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A REVIEW : ALZHEIMER'S DISEASE

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ABSTRACT :

Alzheimer's disease is a long-term, slowly getting worse condition that affects the brain. It causes problems with thinking, memory, and the ability to reason. It is the most common type of dementia in older people. The disease happens because of certain changes in the brain, like the build-up of harmful proteins called amyloid-beta plaques and tangled fibers known as neurofibrillary tangles. These changes damage brain cells, making it hard for people to do everyday tasks and enjoy life. Alzheimer's can't be reversed or cured. The main features of the disease include these plaques and tangles, along with inflammation, problems with brain connections, and the loss of brain cells. Factors that increase the risk of Alzheimer's include genes, family history, lifestyle choices like smoking or diet, environmental exposures such as pollution or harmful chemicals, and health problems like chronic inflammation or other diseases. All these risk factors and how the disease starts and gets worse are linked to high levels of oxidative stress. This review covers what is known about how common the disease is, its genetic and biological causes, the changes in the brain, and how it develops. It then goes on to talk about the signs and symptoms people experience and the treatments currently used. The review also discusses how a better understanding of the disease's development, including the long period before symptoms appear, is helping scientists create new treatments aimed at preventing the disease rather than just treating it. Alzheimer's is a complex condition caused by many factors. Two main theories have been proposed to explain it: the

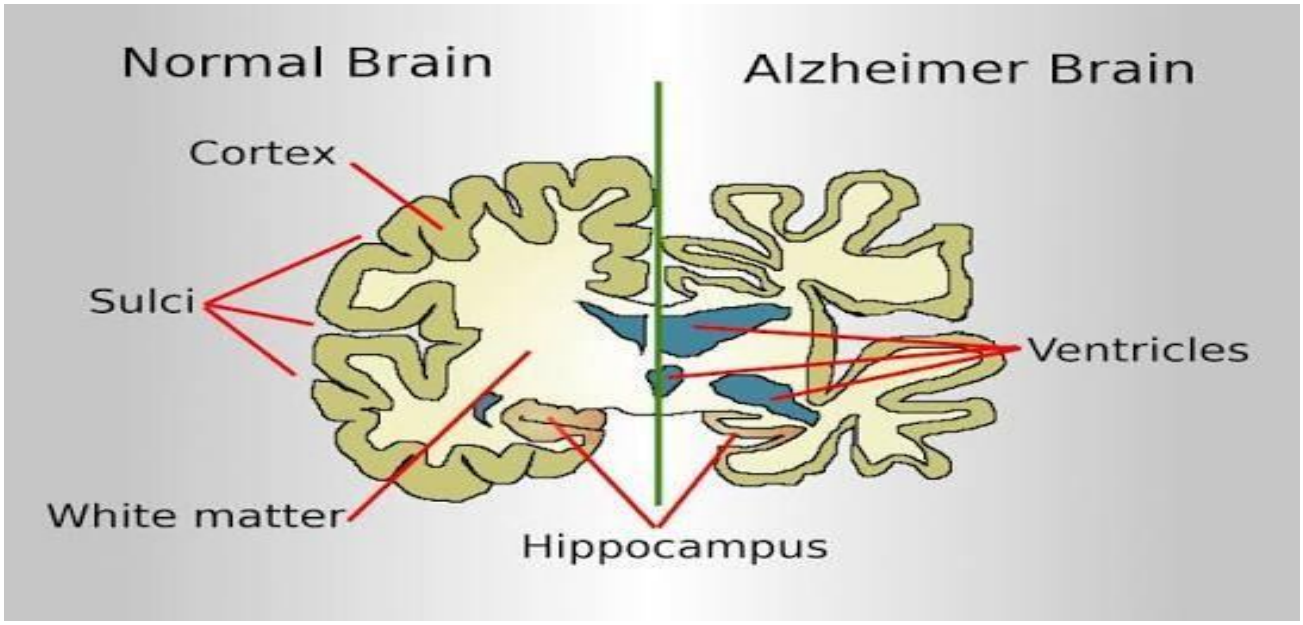
cholinergic hypothesis and the amyloid hypothesis. Other factors, such as getting older, genetics, brain injuries, vascular diseases, infections, and environmental influences, also play a role. Right now, only two types of drugs are approved to treat Alzheimer's: ones that stop the action of an enzyme called cholinesterase and drugs that block the NMDA receptor. These medicines can help with symptoms, but they don't stop or prevent the disease. Today, researchers are working to better understand the disease by looking at several related processes, such as faulty tau protein, amyloid-beta build-up, inflammation, and damage from chemicals and free radicals. The goal is to develop treatments that can stop or slow the progression of Alzheimer's.

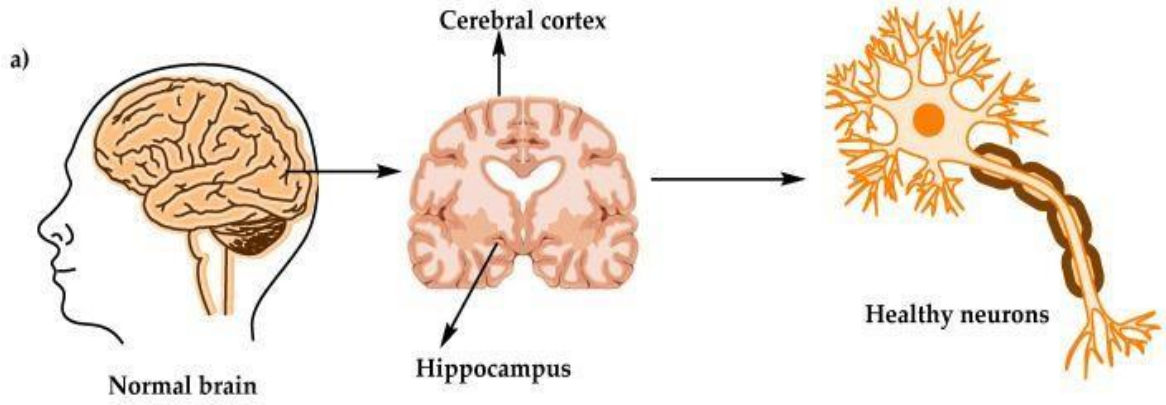
KEYWORDS: Alzheimer's disease, neurodegeneration, β-amyloid peptide, tau protein, risk factors

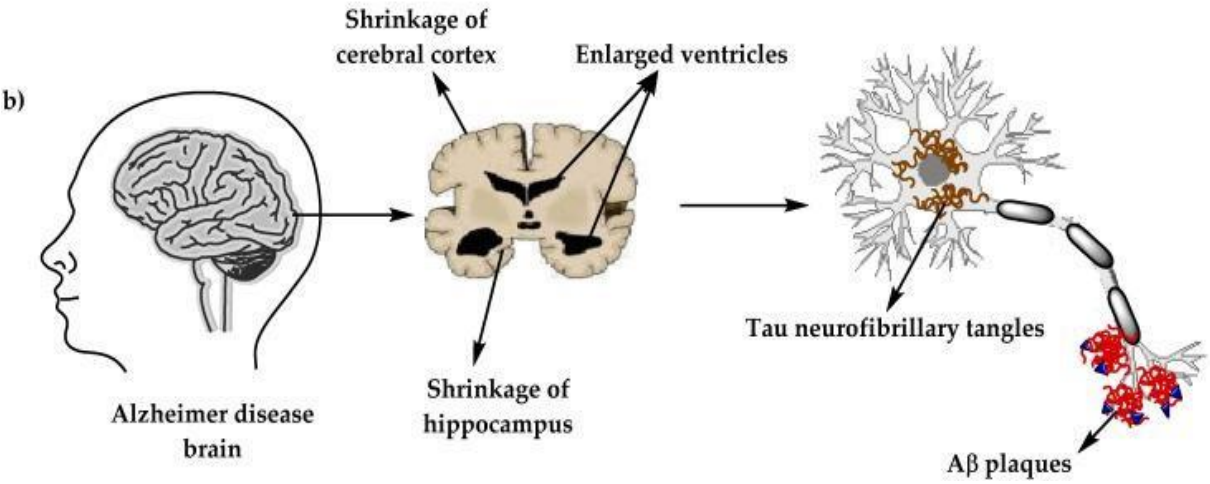
INTRODUCTION:

Dementia has become a major health issue worldwide. The World Health Organization's 2022 plan for dementia research says about 55.2 million people around the world are living with dementia. The number of people affected depends on where they live: in Southeast Asia, about 2.9% of people over 60 have dementia, while in Europe, it's 6.5%. Other areas have rates between 3.1% and 5.7%. The number of people with dementia is generally going up, but in some rich countries, it's coming down. By 2030, the number of people living with dementia is expected to increase to 78 million. Alzheimer's disease is a type of dementia that slowly affects the brain. It causes memory problems and other issues like trouble with language, learning, thinking, and behavior. It can get so bad that it makes it hard to do everyday tasks. Alzheimer's is the most common type of dementia, and it accounts for at least two-thirds of all dementia cases in people aged 65 and older. Alzheimer's is marked by two main changes in the brain: neurofibrillary tangles, which are made of a protein called tau that's been changed in a certain way, and plaques made of a protein called beta-amyloid. In 1906, a doctor named Alois Alzheimer wrote about a patient named Auguste Deter, who was in his care. He described her symptoms in detail. His research, titled "On the peculiar disease process of the cerebral cortex," helped start the study of this disease. Since then, scientists have learned more about Alzheimer's and its effects on the brain. In 1984, two researchers, George Glenner and Cain Wong, found that amyloid protein is the main part of the plaques found in the brain. In 1986, scientists discovered that when the tau protein becomes overly phosphorylated, it forms the tangles that are a key sign of Alzheimer's. Cognitive abilities can slowly get worse due to conditions like Alzheimer's or other factors such as poisoning, infections, problems with the lungs or heart that reduce oxygen to the brain, lack of nutrition, lack of vitamin B12, tumors, and other causes

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PATHOGENESIS:

Alzheimer's disease is a complicated condition that affects the brain and is caused by a mix of factors including genes, education, age, and the environment. Scientists have developed many theories to understand the causes of this disease. One of the oldest is the cholinergic hypothesis. This theory suggests that in people with Alzheimer's, there is less activity of enzymes like choline acetyltransferase and acetylcholinesterase in the brain. Postmortem studies have shown that the brain of someone with Alzheimer's has less activity in the pathways where these chemicals are used. This means that the loss of

cholinergic neurons and the decrease in the communication between these neurons play a big role in the memory and thinking problems that come with the disease.

Another important theory is the tau hypothesis.

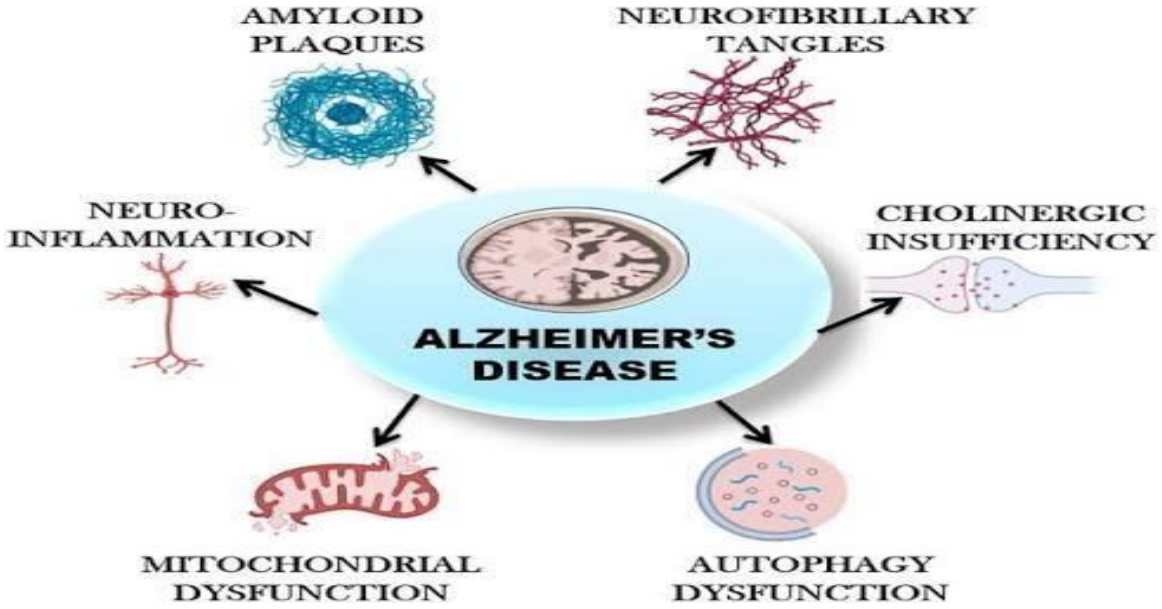
In Alzheimer's, there are tangles made of a protein called tau inside the brain cells. Au is usually important for keeping the structure of neurons stable. However, when tau becomes overly phosphorylated, it forms harmful structures called neurofibrillary tangles. These tangles disrupt the normal function of the neurons, leading to changes in the shape, transport, and connections of the neurons, which can result in neuron damage and brain cell death.

Amyloid-beta (Aβ) is another key factor in Alzheimer's.

It is made when a protein called amyloid precursor protein (APP) is broken down by certain enzymes. Two main types of Aβ, called Aβ40 and Aβ42, are involved in the disease process. These proteins can form small clusters that travel to the area between nerve cells and interfere with their communication. Over time, these clusters can build up into larger structures called amyloid plaques. These plaques are found in various parts of the brain and can cause inflammation, damage to nerve cells, and loss of synapses and brain tissue.

On the other hand, when APP is broken down by a different enzyme called a-secretase, it results in the production of soluble Aβ, which is not harmful. In fact, soluble Aβ is believed to be helpful in keeping neurons healthy and supporting brain development and function.

The future of treating Alzheimer's disease may involve targeting these plaques and tangles, as they can help slow down the process of brain cell damage. This article provides an overview of Alzheimer's disease, its causes, and the current and emerging approaches to treating it.



Mechanisms of AD

Many theories have been suggested to explain how Alzheimer's disease (AD) starts and develops, but there is still no single clear explanation. This is probably because AD is a very complex condition.AD is generally divided into two main types: familial and sporadic. Familial AD makes up about 1-5% of all cases and is mostly caused by inherited gene mutations in APP, PS1, and PS2.These mutations usually appear between the ages of 30 and 65 and lead to a quick progression of the disease. Sporadic AD, also called late-onset AD, usually starts after the age of 65.It is influenced by a mix of genetic factors, environmental influences, and other health conditions. Studies like genome-wide association studies (GWAS) and meta-analyses have found many genetic areas linked to sporadic AD, and these areas are connected to processes like immune response, fat metabolism, amyloid plaques, neurofibrillary tangles, and cell recycling. But there are still many genetic areas that haven't been found. Other non-genetic factors
like lifestyle, social and mental health, environment, and related diseases might increase the chance of developing AD. These factors can change body processes and affect how genes work, making it hard to find one clear reason for the disease's development.

Cholinergic hypothesis

The cholinergic hypothesis was the first to explain how Alzheimer's disease starts.It says that the cholinergic neurons in the nucleus basalis of Meynert (NBM) are seriously damaged, which causes a big drop in choline acetyltransferase (ChAT) activity in key brain areas like the cerebral cortex and hippocampus. These areas are important for learning and memory. Along with this neuron damage, there is also a big rise in the number of senile plaques. This theory suggests that the loss of cholinergic neurons in the basal forebrain is closely linked to the memory and thinking problems seen in Alzheimer's. These cholinergic neurons are a key part of the central cholinergic system, which helps
control things like thinking, attention, and memory.

When a nerve signal comes, acetylcholine (Ache) is released and binds to muscarinic and nicotinic acetylcholine receptors (mAChRs and nAChRs) on the next neuron to pass on the signal. Afterward, acetylcholinesterase (AChE) breaks down ACh in the space between neurons, and the broken pieces are taken back up by the sending neuron.A drop in ChAT activity, along with how Aβ affects the balance of nutrients and the production, release, and breakdown of ACh, causes lower levels of ACh.This reduction harms the body's ability to learn, remember, control movement, and regulate sleep.

Amyloid hypothesis

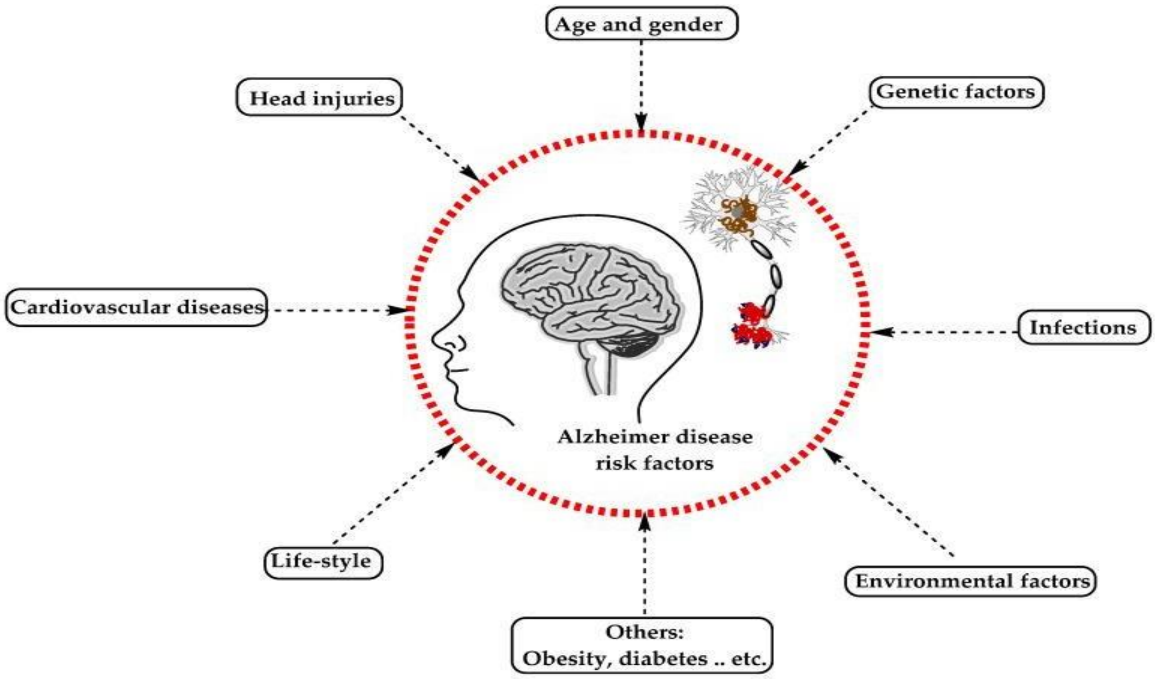
The buildup of AÎ² is a key sign of both the most studied inherited form of Alzheimer's disease and the more common, later-onset version.AÎ² is made when a protein called APP is broken down in a certain way by two enzymes, β-secretase and γ-secretase, which is a group of proteins that includes PS1 or PS2.This process creates different lengths of AÎ² pieces, with AÎ²40 and AÎ²42 being the most common.The part of AÎ²42 at the end is oily, which helps it form into a certain structure called β-sheets, and then clump together to form the main part of the plaques seen in Alzheimer's. Changes in PS1, which are common in early-onset Alzheimer's, can lead to more AÎ² buildup in several ways, such as making more AÎ² or stopping the body's natural cleaning process. But these changes aren't always connected to higher levels of AÎ²42 or a bigger ratio of AÎ²42 to AÎ²40.In the more common, later-onset Alzheimer's, plaque formation is more complex, as it involves a balance between making AÎ² and getting rid of it.

The Stages of Alzheimer's Disease

The clinical stages of Alzheimer's disease can be broken down into four main phases.

1. The pre-clinical or pre-symptomatic stage can last for several years. During this time, there is mild memory loss and early changes in the brain's cortex and hippocampus, but there are no noticeable symptoms or impact on daily life.
2. In the mild or early stage, patients begin to show some symptoms. These may include difficulty with daily tasks, trouble concentrating, memory loss, confusion about time and place, mood changes, and the development of depression.
3. The moderate stage is when the disease affects more areas of the brain. This leads to more severe memory loss, difficulty recognizing family and friends, loss of control over impulses, and trouble reading, writing, and speaking.
4. In the severe or late stage, the disease spreads throughout the entire brain. This causes major loss of brain function and thinking ability. Patients may no longer recognize their family members, become unable to move around on their own, have trouble eating and using the bathroom, and eventually pass away due to these serious complications.

Causes and Risk Factors of Alzheimer's Disease:



Aging

The biggest risk for getting Alzheimer's disease (AD) is getting older. People who are younger usually don't get this illness, and most cases start after the age of 65.Aging is a complicated and can't-be-stopped process that happens in many parts of the body, including the brain. As people age, the brain gets smaller and lighter, there's a loss of connections between brain cells, and certain areas of the brain may expand. This is often linked with the buildup of specific proteins called SP and Natalio, as people get older, other issues may develop, such as poor use of glucose, trouble with cholesterol balance, problems with energy production in cells, depression, and memory loss. These changes can happen naturally as people age, making it hard to tell the difference between normal aging and early signs of Alzheimer's. Alzheimer's can be grouped based on when it starts. Early-onset Alzheimer's (EOAD) is a less common type that affects about 1% to 6% of people with the disease. Most of these cases are inherited, meaning that more than one family member across multiple generations has the condition. This type can start between the ages of 30 and 60 or even later, around 65.

Genetics: In sporadic Alzheimer's disease, there is no clear pattern of genes being passed down from family members. Scientists have found that a gene called Apolipoprotein E, or Ape, is linked to Alzheimer's. This gene helps make a protein that carries cholesterol through blood vessels. One version of this gene, called ApoE4, is connected to a higher chance of getting Alzheimer's. Another version, ApoE2, seems to offer some protection against the disease. In cases where Alzheimer's occurs before the age of 65, it is often due to changes in chromosomes. This
less common type is known as Familial Alzheimer's disease and affects less than 10% of all people with Alzheimer's. It is caused by mutations on chromosomes 1, 14, and 21.If someone inherits a mutation from one parent, they have a 50% chance of developing Alzheimer's.

Diet

In recent years, the number of studies on the role of nutrition in AD have been increased. Several dietary supplements such as antioxidants, vitamins, polyphenols, and fish were reported to decrease the risk of AD, whereas saturated fatty acids and high-calorie intake were associated with increasing the risk of AD.

Metals

Metals are found in nature and biological systems and can be divided into bio-metals that have a physiological function in living organisms (e.g., copper, zinc, and iron), and toxicological metals which do not possess

Diagnosis

Positron emission tomography CT scan
MRI

Treatments

Drug Therapy: There are two kinds of medicine used to treat Alzheimer's disease: acetylcholinesterase inhibitors and N-methyl D-aspartate antagonists. These medicines workin different ways.
Cholinesterase Inhibitors: People with
any biological function (e.g., aluminum and lead).

Obesity and Diabetes

Obesity refers to having too much body fat, which happens when a person consumes more calories than they use up. It can be measured using the body mass index, or Bisharin too much body fat can reduce the blood flow to the brain, leading to problems like brain ischemia, memory issues, and vascular dementia. Obesity, along with poor eating habits and other factors, can lead to impaired glucose tolerance or diabetes. Diabetes is marked by high blood sugar levels, which can harm tissues and blood vessels. Long-term high blood sugar can damage the brain by increasing amyloid-beta buildup, causing oxidative stress, problems with mitochondria, and inflammation in the brain. Obesity also causes the release of more inflammatory chemicals from fat tissues, which activate immune cells like macrophages and lymphocytes, leading to both local and widespread inflammation.
Alzheimer's disease have less of a chemical called acetylcholine in their brain. Acetylcholine is used to send messages between nerve cells. Cholinesterase inhibitors help increase the amount of acetylcholine available in the brain, which can help with memory problems.
NMDA Receptor Antagonists: Memantine is a type of medicine that blocks NMDA receptors.
It is used to treat moderate to severe Alzheimer's disease. By blocking these receptors, it helps reduce damage caused by too much glutamate, which can harm brain cells. A study lasting 28 weeks showed that this medicine helped slow down the worsening of symptoms in patients.
Antidepressants and Antipsychotics: Behavioral and psychological symptoms of dementia (BPSD) are common in Alzheimer's patients and can be very stressful for caregivers. Cholinesterase inhibitors and memantine can help manage these symptoms, but as the disease progresses, these medicines may not be enough. Depression is also very common, especially in the early and later stages of the disease.

Conclusion

In this article, Alzheimer's disease and its clinical features have been briefly discussed. Alzheimer's disease has four stages in order: predementia, mild, moderate, and severe. Pneumonia is the most common reason people with Alzheimer's die, followed by heart attacks and blood infections. Several risk factors, such as age, genetics, and education, are linked to Alzheimer's. Also, environmental, vascular, and psychosocial factors play a role in the development of the disease. Medications like cholinesterase inhibitors, including galantamine, donepezil, and rivastigmine, and NMDA antagonists like memantine, can help improve memory and alertness, but they do not stop the disease from getting worse. Research has shown that changing lifestyle habits such as diet and exercise can improve brain health and reduce Alzheimer's symptoms without medical treatment, and these are considered the first choice of treatment for all Alzheimer's patients. Recently, studies are focusing on targeting the underlying causes of Alzheimer's, such as amyloid-beta and phosphorylated tau proteins.

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