzheimer's disease and current approaches. BSJ Health Sci, 5(2): 322-327.

1. Introduction

Alzheimer's disease (AD) is an illness that leads to the permanent damage of neurons, primarily in the cortex and also in the hippocampus (Figure 1) (McKhann et al., 1984). It is known that this disease usually causes dementia. It is a global health problem that has severe effects on society and individuals, and the efficacy increases day by day (Lane et al., 2018). AD is recognized as a priority public health problem globally by the World Health Organization (WHO). The first case was reported by Alois Alzheimer in 1907 (Alzheimer, 1907). Since then, uncertainties still remain about the treatment of AD despite significant advances in understanding its development and histopathology (Lane et al., 2018).

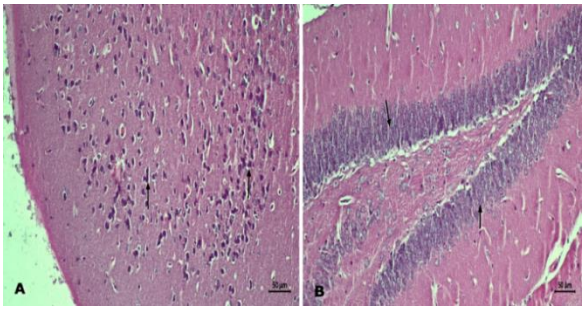

Figure 1. (A) Neuron degeneration in the cortex region of AD rat (B) Neuron degeneration in the hippocampus region of AD rat (McKhann et al., 1984).

AD, the most common of the neurodegenerative diseases, accounts for approximately two-thirds of dementia cases (this ratio varies between 42% and 81% in different studies). Neurodegenerative diseases such as diffuse Lewy body dementia, vascular disorders and Pick's disease constitute the remaining dementia cases (Aronson et al., 1991; Helmer et al., 2001). AD has rapidly become widespread and seriously threatens public health. Despite the fact women are at a somewhat higher risk than males, both women and men are particularly vulnerable to AD. The prevalence of AD rises with age. Its prevalence is about 1% for those aged 65, whereas it increases to about 40-50% for those aged 95. Although the exact etiology of the diseases is yet unknown, the start of the disease is influenced by some factors, including age and heredity (Wang and Ding, 2008).

Most people experience memory loss with age. For this reason, there is a very fine line between age-related forgetfulness and the early symptoms of AD. In order to avoid diagnosing patients with mild cognitive impairment (MCI) with AD, an MCI category was created. However, most individuals diagnosed with MCI can develop AD. AD typically manifests itself as episodic memory loss (for example, not remembering a conversation that was made a day before). In general, this is quite distinctive in AD cases compared to other individuals. Furthermore, AD can appear with difficulty

in finding words, getting lost in familiar areas, and complex behavioral changes in response to changes in the environment (Mucke, 2009).

The prevalence of AD, which is a neurodegenerative disorder, is gradually increasing worldwide with the increase in the average age of the world population. This necessitates the development of more effective innovative treatments and approaches related to the disease and much more understanding of the pathophysiological mechanisms (Mucke, 2009). The aim of this study was to explore the progression of AD from an etiological and histological standpoint, as well as current therapy and prevention options.

2. Etiology

Alzheimer's disease cause has not been completely understood today. Both hereditary and non-genetic variables are thought to have a role in the etiopathogenesis of AD. Genetic factors play a substantial impact in advancing both AD with early-onset (ADEO) and AD with late-onset (ADLO), according to epidemiological studies (Jiang et al, 2013). Studies showed that mutations in three genes (APP, PSEN1, and PSEN2) lead to AD and that the apolipoprotein E (APOE) 4 allele increases the disease risk. More AD-associated genes are being discovered as human genomic research advances. Genetic screening tests are now available for individuals who have a high potential for AD. These tests make it possible to help individuals and their families better prepare to fight AD (Wang and Ding, 2008).

More than 100 mutation types have been determined in the PSEN1, PSEN2, and APP genes for familial ADEO. In ADLO, which is more common among all, APOE gene polymorphisms have a significant effect at a cellular level and have also been associated with neuropathological conditions. Furthermore, according to recent research, these four genes account for less than 30% of Alzheimer genetic variation. According to these studies, more genetic factors should be defined (Tanzi and Bertram, 2001).

Some genetic loci have been demonstrated to cause familial AD cases. A study was examined the link AD with markers located on the long arm of chromosome 21 in 6 families suffering from ADEO. As a result, the link was confirmed, and it was revealed that the disease locus is centromeric to the D21S1/S11 locus on the long arm of the chromosome. These findings support the belief that all patients with genetic-based AD have a predisposing locus on chromosome 21 (Goate et al., 1989).

APOE4 and APOCI a located on chromosome 19 are considered risk factors for ADLO. In a study conducted with large families in which more than one individual was affected by the disease, several microsatellite markers were identified that are distant from the apolipoprotein cluster on chromosome 19 which is associated with ADLO (Poduslo ve Yin, 2001). Apart from these, the majority of familial ADEO cases (~70%) were found to be associated with mutations in two genes, Presenilin 1 and Presenilin 2, located on chromosomes 1 and 14 (Sherrington et al., 1995). Also, one of the most important vulnerable AD hereditary genes is the BIN1 (amphiphysin 2/AMPH2) (Bertram et al., 2007).

PICALM is another gene locus linked with AD. PICALM is expressed almost ubiquitously. It is recognizable with expression in all neurons and shows no selectivity in pre and postsynaptic structures. Similar to BIN1, the PICALM protein was reported to be taken charge in clathrin-mediated endocytosis (CME), which has an important place in the intracellular exchange of proteins and lipids (Tebar et al., 1999; Yao et al., 2005).

Aside from genetic factors, various factors can be effective on AD. One of the factors of AD is occupational exposure (pesticides, electromagnetic fields, organic solvents, volatile anesthetics, etc.). The other one is existing diseases in individuals. Some of these diseases are cerebrovascular and chronic diseases like hypertension, diabetes, or dyslipidemia. Also, traumatic brain injury, psychological problems, cancer, and other diseases can affect AD. And, also the lifestyle of the patients can affect AD prognosis. Lifestyle can be linked with addictions like coffee, high body mass index, smoking, alcohol, low physical activity, and lower cognition. These factors may provide various possibilities for the prevention or handling of AD (Jiang et al., 2013). Apart from these factors, previous head traumas were reported to increase the risk of AD by approximately 15% (Graves et al., 1990).

Age can be shown as the most significant risk factor for AD (Stern et al., 1987). Even in AD patients who are hereditarily susceptible, the disease generally occurs after middle age. Therefore, regardless of genetic susceptibility, age is considered a major factor for AD, strongly supporting the idea that an age-related process plays a role in disease development. Aging is a serious risk factor not only for AD but also for many chronic diseases such as atherosclerosis, arthritis, cancer, emphysema and other neurodegenerative diseases (Castellani et al., 2010).

The prevalence of AD substantially increases between the ages of 65 and 85.2 (Sloane et al., 2002). Older individuals have enlarged cerebral ventricles and sulcus with a lower brain weight and reduced volume (Skullerand, 1985). Aging causes loss of neuron cells in the neocortical and hippocampal regions, suboptimal DNA repair, deterioration of neuron integrity, and a decrease in synaptic density (Simic et al., 1997). Therefore, since age is directly associated with brain atrophy, it is thought that the risk of AD increases with age (Raz et al., 2004). In AD, atrophy occurs in the allocortex and limbic regions of the mesial temporal lobe (Pearson et al., 1985; Bolatlı, 2021). It was demonstrated that hippocampal volume decreases approximately 4-6% per year in AD (Jack et al., 2000).

With normal aging, plaques and tangles accumulate in the cerebral cortex, being a feature of normal aging (Morris, 1991). However, the amount of these plaques

and tangles is much less in the brains of clinically normal individuals than in the brains of Alzheimer's patients. This has led to the development of two hypotheses. The first one is that everyone will have AD if they live long enough. The second is that the age of onset of AD in individuals is determined by genetic and environmental factors (Lendon et al., 1997).

3. Histopathology and Other Diagnostic Approaches

The final diagnosis of AD can be established by histopathological investigation of the brain after death. With various techniques developed today, patients can be diagnosed with AD while alive with 95% accuracy. Patient histories carefully taken from patients and their families, neuropsychological tests, and evaluation of cognitive function are extremely important in diagnosis. In addition, other causes of dementia such as thyroid dysfunction, low vitamin levels, various infections, cancers, and depression should be excluded during diagnosis. It is also extremely important to distinguish AD from neurodegenerative diseases such as Lewy body dementia, frontotemporal dementia and Creutzfeldt-Jakob disease (Mucke, 2009).

Cerebrospinal fluid (CSF) testing and brain imaging techniques help distinguish AD from other neurodegenerative dementias. CSF abnormalities have been seen in AD individuals at a lower level of Aβ peptides with higher tau protein levels. Moreover, magnetic resonance images of Alzheimer's patient's revealed retraction in the brain related to learning and memory regions. In addition, with decreased glucose metabolism, there is an increase in the uptake of radioligands that detect abnormal protein accumulations (amyloid) in positron emission tomography screenings (Mucke, 2009).

The clinically distinctive features of AD include severe impairments in memory, reasoning ability, decision-making, orientation to the physical environment, and speech. Also, histopathologically, Alzheimer's patients have a loss of neurons, neurofibrillary tangles, and senile plaques containing extracellular Aβ. Besides, a hyperphosphorylated form of microtubular protein tau is also encountered (Clark, 1998).

Pathologically, AD has two distinctive features, which have a toxic effect on nerve cells and consist of abnormal proteins. Of these, Aβ neuritic plaques are protein aggregates outside nerve cells in the brain, whereas neurofibrillary tangles are found inside cells (Clark, 1998; Hutton et al., 1998). Figure 2 shows the image of amyloid plaques in the brain parenchyma. Molecular studies showed that the main component of amyloid plaques is Aβ and the main component of neurofibrillary tangles is tau protein (Saka, 2010). These abnormal proteins cause toxic effects on nerve cells, damaging their functions and eventually causing cell death. This can cause memory loss, behavioral disorders, decreased thinking ability, brain dysfunctions, and eventually death (Wang and Ding, 2008).

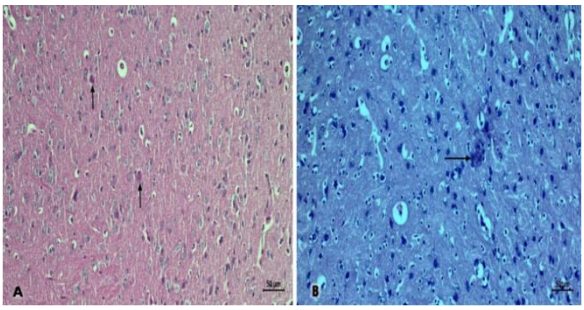

Figure 2. AD rat brain parenchyma images are shown in A and B. Amyloid beta (Aβ) is shown with arrows.

Confusion, agitation, and hallucination, which are common symptoms of AD, are important in diagnosis (Pinsky et al., 2001). Alzheimer's patients generally die from illnesses such as pneumonia, malnutrition, infection and heart failure. Although the average life expectancy of the disease after diagnosis is between 8 and 10 years, this process can be either short, like one year or, long as 25 years. Additionally, the disease leads to a great cost both socially and economically (Ernst and Hay, 1994; Koppel, 2002).

4. Treatment and Prevention

Despite current therapies for AD, it is not possible to terminate its progression. The disease, which manifests itself with insidious memory impairment, continues over time with disorientation, decreased reasoning ability, speech abnormalities, and apraxia. The ability of individuals with the disease for self-care disappears over time. Most of these patients live their end stages bedridden as vegetative and with sacral decubitus due to aggressive treatments they receive. The cause of death of most patients who have already lost many of their functions is pneumonia (Castellani et al., 2010).

Cholinergic synapses are found in every region of the central nervous system in humans. Their concentrations are extremely high in the striatum, thalamus, limbic system, and neocortex. This suggests that cholinergic transfer may have critical importance for other brain functions, especially memory, learning, and attention. The cholinergic system has a significant role in studies on both normal cognitive and age-related cognitive decay in AD and other dementias (Hampel et al., 2018).

The well-accepted therapeutic method in AD is based on the principle of restoring cholinergic function using compounds that block enzymes that break down acetylcholine. Cholinesterase inhibitors, which are designed to maintain activation of cholinergic synapses by preventing the breakdown of acetylcholine, are generally considered a symptomatic treatment for AD (Lovestone and Howard, 1995; Massoud and Gauthier 2010). Even though the fact that clinical evidence and guidelines support the using cholinesterase inhibitors at all levels of AD, these drugs are generally considered

ineffective and underutilized in the treatment of AD (Maneno et al., 2006).

Neurotrophic factors (NTFs) are multi-directional proteins that are involved in the development, survival, and function of certain neurons. Generally, axonal transport is crucial because not all NTFs are synthesized at the reaction site. For example, basal forebrain cholinergic neurons take the Nerve growth factor (NGF), which is produced in the neocortex or hippocampus by retrograde transport. Alzheimer's disease and other neurodegenerative dementias are associated with defects in axonal transport. These diseases are also associated with unevenly distributed NTFs (Schindowski, 2008).

Brain-derived neurotrophic factor (BDNF) involves in memory formation, cognition, and learning through maintaining synaptic plasticity. Therefore, BDNF is considered an essential substance in dementia and neurodegenerative diseases (Patapoutian, 2001). BDNF contributes to the survival of cholinergic neurons along with their function. In a study, BDNF was shown to be synthesized in the basal forebrain by using real-time reverse transcription polymerase chain reaction (RT-PCR) and known BDNF provides a source for cholinergic neurons. The cortex and hippocampus cholinergic neurons in patients with AD have lower BDNF, mRNAs, and protein levels (Fahnestock et al., 2002). It is known that neurotrophic factors have critical roles in advancing the nervous system. These factors are considered suitable drug candidates to manage many neurodegenerative diseases. Neurotrophic factors have a severe potential for survival and increase the functioning of neurons of the peripheral nervous system and central nervous systems (Weissmiller and Wu, 2012).

N-methyl-D-aspartate (NMDA) receptor-mediated glutamate excitotoxicity has an important role in neuronal death. Therefore, it is hypothesized that NMDA receptors may be an important target for inhibiting the progression of AD. Studies showed that memantine (1-amino-3, 5-dimethyladamantane), an NMDA-receptor antagonist, has therapeutic effects in AD (Sonkusare et al., 2005). However, memantine is also demonstrated as having benefits in central nervous system disorders such as Parkinson's disease, strokes, epilepsy, and Amyotrophic lateral sclerosis (ALS) (Jain, 2000; Olivares et al., 2012).

Studies showed that there is an association between the neurofibrillary pathology of AD and cholesterol metabolism. Cholesterol and its transport maintain amyloid plaques production and hyperphosphorylation of the tau in the brain. Furthermore, these studies revealed that aside from AD, cholesterol metabolism contributes to intracranial vascular diseases and cerebral ischemia (Kandiah and Feldman, 2009). Statins catalyze the rate-limiting step during cholesterol biosynthesis. Thus, it inhibits HMG-CoA reductase, one of the enzymes in the pathogenesis of AD. This link between cholesterol and AD shows that lipid-lowering agents, especially namely statins which are HMG-CoA reductase inhibitors may have a curative effect in preventing and treating AD (Jick et al., 2000; Rockwood et al., 2002).

Microglial cells are among the glial cells, and they play a crucial role in repairing central nervous system (CNS) damages. On the pathological state of AD, Aβ peptides and various proinflammatory factors can activate microglia, causing the secretion of various inflammatory factors and neurotoxins. Thus, Aβ peptides trigger AD by causing neuronal damage and even more apoptosis. On the other hand, microglia's phagocytizing Aβ protects the CNS by slowing down AD development (Li et al., 2021).

Nonsteroidal anti-inflammatory drug (NSAID) therapy reduces the possibility of advancing AD. NSAID is characterized by a microglia-mediated inflammatory response due to intense amyloid accumulation in the brain. However, the basis of these effects is not fully known (Yan et al., 2003). Some studies stated that such treatment methods like glucocorticoids and NSAID treatments are beneficial in preventing or ameliorating AD (Breitner et al., 1996).

It has been predicted that estrogen may involve in the pathophysiology of AD. There are three different mechanisms for estrogen; stimulation of neural cells and glias, improvement of cerebral blood flow, and interaction with genetic factors (Van Duijn, 1999). In addition, replacement therapy with estrogen has a protective effect on AD has been reported by some investigators (Henderson et al., 1994; Kawas et al., 1997), whereas some studies mentioned that this effect is controversial (Graves et al., 1990; Van Duijn et al., 1996). Estrogen replacement therapy methods with long-term and low-dose provided some benefits. These were improved everyday activities, cognitive functions, and symptoms of dementia in mild and moderate AD women (Ohkura et al., 1995).

Alzheimer's patient's brains have been shown to have oxidative damage in studies. Toxic substances caused by oxidative stress play a critical role in the activation of cellular signaling pathways that support the formation and development of lesions (Feng and Wang, 2012). Therefore, it is stated that antioxidant treatments will be beneficial in slowing down the progression of both cognitive and functional loss caused by oxidative stress in AD (Grundman and Delaney, 2002).

In a critical organ like the brain that does not have a lymphatic system, there is a need for an alternative mechanism that eliminates toxic substances that accumulate over time. This mechanism is called the 'glymphatic system'. The glymphatic system is the removal of waste materials accumulated in the cerebral interstitial fluid from the brain parenchyma through the cerebrospinal fluid and astrocytic aquaporin-4 channels. Accordingly, it can be said that the glymphatic system plays a significant role in the removal of toxic molecules that accumulate over time in the CNS (Taş and Erdoğan, 2020). Studies showed that the activity of the glymphatic system is higher in the sleep state than in the awake period (Chong et al., 2022). In another study, it was

stated that the melatonin hormone might also support the functioning of the glymphatic system. Therefore, regular sleep in a dark environment is thought to be preventive in terms of the development of neurodegenerative diseases, especially AD, by increasing the efficiency of the glymphatic system (Taş and Erdoğan, 2020).

There are some manifestations that homocysteine-associated vitamins, alcohols and fats play a role in the pathogenesis of AD. Certain epidemiological examinations showed that individuals who include high amounts of antioxidants (Zandi et al., 2004), vitamins B6 and B12, folate (Snowdon et al., 2000), unsaturated fatty acids, and fish in their diets have a lower risk of progress of AD (Morris et al., 2003). Additionally, a number of studies demonstrated that the Mediterranean diet minimizes the risk for this disease (Trichopoulos, 2004). However, the evidence presented is not consistent enough, and more comprehensive studies are required to support them.

5. Conclusion

Despite studies on AD, epidemiological research with bigger samples is required for the etiology, histopathology, and treatment of this disease. The cause of ADEO is mostly genetic-based, whereas genetic factors and age take place on the basis of ADLO. In addition, the relationship between the disease's familial and nonheritable risk factors should be further investigated, and public health organizations that will aim to eliminate non-genetic risk factors should be developed. The main histopathological symptoms of the disease include Aβ plaques and neurofibrillary tangles; however, studies on other histopathological symptoms for the diagnosis of the disease should be continued. Finally, although studies on various preventive, retarding, and curative treatment approaches are continuing, there is no definitive treatment for the disease yet, making future multidisciplinary studies extremely important.

Author Contributions

All authors have equal contribution and all authors read and approved the final manuscript.

Conflict of Interest

The authors declare that there is no conflict of interest.

References

Alzheimer A. 1907. Uber eine eigenartige Erkrankung der Hirnrinde. Allg. Zeitschrife Psychiatr, 64: 146-148.

Aronson MK, Ooi WL, Geva DL, Masur D, Blau A, Frishman W. 1991. Dementia: age-dependent incidence, prevalence, and mortality in the old old. Arch Internal Medic, 151(5): 989-992.

Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. 2007. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. Nat Genet, 39: 17-23.

Bolatlı G. 2021. Limbik Sistem. In: Taş F (ed) Nörobilim Alanında Multidisipliner Yaklaşımlar. İksad Publications, Ankara, Turkey, pp: 182.

Breitner MD, MPH JC. 1996. The role of anti-inflammatory drugs in the prevention and treatment of Alzheimer's disease. Annual Rev Medic, 47(1): 401-411.

Castellani RJ, Rolston RK, Smith MA. 2010. Alzheimer disease. Disease-a-month, 56(9): 484-546.

Chong PL, Garic D, Shen MD, Lundgaard I, Schwichtenberg AJ. 2022. Sleep, cerebrospinal fluid, and the glymphatic system: A systematic review. Sleep Medic Rev, 61: 101572.

Clark CM, Ewbank D, Lee VM-Y, Trojanowski JQ. 1998. Molecular pathology of Alzheimer's disease: neuronal cytoskeletal abnormalities. In: Growdon JH, Rossor MN (eds) The dementias Vol 19 of Blue books of practical neurology. Butterworth–Heinemann, Boston, US, pp: 304.

Ernst RL, Hay JW. 1994. The U.S. economic and social costs of Alzheimer's disease revisited. Am J Pub Health, 84(8): 1261-1264.

Fahnestock M, Garzon D, Holsinger RMD, Michalski B. 2002. Neurotrophic factors and Alzheimer's disease: are we focusing on the wrong molecule? In Ageing and Dementia Current and Future Concepts. Springer, Vienna, Austria, pp: 252.

Feng Y, Wang X. 2012. Antioxidant therapies for Alzheimer's disease. Oxidative Medic Cell Longev, 2012: 472932.

Goate A, Owen M, James L, Mullan M, Rossor M, Haynes A, Hardy J. 1989. Predisposing locus for Alzheimer's disease on chromosome 21. The Lancet, 333(8634): 352-355.

Graves AB, White E, Koepsell TD, Reifler BV, Van Belle G, Larson EB. 1990. The association between head trauma and Alzheimer's disease. Am J Epidemiol, 131(3): 491-501.

Grundman M, Delaney P. 2002. Antioxidant strategies for Alzheimer's disease. Proc Nutri Soc, 61(2): 191-202.

Hampel H, Mesulam MM, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, Khachaturian ZS. 2018. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain, 141(7): 1917-1933.

Helmer C, Joly P, Letenneur L, Commenges D, Dartigues JF. 2001. Mortality with dementia: results from a French prospective community-based cohort. American J Epidemiol, 154(7): 642-648.

Henderson VW, Paganini-Hill A, Emanuel CK. 1994. Estrogen replacement therapy in older women. Comparisons between Alzheimer's disease cases and nondemented control subjects. Arch Neurol, 51: 896-900.

Hutton M, Perez-Tur J, Hardy J. 1998. Genetics of Alzheimer's disease. Essays Biochem, 33: 117-131.

Jack CR, Petersen RC, Xu Y. 2000. Rates of hippocampal atrophy correlate with change in clinical status in aging and AD. Neurol, 55(4): 484-489.

Jain KK. 2000. Evaluation of memantine for neuroprotection in dementia. Expert Ppinion Investig Drugs, 9(6): 1397-1406.

Jiang T, Yu JT, Tian Y, Tan L. 2013. Epidemiology and etiology of Alzheimer's disease: from genetic to non-genetic factors. Current Alzheimer Res, 10(8): 852-867.

Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. 2000. Statins and the risk of dementia. The Lancet, 356(9242): 1627–1631.

Kandiah N, Feldman HH. 2009. Therapeutic potential of statins in Alzheimer's disease. J Neurol Sci, 283(1-2): 230-234.

Kawas C, Resnick S, Morrison A. 1997. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore longitudinal study of aging. Neurol, 48(6): 1517–1521.

Koppel R. 2002. Alzheimer's disease: The Costs to U.S.

Businesses in 2002. URL: http://www.alz.org/Media/newsreleases/current/062602ADCosts.pdf (access date: January 03, 2022).

Lane CA, Hardy J, Schott JM. 2018. Alzheimer's disease. European J Neurol, 25(1): 59–70.

Lendon CL, Ashall F, Goate AM. 1997. Exploring the etiology of Alzheimer disease using molecular genetics. Jama, 277(10): 825-831.

Li Q, Wu Y, Chen J, Xuan A, Wang X. 2021. Microglia and immunotherapy in Alzheimer's disease. Acta Neurologica Scandinavica, 145(3): 273-278.

Lovestone S, Howard R. 1995. Alzheimer's disease: a treatment in sight? J Neurol Neurosurg Psychiatry, 59(6): 566-567.

Maneno MK, Lee E, Wutoh AK, Zuckerman IH, Jackson P, Lombardo FA. 2006. National patterns of dementia treatment among elderly ambulatory patients. J Natl Med Assoc, 98(3): 430-435.

Massoud F, Gauthier S. 2010. Update on the pharmacological treatment of Alzheimer's disease. Curr Neuropharmacol, 8(1): 69-80.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. 1984. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurol, 34(7): 939-939.

Morris JC. 1991. The neurology of aging: normal versus pathologic change. Geriatrics, 46(8): 47-54.

Morris MC, Evans DA, Bienias JL. 2003. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol, 60(7): 940-946.

Mucke L. 2009. Alzheimer's disease. Nature, 461(7266): 895-897.

Ohkura T, Isse K, Akazawa K. 1995. Long-term estrogen replacement therapy in female patients with dementia of the Alzheimer type: 7 case reports. Dementia, 6(2): 99-107.

Olivares D, Deshpande V, Shi Y, Lahiri D, Greig N, Rogers J, Huang X. 2012. N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. Current Alzheimer Res, 9(6): 746-758.

Patapoutian A, Reichardt LF. 2001. Trk receptors: mediators ofneurotrophin action. Curr Opin Neurobiol, 11(3): 272-280.

Pearson RCA, Esiri MM, Hiorns RW, Wilcock GK, Powell TPS. 1985. Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer's disease. Proc Natl Acad Sci USA, 82(13): 4531-4534.

Pinsky LE, Burke W, Bird TD. 2001. Why should primary care physicians know about the genetics of dementia? West J Med, 175(6): 412-416.

Poduslo SE, Yin X. 2001. A new locus on chromosome 19 linked with late-onset Alzheimer's disease. Neurorep, 12(17): 3759-3761.

Raz N, Rodrigue KM, Head D, Kennedy KM, Acker JD. 2004. Differential aging of the medial temporal lobe: a study of a five-year change. Neurol, 62(3): 433-438.

Rockwood K, Kirkland S, Hogan DB, MacKnight C, Merry H, Verreault R. 2002. Use of lipid-lowering agents, indication bias, and the risk of dementia in community dwelling elderly people. Arch Neurol Feb, 59(2): 223-227.

Saka, E. 2010. Alzheimer Hastalığı Patofizyolojisi: Deneysel ve Genetik Bulgular. Turkish J Geriatrics, 3: 21-26.

Schindowski K, Belarbi K, Buee L. 2008. Neurotrophic factors in Alzheimer's disease: role of axonal transport. Genes, brain and behavior, 7(1): 43-56.

Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M. 1995. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. Nature, 375(6534): 754-760.

Simic G, Kostovic I, Winblad B, Bogdanovic N. 1997. Volume and number of neurons of the human hippocampal formation in normal aging and Alzheimer's disease. J Comp Neurol, 379(4): 482-494.

Skullerand K. 1985. Variations in the size of the human brain: influence of age, sex, body length, body mass index, alcoholism, Alzheimer changes, and cerebral atherosclerosis. Acta Neurol Scand Suppl, 102: 1-94.

Sloane PD, Zimmerman S, Suchindran C. 2002. The public health impact of Alzheimer's disease, 2000 –2050: potential implication of treatment advances. Annu Rev Public Health, 23(1): 213-231.

Snowdon DA, Tully CL, Smith CD. 2000. Serum folate and the severity of atrophy of the neocortex in Alzheimer disease: findings from the Nun study. Am J Clin Nutr, 71(4): 993-998.

Sonkusare SK, Kaul CL, Ramarao P. 2005. Dementia of Alzheimer's disease and other neurodegenerative disorders—memantine, a new hope. Pharm Res, 51(1): 1-17.

Stern Y, Mayeux R, Sano M, Hauser WA, Bush T. 1987. Predictors of disease course in patients with probable Alzheimer's disease. Neurol, 37(10): 1649-1653.

Tanzi RE, Bertram L. 2001. New frontiers in Alzheimer's disease genetics. Neuron, 32(2): 181-184.

Taş F, Erdoğan E. 2020. Sıçan ependim hücrelerinde aquaporin 4 kanallarının immünohistokimyasal dağılımı ve glimfatik sisteme etkisi. Ahi Evran Medic J, 4(2): 41-46.

Tebar F, Bohlander SK, Sorkin A. 1999. Clathrin assembly lymphoid myeloid leukemia (CALM) protein: localization in endocytic-coated pits, interactions with clathrin, and the impact of overexpression on clathrin-mediated traffic. Mol Biol Cell, 10(8): 2687-2702.

Trichopoulos D, Lagiou P. 2004. Mediterranean diet and cardiovascular epidemiology. Eur J Epidemiol, 19(1): 7-8.

Van Duijn CM, Meijer H, Witteman JCM. 1996. Estrogen, apolipoprotein E and the risk of Alzheimer's disease. Neurobiol Ageing, 17: 79.

Van Duijn CM. 1999. Hormone replacement therapy and Alzheimer's disease. Maturitas, 31(3): 201-205.

Wang XP, Ding HL. 2008. Alzheimer's disease: epidemiology, genetics, and beyond. Neurosci Bul, 24(2): 105-109.

Weissmiller AM, Wu C. 2012. Current advances in using neurotrophic factors to treat neurodegenerative disorders. Translational Neurodegeneration, 1(1): 1-9.

Yan Q, Zhang J, Liu H, Babu-Khan S, Vassar R, Biere AL, Landreth G. 2003. Anti-inflammatory drug therapy alters β-amyloid processing and deposition in an animal model of Alzheimer's disease. J Neurosci, 23(20): 7504-7509.

Yao PJ, Petralia RS, Bushlin I, Wang Y, Furukawa K. 2005. Synaptic distribution of the endocytic accessory proteins AP180 and CALM. J Comp Neurol, 481(1): 58-69.

Zandi PP, Anthony JC, Khachaturian AS. 2004. Reduced risk of Alzheimer disease in users of antioxidant vitamin supplements: The Cache County Study. Arch Neurol, 61(1): 82-88.