

# Diagnosis and Treatment of Alzheimer's Disease: The Original Article

Iman Seifi<sup>1</sup>, Hemin Ashayeri<sup>2</sup>, Daryanaz Shojaei<sup>3</sup>, Alireza Bahmani<sup>4</sup>, Zeinab Seraj<sup>5\*</sup>

<sup>1</sup>Department of Nursing, Master's in Pediatric Nursing, Yasuj University of Medical Sciences, Yasuj, Iran

Email: [i.seyfi313@gmail.com](mailto:i.seyfi313@gmail.com)

<sup>2</sup>Faculty of Medicine, Tehran Medical Sciences Branch, Islamic Azad university, Tehran, Iran

Email: [Hemin.Ashayeri@gmail.com](mailto:Hemin.Ashayeri@gmail.com)

<sup>3</sup>MD, Specialist in Anesthesiology, Graduated from Arak university, Tehran, Iran

Email: [daryanazshojaei@yahoo.com](mailto:daryanazshojaei@yahoo.com)

<sup>4</sup>Department of Emergency Medicine, Khatam Al Anbia Hospital, Zahedan university of Medical sciences, Zahedan, Iran

Email: [drbahmani@yahoo.com](mailto:drbahmani@yahoo.com)

<sup>5</sup>Masters Student in Geriatric Nursing, Faculty of Nursing and Midwifery, Golestan university of Medical Sciences, Gorgan, Iran

Email: [serajzynb@gmail.com](mailto:serajzynb@gmail.com)

\*Corresponding Author: Zeinab Seraj

\*Corresponder Email: [serajzynb@gmail.com](mailto:serajzynb@gmail.com)

## Abstract

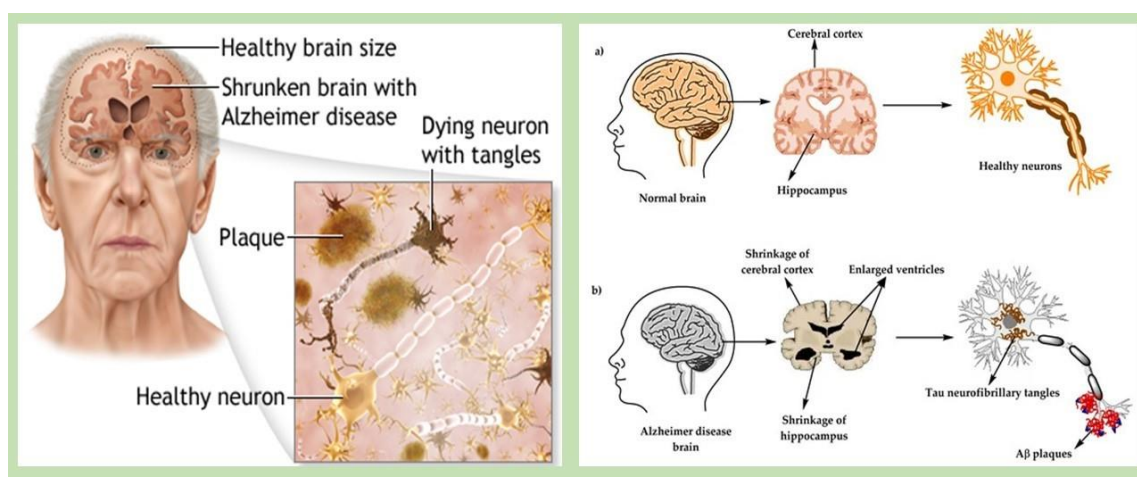
The real cause of this disease is still unknown, no one knows exactly why some people get it and some survive. Almost 10% of people over the age of 60 have dementia, and about half of them have Alzheimer's disease. Alzheimer's is a genetically heterogeneous disease that can be seen in all races. 5% of patients have familial disease with early onset, 15-20% have familial disease with late onset, 75% have isolated disease. 10% of familial Alzheimer's cases show autosomal dominant inheritance and the rest show multifactorial inheritance. The most important cognitive findings of Alzheimer's disease are the deposition of two filament proteins of beta-amyloid tau peptide in the brain. Beta-amyloid peptide, which is formed from the protein encoded by one of the genes predisposing to familial Alzheimer's disease, is found in amyloid plaques or aging in the extracellular space of the brain of Alzheimer's patients. Amyloid plaques contain other proteins besides beta amyloid. including Apo lipoprotein E, which is encoded by a type of gene that predisposes to Alzheimer's disease (APOE). Hyper phosphorylated forms of tau protein (TAU) form neurofibrillary tangles, unlike amyloid plaques, found inside Alzheimer's neurons. Tau is a microtubule-related protein that is abundantly expressed in brain neurons. This protein strengthens the accumulation and stability of microtubules, which is reduced due to phosphorylation. The formation of tangles and tau neurofibrillation is apparently one of the causes of neuronal transformation in Alzheimer's disease.

**Key words:** Alzheimer's, Amyloid Plaques, Neurofibrillary Tangles, Family Disease.

## Introduction

Some scientists believe that "what is the cause of Alzheimer's" is not important because in the end it is the oxidative damage that affects the brain due to time and plays a role in causing this disease [1-3]. When the body burns oxygen to produce energy, this process produces unstable molecules known as free radicals [4-6]. These unstable molecules steal electrons from healthy molecules in the body, to balance themselves, and in this way they harm all the cells of the body, including the brain cells [7]. Air pollution, cigarette smoke, alcohol consumption are factors that cause free radicals. Diagnosis of Alzheimer's disease from other brain disorders. It is done in an elimination method (because some of these disorders can be treated), so first the neurologist tries to determine the type of disorder and excludes all other factors that may cause the symptoms of Alzheimer's disease: Depression disease, secondary effect of drugs in interaction with other drugs, lack of vitamins, hormonal and metabolic disorders, diseases caused by alcoholism; Also, diseases that affect the center of the nervous system. Such as infection caused by syphilis, Parkinson's disease, Huntington's disease, cerebral glands and increased cranial water with natural water. Each of these diseases has symptoms that may mislead the doctor in diagnosis [8-10]. When the doctor is sure that the brain disorder of his disease (Figure 1) is not caused by any of the above diseases, he orders a complete physical examination [11-13].

This work includes electrocardiogram, blood count, measurement of electrolytes, liver and thyroid tests, searching for possible syphilis infection, calculating the sedimentation rate of the blood, the concentration of drugs and the patient's blood [14].



**Figure 1. Alzheimer disease**

In addition, the doctor orders an electroencephalogram, a CT scan and an MRI of the lungs to detect the possibility of vascular insufficiency. If after this careful examination, the doctor suspects the existence of Alzheimer's disease, he sends the patient for a psychiatric examination, neurological examination, and psychological tests and psychological tests. The differential diagnosis of

Alzheimer's disease is made, in particular, through the examination of all psychological tests to reveal a decrease in the higher functions of the brain; But these tests are really valuable when the patient is in the early stages of the disease [15-17]. Sometimes, the patient's close relatives ignore some of his behaviors, which causes them to notice the disease too late and go to the doctor when it is already too late and the disease has progressed a lot [18-20]. Due to the fact that the cause, mode of occurrence and procedure of occurrence of brain lesions in Alzheimer's disease are still unknown despite the progress of scientific research. Currently, there is no specific medicine to treat this disease or stop brain disorders caused by it. However, some symptoms of this disease such as insomnia, restlessness, aggressiveness, nervousness, depression and anxiety can be treated with medication.

#### **The first symptoms of Alzheimer's disease:**

- Forgetting recent events;
- Increasing difficulty in performing tasks that require intellectual ability, such as job duties, handling tax affairs, or managing the home [21];
- Personality changes, including the inability to control emotions and impaired judgment of the next steps;
- Difficulty doing simple tasks such as choosing clothes, or doing simple math calculations;
- Inability to recognize familiar people;
- Lack of interest in personal hygiene or appearance;
- Difficulty eating;
- Getting aggressive and denying that there is a problem at all;
- Loss of sexual continence [22];
- Getting lost on the street;
- Anxiety and insomnia prevention steps;
- Complete loss of memory, speech and muscle function (including bowel and stool control) in this case, the person needs full care and supervision;
- Extreme aggressiveness;
- They showed their childish emotions;
- Not being able to handle personal hygiene and dressing.

Elderly people who suffer from Alzheimer's disease or mild memory disorders can adapt their habits. All of us, young and old, can have a notebook and a pencil in our pocket or next to the phone and write our messages very easily [23-25]. In fact, we can carry a calendar with us and write down planned events, even daily tasks. People who suffer from memory loss can draw a line on the days that pass [26]. They can use medicines (Figure 2) whose amount is determined for each day of the week and month. Establishing a daily routine and taking help from memory aids will save many elderly people who are unable to form new memories from acute difficulties [27].

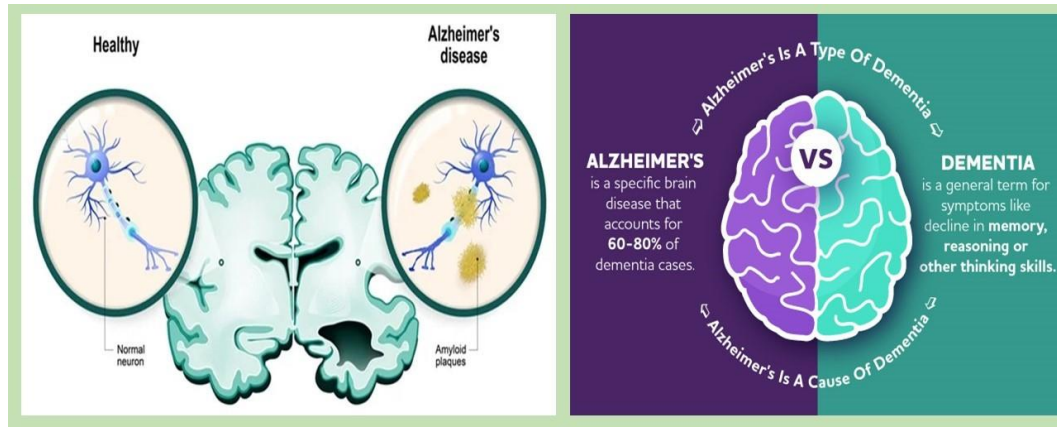


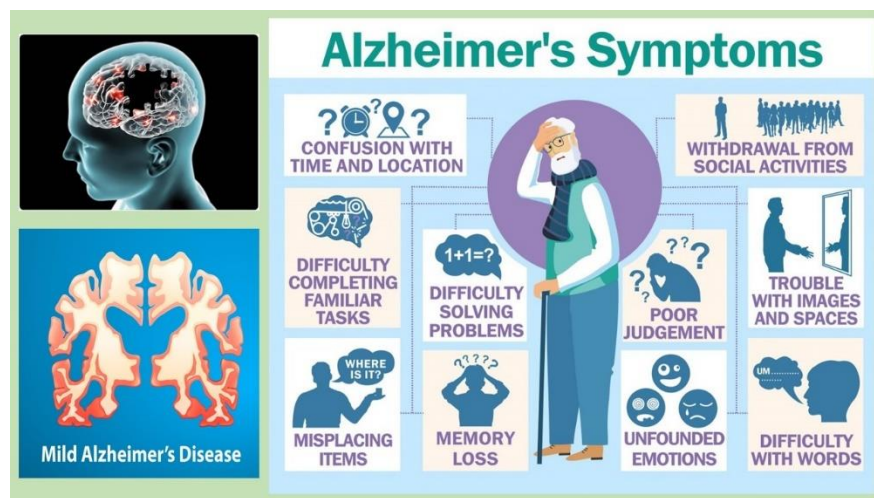
Figure 2. Overview of Alzheimer's

### Causes and agents of Alzheimer's disease

In some large families where there are many consanguineous marriages, several similar cases of Alzheimer's disease have been seen, which are of course very rare. This disease is not contagious and it is not a natural result of aging [28-30]. Men and women are equally affected by this disease, but because men die earlier than women, women make up three quarters of the patients. Alzheimer's disease is not specific to race, profession, and social or economic class, nor is it related to people's intelligence level [31]. The characteristic factor of this disease is a disorder in the concept of using objects, a disorder in performance and movements, as well as a disorder in speech. Research shows that this disease is not caused by the swelling of cerebral arteries, nor excessive fatigue, nor excessive brain activity or its inactivity [32]. In addition, emotional and mental shocks such as the death of a spouse or child, retirement, unemployment, change of residence, divorce, or severe grief are not the cause of this disease, but each of these shocks may make the existence of this disease more obvious in a person and its emergence [33-35]. However, there are several hypotheses about the cause of this disease, but the most important of them is the genetic or multi-genetic hypothesis, which seems more serious than other hypotheses. Until recently, the biochemical mechanisms of almost all neurodegenerative diseases starting in adulthood were completely unknown, one of the most common of these disorders is Alzheimer's disease, which affects about 74% of people in developed countries [36]. Alzheimer's usually manifests itself in the 7th to 9th decade of life (70 to 90 years old), but some of its forms often show symptoms earlier and sometimes even in the third decade. The clinical stages of this disease are variable. But it includes progressive deterioration of memory and higher cognitive functions such as reasoning power, plus behavioral changes. These disorders represent the transformation and destruction of nerve cells in certain areas of the cerebral cortex, especially the temporal cortex, parietal cortex, and hippocampus. You may have heard about Alzheimer's before (Figure 3), but some people don't know exactly what Alzheimer's disease is. Below is information about this disease:

- Alzheimer's is a chronic disease;

- The symptoms of this disease gradually appear in the affected person, causing damage to the brain and gradually causing destructive effects;
- There is no definitive treatment for Alzheimer's disease, however, methods are suggested to prevent the progression of the disease and improve the quality of life;
- Anyone can get Alzheimer's. However, some people are more susceptible to this disease than others. People over the age of 65, as well as people with a family history of this disease, are more susceptible to Alzheimer's than others;
- Alzheimer's and dementia are not exactly the same thing, but Alzheimer's is a type of dementia;
- The symptoms of this disease will not appear in the same way in all affected people. In some people, the symptoms of this disease appear mildly and last for a long time. While, in the other group, the symptoms progress quickly and the disease is more severe [37].



**Figure 3.** Blood tests for biomarkers and the possibility of the first disease-modifying treatment on the horizon

### Differences between dementia and Alzheimer's

The terms dementia and Alzheimer's are sometimes used interchangeably. However, these two diseases are not the same; Alzheimer's is a type of dementia. Dementia is a general term for a set of diseases with symptoms related to memory loss such as forgetfulness and confusion. This term also includes specific diseases such as Alzheimer's disease, Parkinson's disease and other brain injuries that lead to the occurrence of the mentioned symptoms. The causes of the disease, symptoms and treatment methods for these diseases are different [38-40].

### Causes and risk factors of Alzheimer's disease

Experts have not identified a specific cause of Alzheimer's disease. However, some factors that lead to the occurrence of this disease are:

- **Age.** Most people are diagnosed with Alzheimer's at the age of 65 or older [41].
- **Family history.** If you are a member of a family that has been affected by this disease before, you are more likely to develop this disease.
- **Genetics.** The presence of some genes causes Alzheimer's disease.

Having one or all of these factors does not mean getting Alzheimer's disease, these factors only increase the probability of the disease. In order to check the factors that expose you to this disease, it is better to consult a doctor [42].

### **Alzheimer's and genetics**

Although the main cause of Alzheimer's disease is not known, genetics play an important role in developing Alzheimer's disease. Apo lipoprotein E (APOE) is a gene that has attracted the attention of researchers, this gene is related to the symptoms of Alzheimer's disease in elderly people. Using a blood test, you can find out the presence of this gene in your body, which increases the chance of getting Alzheimer's [43]. Try to keep in mind that even if you have this gene, it does not mean that you are definitely infected. The opposite of this case is also true: Some people get Alzheimer's even though they don't have this gene. Other genes may also increase the chance of developing Alzheimer's [44].

### **Symptoms of Alzheimer's disease**

All humans may experience forgetfulness sometimes, but symptoms appear in people with Alzheimer's disease that worsen over time. These symptoms include memory loss that interferes with daily activities, such as forgetting appointments.

- Difficulty doing normal tasks, such as using a microwave;
- Problems occur while solving the problem;
- Difficulty speaking and writing;
- Forgetting certain times and places;
- Inability to think;
- Loss of personal hygiene;
- Mood and personality changes;
- Separation from friends, family and community [45].

### **Alzheimer's stages**

Alzheimer's is a progressive disease, in the sense that the symptoms of involvement worsen over time. This disease consists of seven stages:

- **Step 1.** At this stage, the symptoms of Alzheimer's disease are not visible, but according to the family history, this disease may be diagnosed [46].
- **Step 2.** Early onset of symptoms such as amnesia
- **Step 3.** Appearance of mild physical and mental symptoms, such as loss of memory and concentration. The occurrence of these symptoms are recognized only by people close to the affected person [47].
- **Step 4.** Alzheimer's disease is often diagnosed at this stage, although symptoms are still mild. At this stage, memory loss and inability to do daily tasks are observed.
- **Step 5.** The symptoms become more and more severe and the affected person needs care.



- **Step 6.** At this stage, a person with Alzheimer's disease needs help from others to perform basic tasks such as eating and dressing [48].
- **Step 7.** The last and most severe stage of Alzheimer's disease in which the affected person faces problems with facial expressions and speech ability.

As the disease progresses through these stages, the patient's need for a caregiver increases over time (Figure 4).

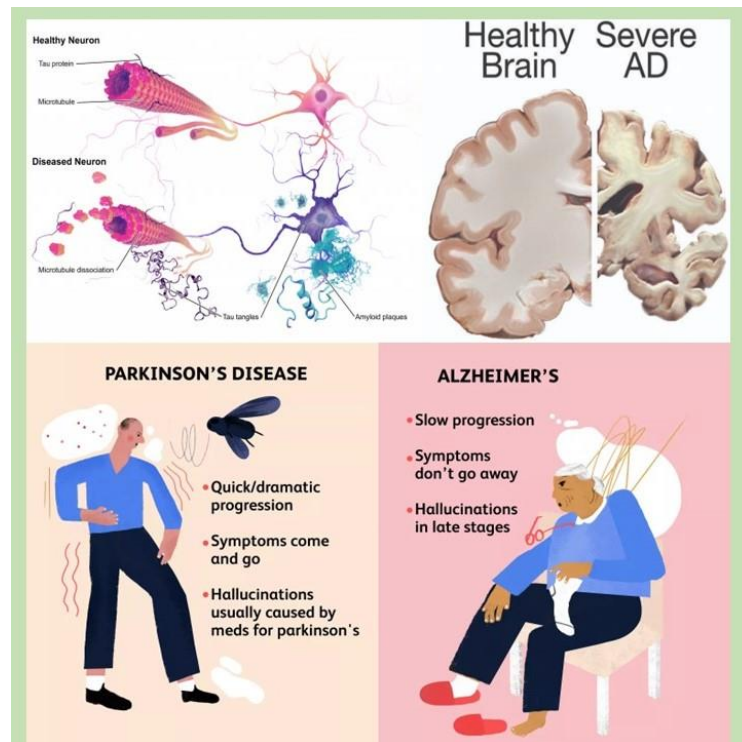


Figure 4. Alzheimer's stages

### Early onset of Alzheimer's

Alzheimer's usually affects people over 65 years old. Nevertheless, sometimes we see this disease at the age of 40 or 50; which is called early infection. This type of disease includes 5% of affected people. Symptoms of early Alzheimer's include mild forgetfulness, difficulty concentrating and performing daily tasks [49-51]. Also, it becomes difficult to find the right words and you may not feel the passage of time. The appearance of mild symptoms in vision, such as distance estimation, is sometimes inevitable. Some people are more susceptible to this disease.

### Alzheimer's disease diagnosis

The only way to diagnose Alzheimer's disease is to examine brain tissue after death. Nevertheless, the attending physician can use other treatments and tests in order to evaluate the mental ability of the patient, diagnose dementia and the possibility of other diseases. The attending physician will first ask about your medical history:

- Signs;
- Family medical history;

- Other previous and current complications of the patient;
- Medications you are currently or previously taking;
- Diet, alcohol use, or other common lifestyle habits.

### Alzheimer's trials

There is no specific test to diagnose Alzheimer's disease. However, in order to diagnose the disease, the doctor will ask you to do a series of tests. These tests may include mental, physical, neurological, and imaging tests. The attending physician will first order a psychological test. Performing this test evaluates short-term memory, long-term memory and correct orientation in time and place. Then, physical tests are performed. For example, they check your blood pressure, check your heart health, and take your temperature. In some cases, blood and urine samples will be taken from you to perform some tests in the laboratory. Your doctor may also suggest you undergo a nerve health test to check for other possibilities, such as a variety of acute medical problems including infection or stroke [52].

In these examinations, reflex and muscle power and speech are also checked. Next, the doctor may ask you to do brain imaging. Brain imaging includes the following:

- **Magnetic resonance imaging (MRI).** These images show any kind of inflammation, bleeding and structural damage.
- **Computed tomography (CT scan).** CT scan is a type of X-ray imaging that shows any abnormal features in the brain.
- **Positron emission tomography (PET).**
- **PET images** help the doctor in identifying any suspicious platelet aggregation. Platelet is a protein substance that is related to Alzheimer's disease [53].

### Drug prescription for Alzheimer's disease

Alzheimer's disease has no definitive cure. Nevertheless, the treating doctor will prescribe you medicines in order to reduce the symptoms and delay the progress of the disease. In order to treat mild Alzheimer's in the early stages of the disease, the doctor prescribes drugs such as donepezil (Aricept) or rivastigmine (Exlon). These drugs help maintain high levels of acetylcholine in the brain, which is actually a neurotransmitter that helps with memory. To treat severe Alzheimer's, your doctor may prescribe donepezil (Aricept) or memantine (Namanda). Memantine reverses the effects of excess glutamate, a chemical in the brain that is over-released in Alzheimer's patients and damages brain cells. The attending physician may also suggest you to use anti-depressant, anti-anxiety or anti-psychotic drugs to treat the symptoms associated with Alzheimer's disease. These symptoms include the following:

- Depression;
- Restlessness;
- Aggression;
- Thrill;



- Delusion.

### **Other Alzheimer's treatment methods**

In addition to drug therapy, lifestyle changes are also effective in treating the disease. For example, your doctor may suggest a series of strategies to help you and your loved ones:

- Focus on tasks;
- Avoid confrontation;
- Adequate rest during the day;
- To have peace of mind.

Some people think that taking vitamin E is effective in preventing mental illnesses, but studies show that more research is needed. Be sure to consult your doctor before taking this vitamin or other supplements; Because taking these vitamins together with other Alzheimer's drugs may cause disorders in the person [54]. In addition to lifestyle changes, there are other alternatives you can ask your doctor about.

### **Discussion**

Alzheimer's is a complex disease about which many things are still unknown. What is clear is that this disease becomes more severe over time; It is necessary to know that the proposed treatments are very successful in delaying the progression of the disease and improving the quality of life. Cholinesterase inhibitors are prescribed for mild cases of Alzheimer's disease. These drugs help to improve the symptoms and have a controlling role in some behavioral symptoms. Some examples of these drugs are: Razadine (Galantamine), Exelon (Rivastigmine) and Aricept (Donepezil) [55-57]. While other drugs improve the symptoms of the disease, the new drug of this disease called Adohelmin is the first drug that many believe, because it attacks the root of this disease and prevents its progress. This drug attacks and destroys a type of toxic protein that some believe damages nerve cells and causes dementia [58-60]. There is currently no cure for early-onset Alzheimer's disease. But health care providers have been quite successful in helping to improve mental function, control behavior and prevent disease progression. It should be noted that drugs are used to maintain the function of the mind [61].

### **Methods to prevent Alzheimer's**

So far, no guaranteed way to prevent Alzheimer's has been defined, but researchers believe that some activities can be effective in preventing Alzheimer's. According to the researchers; With a good chance, many simple daily activities and routines will delay memory loss due to Alzheimer's. Here are some ways to prevent Alzheimer's:

➤ **Doing mental exercises**

Continuous and regular reading, memorizing poetry, learning a new language, playing mental games, solving tables, learning different subjects, etc. can save memory and prevent the occurrence of Alzheimer's [62].

➤ **Doing physical exercises**

Regular exercise with moderate intensity 3 days a week for 30-45 minutes, doing yoga and meditation exercises daily, walking, cleaning the house, gardening, etc. are physical activities that can prevent the onset of Alzheimer's or to delay.

➤ **Drink enough fluids**

Since dehydration is one of the variable and effective factors in memory loss, consuming enough fluids and avoiding alcoholic beverages can be effective.

➤ **Having a healthy diet**

Use of antioxidants and vitamin C in diet. Daily consumption of fruits and vegetables, especially broad leaf vegetables such as broccoli, lettuce and spinach. Drinking apple juice daily or eating 1-2 apples a day. Weekly or monthly consumption of fish such as salmon and sardines, cooked or grilled and not fried. Some researchers introduce fish as brain food. Daily coffee drinking for middle-aged people. Also, taking some supplements like vitamin D can be effective.

➤ **Accuracy in taking medicine**

Because the combination of some medications can cause confusion, forgetfulness, or long-term memory damage, it is important that your doctor is aware of all prescription and over-the-counter medications you are taking [63].

➤ **Working on musical instruments**

Making songs and learning music increases the life of the brain. People who work with one of the music devices perform better in performing mental activities compared to others.

➤ **Socializing with others**

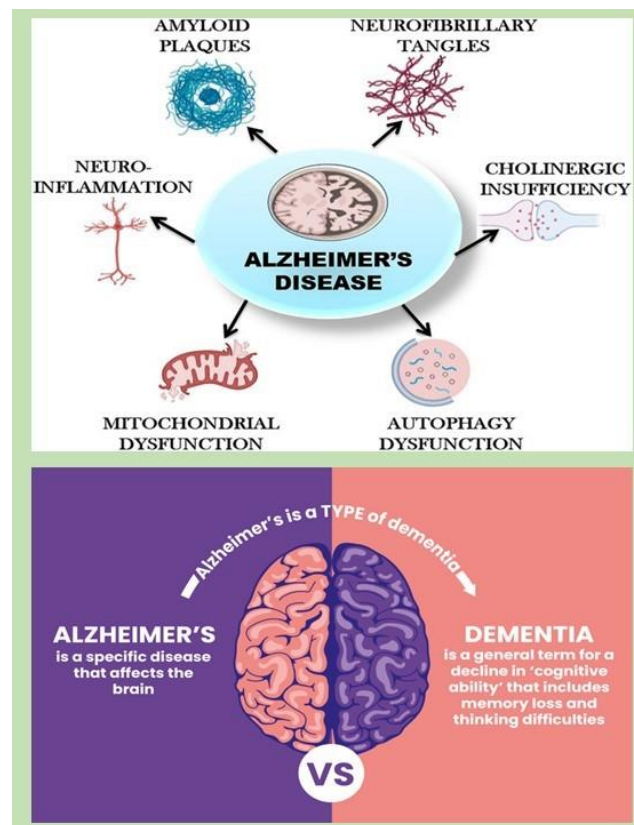
Having constant social contact, marriage, contact and friendships will keep your brain young. Our advice to you is to do hobbies that have a combination of social, physical, mental and psychological activity such as hanging out with friends in nature, playing group brain games, participating in public activities, traveling, etc [64].

➤ **Maintaining dental hygiene and avoiding infections**

Based on research at the University of Southern California, it has been determined that oral and dental diseases before the age of 35 increase the possibility of memory loss up to 4 times. Only 1-2% of Alzheimer's cases are hereditary. These cases are known as early-onset and familial Alzheimer's, which appears at a very young age and has a higher rate of progression. Early and familial onset of Alzheimer's disease can be attributed to a mutation in one of these three genes: Genes related to amyloid beta precursor protein (APP) and presenilins PSEN1 and PSEN2. Most mutations in presenilin genes increase the production of a small protein called amyloid beta, which is the main element in the formation of amyloid plaques. Some mutations only change the ratio

between amyloid-beta and other major forms (especially A $\beta$ 40) and do not change the level of amyloid-beta. Two other genes associated with genetic Alzheimer's are ABCA7 and SORL1 [65]. Most cases of Alzheimer's are not hereditary and are called sporadic Alzheimer's, which may be caused by various risk factors, including environmental and genetic factors. Most sporadic cases of Alzheimer's (Figure 5), unlike familial cases, appear at ages over 65. Less than 5% of sporadic Alzheimer's cases have early onset [66].

The strongest genetic risk factor in diffuse Alzheimer's disease is Apo lipoprotein E4 (APOE $\epsilon$ 4). This protein is one of the four alleles of Apo lipoprotein E (APOE). APOE plays a very important role in linking lipid proteins in lipoprotein particles, and the epsilon4 allele disrupts this function. Between 40 and 80% of Alzheimer's patients have at least one APOE $\epsilon$ 4 allele, which increases the risk of developing this disease up to 3 times in heterozygotes and in homozygotes. It increases up to 15 times. In Alzheimer's, like many other diseases, environmental effects and genetic factors lead to incomplete penetration [67].



**Figure 5.** The Difference Between Alzheimer's Disease & Dementia Explained

For example, in a part of the people of Nigeria, there is no correlation between APOE $\epsilon$ 4 and the occurrence of early Alzheimer's disease. Initial attempts to examine 400 genes that were thought to be related to the occurrence of sporadic Alzheimer's disease in old age did not yield much results. Genome-wide concordance studies in recent years have found 19 regions in genes that seem to affect the risk of Alzheimer's. These genes include: CASS<sub>4</sub>, CELF1, FERMT<sub>2</sub>, HLA-DRB<sub>5</sub>, INPP<sub>3D</sub>, MEF<sub>2C</sub>, NME<sub>8</sub>, PTK<sub>2B</sub>, SORL1, ZCWPW1, SLC<sub>24A4</sub>, CLU, PICALM, CR<sub>1</sub>, BIN<sub>1</sub>,

MS<sub>4</sub>A, ABCA<sub>7</sub>, EPHA1, and CD<sub>2</sub>AP. In the TREM<sub>2</sub> gene, it increases the risk of Alzheimer's by 3 to 5 times. It is thought that in some TREM<sub>2</sub> variations, the white blood cells in the brain are no longer able to control the amount of amyloid beta. Many single-nucleotide polymorphisms (SNPs) are associated with Alzheimer's disease [68].

### **Osaka leap**

A study on familial Alzheimer's disease in a Japanese family showed that there is a connection between the deletion of the 693 code of the amyloid beta precursor protein (APP) and the development of Alzheimer's. This mutation and its association with Alzheimer's were first reported in 2008 and is known as the Osaka leap. Only homozygotes with this mutation develop Alzheimer's. The Osaka mutation accelerates A $\beta$  oligomerization, but the proteins do not form amyloid fibrils and become amyloid plaques, suggesting that A $\beta$  oligomerization is the cause of Alzheimer's, not the fibrils. Laboratory mice carrying this genetic mutation all showed the typical pathology of Alzheimer's disease [69].

### **Cholinergic hypothesis**

The oldest hypothesis on which most drug treatments are based is the cholinergic hypothesis, which states that Alzheimer's is caused by a decrease in the synthesis of acetylcholine neurotransmitters. This hypothesis has failed to gain widespread scientific support because drugs prescribed to treat acetylcholine deficiency have not been very effective in Alzheimer's disease.

### **Amyloid hypothesis**

In the amyloid hypothesis (1991), it is proposed that the accumulation of extracellular amyloid beta (A $\beta$ ) is the main cause of Alzheimer's. The support of this hypothesis is the location of the gene related to the amyloid beta precursor protein on chromosome 21 and the fact that almost all people with down syndrome, who have an extra dose of the gene, show at least the initial symptoms of Alzheimer's at around 40 years old [70]. Also, a specific isoform of Apo lipoprotein (APOE<sub>4</sub>) is an important risk factor in Alzheimer's. Apo lipoprotein furosemide increases amyloid beta, but some isoforms, such as APOE<sub>4</sub>, are not very effective in doing this, causing excess amyloid to accumulate in the brain.

### **Tau hypothesis**

In Alzheimer's disease, changes in the tau protein cause the breakdown of microtubules in brain cells. The tau hypothesis suggests that tau protein abnormalities initiate the cascade of Alzheimer's disease. In this hypothesis, the tau protein undergoes hyper phosphorylation (dephosphorylation) and begins to connect with other tau protein strands and make spiral strands. Finally, neurofibrillary aggregates are formed inside nerve cells, as a result of which, the microtubule of the cell is broken down and the structure of the cell skeleton and, as a result, the individual's nerve

transmission system is destroyed [71]. In the first place, this causes a disruption in the biochemical communication between nerve cells and in the next step leads to the death of these cells.

### **Inflammation hypothesis**

In some researches, it has been pointed out that amyloid beta and tau protein staining leads to oxidative stress and as a result chronic inflammation and is related to Alzheimer's pathology. Neuroinflammation is one of the characteristics of other neurodegenerative diseases, including Parkinson's and ALS. Spirochete infections have also been linked to dementia. Sleep disorders are one of the possible risk factors for Alzheimer's disease. Previously, sleep problems were considered as a consequence of Alzheimer's disease, but research indicates that sleep disorder is one of the causes of this disease. Sleep disorders are thought to be associated with persistent inflammation. Some have suggested that chronic gum infection and gut microbiota may also play a role in Alzheimer's [72].

### **Pathophysiology**

**Neuropathology:** One of the characteristics of Alzheimer's disease is the destruction of neurons (nerve cells) and synapses in the cerebral cortex and some subcortical areas of the brain. Destruction of these cells leads to severe atrophy in the affected areas, including degeneration (degeneration) in the temporal lobe and parietal lobe, and parts of the frontal lobe and cingulate cortex. Degeneration also appears in the nuclei of the brain stem, especially in the locus ceruleus located in the pons of the brain [73]. MRI and PET scan images of people with Alzheimer's have shown that the progress of cognitive impairment in these people, along with a gradual reduction in the size of specific areas [74]. It was from their brain. In Alzheimer's brain microscopy, amyloid-beta plaques and neurofibrillary tangles are clearly visible, especially in the hippocampus. However, Alzheimer's may develop in the neocortex without neurofibrillary tangles. Amyloid-beta plaques and bodies It is hard and insoluble composed of beta amyloid peptide and cellular material outside and around nerve cells [75-77]. Neurofibrillary aggregates are the result of the condensation of tau proteins, which undergo transphosphorylation and accumulate inside the cells themselves. Although these plaques and masses are formed in the brain of many people as a result of aging, their number is more in the brain of Alzheimer's patients and they are formed in specific areas of

the brain such as the temporal lobe (Figure 6 & 7). The formation of Lewy bodies in the brain of Alzheimer's patients is also not rare [78].

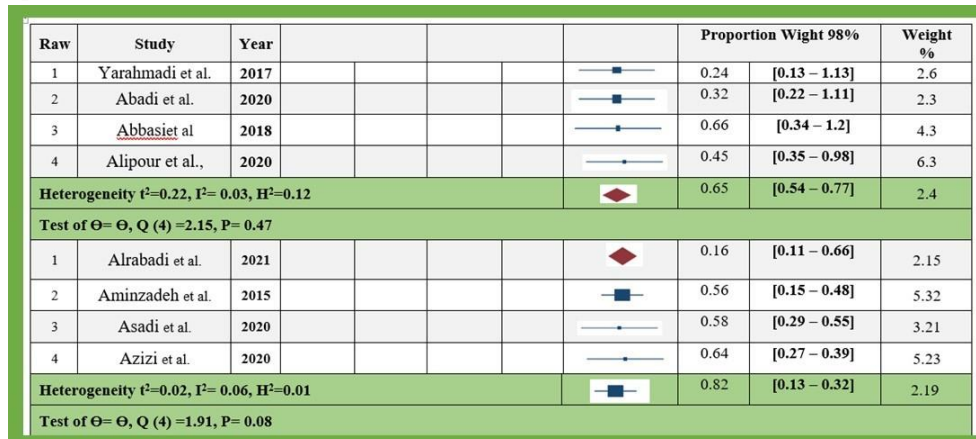


Figure 6. Forest plot showed Analysis of Alveolar Crestal Bone

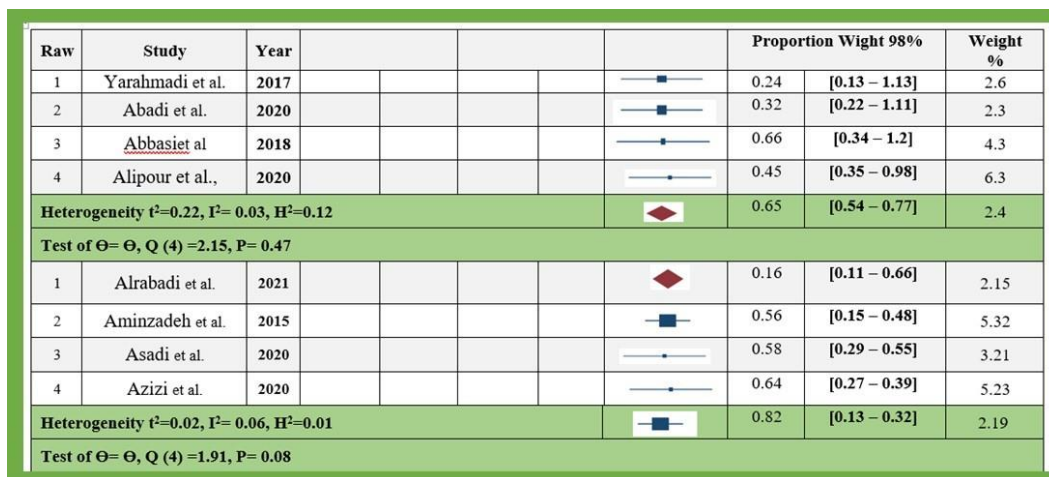


Figure 7. Forest plot showed Cantilever Base Implants Using Scientific Sources

## Biochemistry

Enzymes act on "amyloid beta precursor protein" and divide it into smaller parts. Beta amyloid fragments cause the formation of amyloid plaques, which are among the symptoms of Alzheimer's disease. Alzheimer's is known as one of the protein misfolding diseases (proteopathy) which is caused by the accumulation of folded amyloid beta proteins in the form of amyloid plaques and tau proteins in the form of neurofibrillary masses in the brain. Plaques are composed of small peptides that are 39 to 43 amino acids long and are called amyloid beta ( $A\beta$ ). Amyloid-beta is a fragment of a larger protein called amyloid-beta precursor protein (APP), which is a transgenic protein that penetrates the membrane of nerve cells [79-81]. APP is necessary for growth, survival and repair of nerve cells. In Alzheimer's disease, two enzymes, gamma secretase and beta secretase, work together in the process of protein folding, which causes APP to be divided into smaller parts. These smaller particles form first as amyloid fibrils and then as clumps outside nerve cells called amyloid plaques [80].



### Conclusion

Although there is still no cure for Alzheimer's disease, using drugs can slow down the progress of the disease and reduce the severity of the patient's memory impairment and behavioral problems. Drugs approved for Alzheimer's disease include:

**Sedative and antipsychotic drugs:** If non-pharmacological methods cannot reduce the patient's annoying, restless and aggressive behaviors, new antipsychotic drugs such as olanzapine, quetiapine and risperidone can be used. Sometimes depression is the cause of the patient's aggression, which can be treated by using antidepressants such as fluoxetine.

**Anticholinesterase drugs:** In Alzheimer's disease, the amount of acetylcholine, which is one of the chemical mediators interfering with memory, decreases. Various drugs are used to increase the amount of acetylcholine in nerve terminals, including rivastigmine (Exelon), donepezil (Aricept), and galantamine (Razadyne). These drugs improve the patient's memory, cognitive function and social function.

These drugs also correct the patient's abnormal behaviors to some extent. The main problem of these drugs is gastrointestinal side effects, nausea, vomiting, heartburn and diarrhea, which can be reduced by gradually increasing the drug, taking it with breakfast and dinner and with liquids or fruit juice.

**Memantine (Ebixa, Namenda):** Another drug that is used in the treatment of moderate to severe cases of Alzheimer's disease and has some protective effects on brain cells is memantine. This drug also improves the patient's cognitive ability and memory. Confusion and dizziness are the most important side effects of this drug. The medicine can be taken with food.

**Drugs whose effectiveness has not been confirmed:** There are various chemical and herbal drugs that have been recommended for Alzheimer's disease based on some studies, but their effectiveness has not yet been confirmed. Vitamins such as vitamin E, group B vitamins, omega 3, estrogen, ginkgo biloba, anti-inflammatory drugs such as ibuprofen are among these drugs. A healthy diet including the daily consumption of vegetables and fruits and reducing the consumption of saturated fats in addition to the proper consumption of foods containing vitamins "A, C and E" is one of the important ways to prevent Alzheimer's. Gamma-secretase was previously tested for the treatment of Alzheimer's. Recently, American researchers, by examining the results of a study, have found that blood pressure drugs, which are used to treat patients with high blood pressure, reduce the risk of Alzheimer's in people. It's possible that high blood pressure has a protective effect, or that something that people with high blood pressure are often exposed to, such as blood pressure medication, protects them from developing Alzheimer's. MIT researchers have taken a step towards curing the disease. By irradiating 40 Hz LED on laboratory mice, they have observed that beta-amyloid plaques have decreased by 40 to 50% and the level of tau protein has also decreased. These

findings are obtained while other frequencies, between 20 and 80 Hz, did not have an effect. Planning for human trials is under preparation.

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