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What Causes Alzheimer's Disease

Scientists don't yet fully understand what causes Alzheimer's disease in most people. In people with early-onset Alzheimer's, a genetic mutation may be the cause. Late-onset Alzheimer's arises from a complex series of brain changes that occur over decades. The causes probably include a combination of genetic, environmental, and lifestyle factors. The importance of any one of these factors in increasing or decreasing the risk of developing Alzheimer's may differ from person to person.

The Basics of Alzheimer's Disease

Scientists are conducting studies to learn more about plaques, tangles, and other biological feature of Alzheimer's disease. Advances in brain imaging techniques allow researchers to see the development and spread of abnormal amyloid and tau proteins in the living brain, as well as changes in brain structure and function. Scientists are also exploring the very earliest steps in the disease process by studying changes in the brain and body fluids that can be detected years before Alzheimer's symptoms appear. Findings from these studies will help in understanding the causes of Alzheimer's and make diagnosis easier.

One of the great mysteries of Alzheimer's disease is why it largely strikes older adults. Research on normal brain aging is exploring this question. For example, scientists are learning how age-related changes in the brain may harm neurons and affect other types of brain cells to contribute to Alzheimer's damage. These age-related changes include atrophy (shrinking) of certain parts of the brain, inflammation, vascular damage, production of unstable molecules called free radicals, and mitochondrial dysfunction (a breakdown of energy production within a cell).

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Alzheimer's Disease Genetics

Most people with Alzheimer's have the late-onset form of the disease, in which symptoms become apparent in their mid-60s. Researchers have not found a specific gene that directly causes late-onset Alzheimer's. However, having one form of the apolipoprotein E (APOE) gene does increase a person's risk. This gene has several forms. One of them, APOE ε4, increases a person's risk of developing the disease and is also associated with an earlier age of disease onset. However, carrying the APOE ε4 form of the gene does not mean that a person will definitely develop Alzheimer's disease, and some people with no APOE ε4 may also develop the disease.

Also, scientists have identified a number of regions of interest in the genome (an organism's complete set of DNA) that may increase or decrease a person's risk for late-onset Alzheimer's to varying degrees.

Early-onset Alzheimer's disease occurs between a person's 30s and mid-60s and represents less than 10 percent of all people with Alzheimer's. Some cases are caused by an inherited change in one of the three genes. For others, research shows that other genetic components are involved.

Most people with Down syndrome develop Alzheimer's. This may be because people with Down syndrome have an extra copy of chromosome 21, which contains the gene that generates harmful amyloid.

Health, Environmental, and Lifestyle Factors that May Contribute to Alzheimer's Disease

Research suggests that a host of factors beyond genetics may play a role in the development and course of Alzheimer's disease. There is a great deal of interest, for example, in the relationship between cognitive decline and vascular conditions such as heart disease, stroke, and high blood pressure, as well as metabolic conditions such as diabetes and obesity. Ongoing research will help us understand whether and how reducing risk factors for these conditions may also reduce the risk of Alzheimer's.

A nutritious diet, physical activity, social engagement, and mentally stimulating pursuits have all been associated with helping people stay healthy as they age. These factors might also help reduce the risk of cognitive decline and Alzheimer's disease. Clinical trials are testing some of these possibilities.

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How is Alzheimer's Disease Diagnosed?

Doctors use several methods and tools to help determine whether a person who is having memory problems has "possible Alzheimer's dementia" (dementia may be due to another cause) or "probable Alzheimer's dementia" (no other cause for dementia can be found).

To diagnose Alzheimer's, doctors may:

- Ask the person and a family member or friend questions about overall health, use of prescription and over-the-counter medicines, diet, past medical problems, ability to carry out daily activities, and changes in behavior and personality.
- Conduct tests of memory, problem solving, attention, counting, and language.
- Carry out standard medical tests, such as blood and urine tests, to identify other possible causes of the problem
- Perform brain scans, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET, to rule out other possible causes for symptoms

These tests may be repeated to give doctors information about how the person's memory and other cognitive functions are changing over time.

Alzheimer's disease can be ***definitely*** diagnosed only after death, by linking clinical measures with an examination of brain tissue in an autopsy.

People with memory and thinking concerns should talk to their doctor to find out whether their symptoms are due to Alzheimer's or another cause, such as stroke, tumor, Parkinson's disease, sleep disturbances, side effects of medication, an infection, or a non-Alzheimer's dementia. Some of these conditions may be treatable and possibly reversible.

If the diagnosis is Alzheimer's, beginning treatment early in the disease process may help preserve daily functioning for some time, even though the underlying disease process cannot be stopped or reversed. An early diagnosis also helps families plan for the future. They can take care of financial and legal matters, address potential safety issues, learn about living arrangements, and develop support networks.

In addition, an early diagnosis gives people greater opportunities to participate in clinical trials that are testing possible new treatments for Alzheimer's disease or other research studies.

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How is Alzheimer's Disease Treated?

Alzheimer's disease is complex, and it is unlikely that any one drug or other intervention can successfully treat it. Current approaches focus on helping people maintain mental function, manage behavioral symptoms, and slow down certain problems, such as memory loss. Researchers hope to develop therapies targeting specific genetic, molecular, and cellular mechanisms so that the actual underlying cause of the disease can be stopped or prevented.

Medications to Maintain Mental Function in Alzheimer's Disease

Several medications are approved by the U.S. Food and Drug Administration (FDA) to treat symptoms of Alzheimer's. Donepezil (Aricept ®), rivastigmine (Exelon ®), and galantamine (Razadyne ®) are used to treat mild to moderate Alzheimer's (donepezil can be used for severe Alzheimer's as well). Mementine (Namenda ®), the Exelon ® patch, and Namzaric ® (a combination of memantine and donepezil) are used to treat moderate to severe Alzheimer's. These drugs work by regulating neurotransmitters, the chemicals that transmit messages between neurons. They may help reduce symptoms and help with certain behavioral problems. However, these drugs don't change the underlying disease process. They are effective for some but not all people and may help only for a limited time.

Medications to Manage Behaviors in Alzheimer's Disease

Common behavioral symptoms of Alzheimer's include sleeplessness, wandering, agitation, anxiety, and aggression. Scientists are learning why these symptoms occur and are studying new treatments, drug and non-drug, to manage them. Research has shown that treating behavioral symptoms can make people with Alzheimer's more comfortable and makes things easier for caregivers.

Looking for New Treatments for Alzheimer's Disease

Alzheimer's research has developed to a point where scientists are exploring ways to delay or prevent the disease as well as treat its symptoms. In ongoing clinical trials supported by NIA, scientists are developing and testing several possible interventions. Under study are drug therapies aimed at a variety of targets, including the beta-amyloid protein, cerebrovascular function, loss of synapses, and specific neurotransmitters, as well as nondrug interventions, such as physical activity, diet, cognitive training, and combinations of these approaches.

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What Happens to the Brain in Alzheimer's Disease?

The healthy human brain contains tens of billions of neurons; specialized cells that process and transmit information via electrical and chemical signals. They send messages between different parts of the brain, and from the brain to the muscles and organs of the body. Alzheimer's disease disrupts this communication among neurons, resulting in loss of function and cell death.

Key Biological Processes in the Brain

Most neurons have three basic parts: a cell body, multiple dendrites, and an axon.

- The **cell body** contains the nucleus, which houses the genetic blueprint that directs and regulates the cell's activities.
- **Dendrites** are branch-like structures that extend from the cell body and collect information from other neurons.
- The **axon** is a cable-like structure at the end of the cell body opposite the dendrites and transmits messages to other neurons.

The function and survival of neurons depend on several key biological processes:

- **Communication**. Neurons are constantly in touch with neighboring brain cells. When a neuron receives signals from other neurons, it generates an electrical charge that travels down the length of its axon and releases neurotransmitter checicals across a tiny gap, called a synapse. Like a key fitting into a lock, each neurotransmitter molecule then binds to specific receptor sites on a dendrite of a nearby neuron. This process triggers chemical or electrical signals that either stimulate or inhibit activity in the neuron receiving the signal. Communication often occurs across networks of brain cells. In fact, scientists estimate that in the brain's communications network, one neuron may have as many as 7,000 synaptic connections with other neurons.
- **Metabolism**. Metabolism, the breaking down of checmicals and nutrients within a cell, is critical to healthy cell function and survival. To perform this function, cells require energy in the form of oxygen and glucose, which are supplied by blood circulating through the brain. The brain has one of the richest blood supplies of any organ and consumes up to 20 percent of the energy used by the human body, more than any other organ.
- **Repair, remodeling, and regeneration**. Unlike many cells in the body, which are relatively short-lived, neurons have evolved to live a long time, more than 100 years in humans. As a result, neurons must constantly maintain and repair themselves. Neurons also continuously adjust, or "remodel", their synaptic connectsion depending on how much stimulation they receive from other neurons. For example, they may strengthen or weaken synaptic connections, or even break down connections with one group of neurons and build new connections with a different group. Adult brains may een generate new neurons, a process called neurogenesis. Remodeling of synaptic connections and neurogenesis are important for learning, memory, and possibly brain repair.

Neurons are a major player in the central nervous system, but other cell types are also key to healthy brain function. In fact, glial cells are by far the most numerous cells in the brain, outnumbering neurons by about 10 to 1. These cells, which come in various forms, such as microglia, astrocytes, and oligodendrocytes, surround and support the function and healthy of neurons. For example, microglia protect neurons from physical and chemical damage and are responsible for clearing foreign substances and cellular debris from the brain. To carry out these function, glial cells often collaborate with blood vessels in the brain. Together, glial and blood vessel cells regulate the delicate balance within the brain to ensure that it functions at its best.

How Does Alzheimer's Disease Affect the Brain?

The brain typically shrinks to some degree in healthy aging but, surprisingly, does not lose neurons in large numbers. In Alzheimer's disrupts processes vital to neurons and their networks, including communication, metabolism, and repair.

At first, Alzheimer's disease typically destroys neurons and their connections in parts of the brain involved in memory, including the entorhinal cortex and hippocampus. It later affects areas in the cerebral cortex responsible for language, reasoning, and social behavior. Eventually, many other areas of the brain are damaged. Over time, a person with Alzheimer's gradually loses his or her ability to live and function independently. Ultimately, the disease is fatal.

What are the Main Characteristics of the Brain with Alzheimer's?

Many molecular and cellular changes take place in the brain of a person with Alzheimer's disease. These changes can be observed in brain tissue under the microscope after death. Investigations are underway to determine which changes may cause Alzheimer's and which may be a result of the disease.

Amyloid Plaques

The beta-amyloid protein involved in Alzheimer's comes in several different molecular forms that collect between neurons. It is formed from the breakdown of a larger protein, called amyloid precursor protein. One form, beta-amyloid 42, is thought to be especially toxic. In the Alzheimer's brain, abnormal levels of this naturally occurring protein clump together to form plaques that collect between neurons and disrupt cell function. Research is ongoing to better understand how, and at what stage of the disease, the various forms of beta-amyloid influence Alzheimer's.

Neurofibrillary Tangles

Neurofibrillary tangles are abnormal accumulations of a protein called tau that collect inside the neurons. Healthy neurons, in part, are supported internally by structures called microtubules, which help guide nutrients and molecules from the cell body to the axon and dendrites. In healthy neurons, tau normally binds to and stabilizes microtubules. In Alzheimer's disease, however, abnormal chemical changes cause tau to detach from microtubules and stick to other tau molecules, forming threads that eventually join to form tangles inside neurons. These tangles block the neuron's transport system, which harms the synaptic communication between neurons.

Emerging evidence suggests that Alzheimer's-related brain changes may result from a complex interplay among abnormal tau and beta-amyloid proteins and several other factors. It appears that abnormal tau accumulates in specific brain regions involved in memory. Beta-amyloid clumps into plaques between neurons. As the level of beta-amyloid reaches a tipping point, there is a rapid spread of tau throughout the brain.

Chronic Inflammation

Research suggests that chronic inflammation may be caused by the buildup of glial cells normally meant to help keep the brain free of debris. One type of glial cell, microglia, engulfs and destroys waste and toxins in a healthy brain. In Alzheimer's, microglia fail to clear away waste, debris, and protein collections, including beta-amyloid plaques. Researchers are trying to find out why microglia fail to perform this vital function in Alzheimer's.

One focus of study is a gene called TREM2. Normally, TREM2 tells the microglia cells to clear beta-amyloid plaques from the brain and helps fight inflammation in the brain. In the brains of people where this gene does not function normally, plaques build up between neurons. Astrocytes, another type of glial cell, are signaled to help clear the buildup of plaques and other cellular debris left behind. These microglia and astrocytes collect around the neurons but fail to perform their debris-clearing function. In addition, they release chemicals that cause chronic inflammation and further damage the neurons they are meant to protect.

Vascular Contributions to Alzheimer's Disease

People with dementia seldom have only Alzheimer's-related changes in their brains. Any number of vascular issues, problems that affect blood vessels, such as beta-amyloid deposits in brain arteries, atherosclerosis (hardening of the arteries), and mini-strokes, may also be at play.

Vascular problems may lead to reduced blood flow and oxygen to the brain, as well as a breakdown of the blood-brain barrier, which usually protects the brain from harmful agents while allowing in glucose and other necessary factors. In a person with Alzheimer's, a faulty blood-brain barrier prevents glucose from reaching the brain and prevents the clearing away of toxic beta-amyloid and tau proteins. This results in inflammation, which adds to vascular problems in the brain. Because it appears that Alzheimer's is both a cause and consequence of vascular problems in the brain, researchers are seeking interventions to disrupt this complicated and destructive cycle.

Loss of Neuronal Connections and Cell Death

In Alzheimer's disease, as neurons are injured and die throughout the brain, connections between networks of neurons may break down, and many brain regions begin to shrink. By the final stages of Alzheimer's, this process, called brain atrophy, is widespread, causing significant loss of brain volume.

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Alzheimer's Disease Fact Sheet

Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills, and, eventually, the ability to carry out the simplest tasks. In most people with Alzheimer's, symptoms first appear in their mid-60s. Estimates vary, but experts suggest that more than 6 million Americans, most of them age 65 or older, may have dementia caused by Alzheimer's.

Alzheimer's disease is currently ranked as the sixth leading cause of death in the United States, but recent estimates indicate that the disorder may rank third, just behind heart disease and cancer, as a cause of death for older people.

Alzheimer's is the most common cause of dementia among older adults. Dementia is the loss of cognitive functioning, thinking, remember, and reasoning, and behavioral abilities to such an extent that it interferes with a person's daily life and activities. Dementia ranges in severity from the mildest stage, when it is just beginning to affect a person's functioning, to the most severe stage, when the person must depend completely on others for basic activities of daily living.

The causes of dementia can vary, depending on the types of brain changes that may be taking place. Other dementias include Lewy body dementia, frontotemporal disorders, and vascular dementia. It is common for people to have mixed dementia, a combination of two or more types of dementia. For example, some people have both Alzheimer's disease and vascular dementia.

Alzheimer's disease is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms included memory loss, language problems, and unpredictable behavior. After she died, he examined her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary, or tau, tangles.

These plaques and tangles in the brain are still considered some of the main features of Alzheimer's disease. Another feature is the loss of connections between nerve cells (neurons) in the brain. Neurons transmit messages between different parts of the brain, and from the brain to muscles and organs in the body.

How Does Alzheimer's Disease Affect the Brain?

Scientists continue to unravel the complex brain changes involved in the onset and progression of Alzheimer's disease. It seems likely that changes in the brain may begin a decade or more before memory and other cognitive problems appear. During this preclinical stage of Alzheimer's disease, people seem to be symptom-free, but toxic changes are taking place in the brain. Abnormal deposits of proteins form amyloid plaques and tau tangles throughout the brain. Once-healthy neurons stop functioning, lose connections with other neurons, and die. Many other complex brain changes are thought to play a role in Alzheimer's too.

The damage initially appears to take place in the hippocampus and the entorhinal cortex, parts of the brain essential in forming memories. As more neurons die, additional parts of the brain are affected and begin to shrink. By the final stage of Alzheimer's, damage is widespread, and brain tissue has shrunk significantly.

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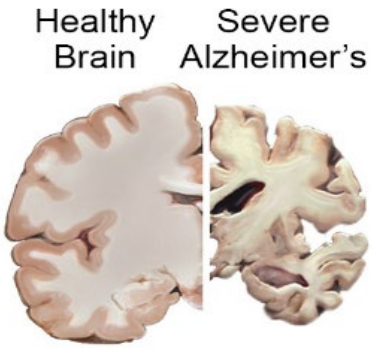

Signs and Symptoms of Alzheimer's Disease

Memory problems are typically one of the first signs of cognitive impairment related to Alzheimer's disease. Some people with memory problems have a condition called mild cognitive impairment (MCI). In MCI<, people have more memory problems than normal for their age, but their symptoms do not interfere with their everyday lives. Movement difficulties and problems with the sense of smell have also been linked to MCI. Older people with MCI are at greater risk for developing Alzheimer's, but not all of them do. Some may even go back to normal cognition.

The first symptoms of Alzheimer's vary from person to person. For many, decline in non-memory aspects of cognition, such as word-finding, vision/spatial issues, and impaired reasoning or judgment, may signal the very early stages of Alzheimer's disease. Researchers are studying biomarkers (biological signs of disease found in brain images, cerebrospinal fluid, and blood) to detect early changes in the brains of people with MCI and in cognitively normal people who may be at greater risk for Alzheimer's. Studies indicate that such early detection is possible, but more research is needed before these techniques can be used routinely to diagnose Alzheimer's disease in everyday medical practice.

Stages of Alzheimer's Disease

Mild Alzheimer's Disease

As Alzheimer's disease progresses, people experience greater memory loss and other cognitive difficulties. Problems can include wandering and getting lost, trouble handling money and paying bills, repeating questions, taking longer to complete normal tasks, and personality and behavior changes. People are often diagnosed in this stage.

Moderate Alzheimer's Disease

In this stage, damage occurs in areas of the brain that control language, reasoning, sensory processing, and conscious thought. Memory loss and confusion grow worse, and people begin to have problems recognizing family and friends. They may be unable to learn new things, carry out multistep tasks such as getting dressed, or cope with new situations. In addition, people at this stage may have hallucinations, delusions, and paranoia and may behave impulsively.

Severe Alzheimer's Disease

Ultimately, plaques and tangles spread throughout the brain, and brain tissue shrinks significantly. People with severe Alzheimer's cannot communicate and are completely dependent on others for their care. Near the end, the person may be in bed most or all of the time as the body shuts down.

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