In-service Training

Causes of Alzheimer's Disease

Length: 1 hour

Goals: By the end of this training session, the participant will be able to:

- Identify at least three potential causes of Alzheimer's disease.
- Describe how genes may be a cause of Alzheimer's disease.
- Identify potential risk factors for developing Alzheimer's disease.
- Identify suggested environmental contributors to the cause of Alzheimer's disease.

Suggestions: This is an in-depth overview of Alzheimer's disease. Consider reviewing reference information prior to providing the in-service or arrange for a guest speaker from the Alzheimer's Association or other group.

Causes of Alzheimer's Disease

Adapted from the National Institutes of Health (NIH) Pamphlet: "Alzheimer's Disease, Unraveling the Mystery" which can be obtained at www.nih.gov.

The Search for Causes

The brain has hundreds of billions of neurons ("brain cells"), any one of which can have thousands, even hundreds of thousands, of connections with other neurons. Within and among their extensive branches travel dozens of chemical messengers--neurotransmitters, hormones, growth factors, and more--linking each neuron with others in a vast communications network.

Somewhere in this complex signaling system lies the cause of Alzheimer's disease. In the past two decades, neuroscientists have combed through it in search of defects that might explain what goes wrong in this disease. One of their earliest findings came from studies of *neurotransmitters*, the chemicals that relay messages between neurons.

Neurotransmitters

Neurotransmitters reside in tiny sacs at the ends of neurons. Released when electrical impulses pass along the cell, the chemicals cross a minute space called the *synapse* and bind to the membrane of the next neuron. The neurotransmitters then either break down or pass back into the first neuron, while other substances inside the second neuron take up and relay the message. Put more simply, neurotransmitters function like chemical messengers, passing impulses between brain cells.

In the mid 1970's, scientists discovered that levels of a neurotransmitter called *acetylcholine* fell sharply in people with Alzheimer's disease. The discovery was intriguing for several reasons. Acetylcholine is a critical neurotransmitter in the process of forming memories. Moreover, it is the neurotransmitter used commonly by neurons in the hippocampus and cerebral cortex--regions devastated by Alzheimer's disease.

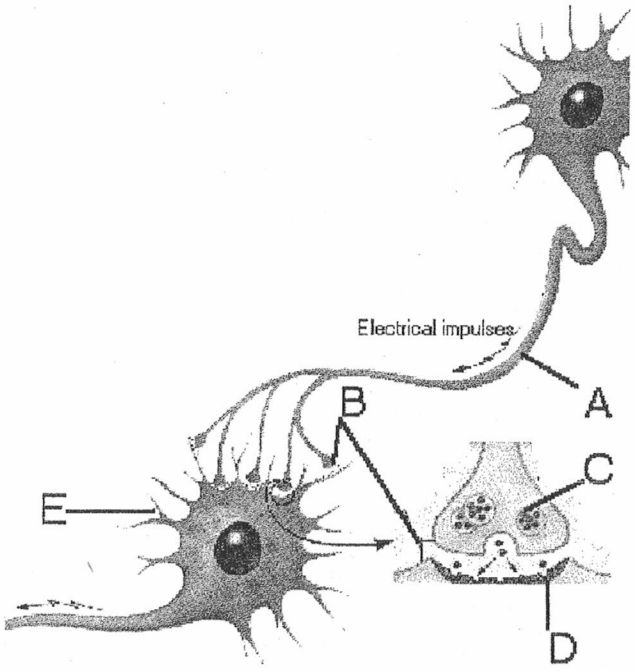
Since that early discovery, which was one of the first to link Alzheimer's disease with biochemical changes in the brain, acetylcholine has been the focus of hundreds of studies. Scientists have found that its levels fall somewhat in normal aging but drop by about 90 percent in people with Alzheimer's disease. They have turned up evidence linking this

decline to memory impairment. And they have looked for ways to boost its levels as a possible treatment for Alzheimer's disease.

How Neurons Communicate

The picture below shows cell bodies **(E)**, axons **(A)**, and dendrites **(B)** of two neurons, the synapse **(C, D)** between them, receptors, and vesicles containing neurotransmitter

molecules; how neurotransmitters are released from the axon, cross the synapse, and bind to receptors on the surface of another neuron; and how electrical impulses pass along the axon.



On the Other Side of the Synapse

Once the message carried by a neurotransmitter has crossed the synapse it passes into another territory, where neuroscientists are beginning to find more clues to Alzheimer's disease. The gateways to this new territory are the receptors, coil-shaped proteins embedded in neuron membranes which hold much interest for researchers investigating the cause of Alzheimer's disease.

The Proteins

Beta amyloid

When Alois Alzheimer observed the plaques now known as a hallmark of this disease, he could say little about them. No one knows still what role they play in the disease process, but scientists have learned that plaques are composed of a protein fragment called beta *amyloid* mixed with other proteins. Beta amyloid is a string of 40 or so amino acids snipped from a larger protein called *amyloid precursor protein* or APP.

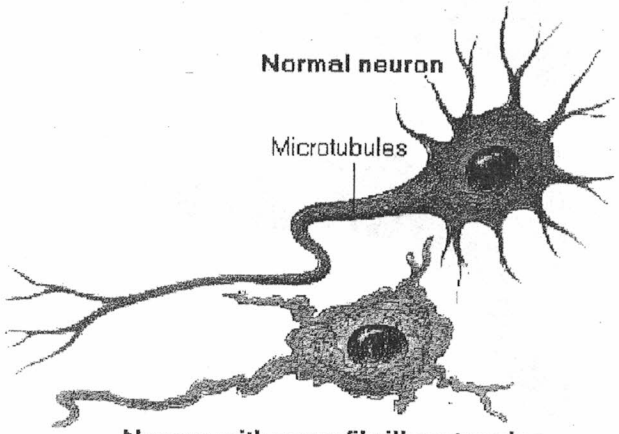
The precise mechanism by which beta amyloid might cause neuron death is still a mystery, but one recent finding suggests that beta amyloid forms tiny channels in neuron membranes. These channels may allow uncontrolled amounts of calcium into the neuron, an event that can be lethal in any cell.

Other recent studies suggest that beta amyloid disrupts potassium channels, which could also affect calcium levels. Still another study links beta amyloid to reduced choline concentrations in neurons; since neurons need choline to synthesize acetylcholine, this finding suggests that beta amyloid may cause the death of cholinergic neurons, which are important in memory and other higher cognitive function affected in Alzheimer's disease.

Tau

Another set of clues centers on a protein called *tau*, the major component of neurofibrillary tangles.

Neurofibrillary tangles resisted analysis until the late 1980's, when researchers discovered they were associated with neurons' internal structures, called microtubules. In healthy neurons, microtubules are formed like train rails, long parallel tracks with crosspieces, that carry nutrients from the body of the cells down to the ends of axons. In cells affected by Alzheimer's, this structure has collapsed. Tau normally forms the crosspieces between microtubules, but in Alzheimer's it twists into *paired helical filaments*, like two threads wound around each other. These are the basic constituents of neurofibrillary tangles.



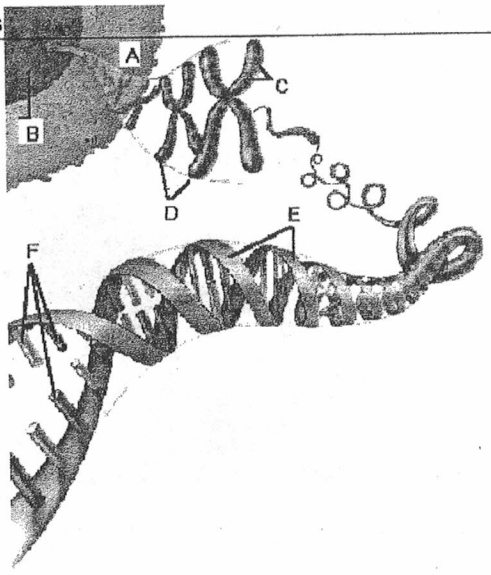
Neuron with neurofibrillary tangles

Having identified beta amyloid and tau, researchers would now like to find out what they do in the brain and in Alzheimer's disease. Some ideas about their functions may come from studies of certain genes.

The Genes

Located along the *DNA* in the nucleus of each cell, genes direct the manufacture of every enzyme, hormone, growth factor, and other protein in the body. Genes are made up of four chemicals, or bases, arranged in various patterns. Each gene has a different sequence of bases, and each one directs the manufacture of a different protein. Even slight alterations in the DNA code of a gene can produce a faulty protein. And a faulty protein can lead to cell malfunction and eventually disease.

Genetic research has turned up evidence of a link between Alzheimer's disease and genes on three *chromosomes*--14, 19, and 21. The *apoE4* gene on chromosome 19 has been linked to late-onset Alzheimer's disease, which is the most common form of the disease.



Chromosomes and Genes

A nerve cell **(A)**, chromosomes **(C)**, genes **(D)**, double DNA strands **(E)**, bases **(F)**, and a cell nucleus **(B)**. Chromosomes contain DNA, or deoxyribonucleic acid, a large double-stranded molecule that includes genes. Every cell in the body contains a nucleus which has 23 pairs of chromosomes. Genes are made up of bases arranged in certain sequences.

ApoE4 and Alzheimer's disease

The apoE4 gene came to light through long, patient detective work topped off by the serendipity that sometimes occurs in science. Alzheimer's researchers knew there were families in which many members developed the disease late in life. And therefore they knew there had to be a gene that the affected family members had in common. Searching for this gene, they combed through the DNA from these families and by 1992 had narrowed the search down to a region on chromosome 19.

In the same laboratory, another group of researchers were looking for proteins that bind to beta amyloid. They were disappointed at first. One version of a protein called *apolipoproteinE* (apoE) did bind quickly and tightly to beta amyloid, but apolipoproteinE was well known as a carrier of cholesterol in blood. No one suspected that it could have anything to do with Alzheimer's disease.

But by coincidence, or so it seemed, the gene apoE, which produces the protein, was also on chromosome 19. Moreover, it was on the same region of chromosome 19 as the Alzheimer's gene for which they had been searching.

The two groups of scientists decided to see if the apoE gene and the still missing Alzheimer's gene could be one and the same, and what they found made headlines: The apoE gene was identical to the gene they had been seeking. ApoE, it turned out, is much more common among Alzheimer's patients than among the general population.

More precisely, one version of apoE is more common among Alzheimer's patients. Like some other genes, the one that produces apoE comes in several forms or alleles. The apoE gene has three different forms--apoE2, apoE3, and apoE4. ApoE3 is the most common in the general population. But apoE4 occurs in approximately 40 percent of all late-onset Alzheimer's patients. Moreover, it is not limited to people whose families have a history of Alzheimer's. Patients with no known family history of the disease, cases of so-called sporadic Alzheimer's disease, are also more likely to have an apoE4 gene.

Since that finding, dozens of studies around the world have confirmed that the apoE4 allele increases the risk of developing Alzheimer's disease. People who inherit two apoE4 genes (one from the mother and one from the father) are at least eight times more likely to develop Alzheimer's disease than those who have two of the more common E3 version. The least common allele, E2, seems to lower the risk even more. People with one E2 and one E3 gene have only one-fourth the risk of developing Alzheimer's as people with two

Genes in early-onset Alzheimer's disease

Two families in Belgium can count back six or seven generations in which some members developed Alzheimer's disease in their 30's and 40's. A Japanese family has 5 members who developed the disease in middle age; a Hispanic family has 12 members; a French-Canadian family, 23; a British family, 8. In families descended from Volga Germans--a group of German families that settled in the Volga River valley in Russia in the 1800s--dozens of descendants have developed Alzheimer's disease in middle age.

Alzheimer's strikes early and fairly often in these and other families around the world--often enough to be singled out as a separate form of the disease and given a label: early-onset *familial Alzheimer's disease* or FAD. Combing through the DNA of these early-onset families, researchers have found a mutation in one gene on chromosome 21 that is common to a few of the families. And they have linked a much larger proportion of early-onset families to a recently-identified gene on chromosome 14. The gene on chromosome 21 occurs less often in people with FAD than the chromosome 14 gene, which codes for a membrane protein whose function is not yet known.

The chromosome 21 gene carries the code for a mutated form of the amyloid precursor protein, APP, the parent protein for beta amyloid. The discovery of this gene supports the theory that beta amyloid plays a role in Alzheimer's disease, although the mutation occurs in only about 5 percent of early-onset families.

The chromosome 21 gene intrigues Alzheimer's researchers also because it is the gene involved in Down syndrome. People with Down syndrome have an extra version of chromosome 21 and, as they grow older, usually develop plaques and tangles like those found in Alzheimer's disease.

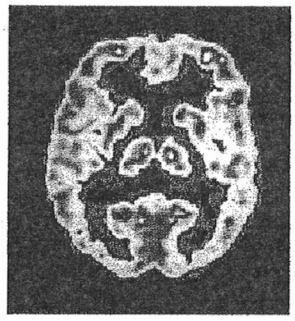
Few researchers think that the search for Alzheimer's genes is over. The Volga Germans, for one thing, have neither the chromosome 14 nor the chromosome 21 abnormality. Most investigators are convinced that there are several genes involved in Alzheimer's disease and, moreover, that other conditions must also be present for the disease to develop. One of these conditions may be a problem with the way in which neurons turn sugar, or glucose, into energy, a process known as *glucose metabolism.*
[photograph] A researcher uses an automated DNA sequencer to study genes involved in aging and Alzheimer's disease.

Metabolism

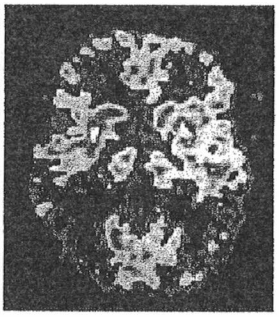
Every few months, Alzheimer's patients travel to the National Institutes of Health outside of Washington, D.C., and to other centers around the country to take part in research studies. One of the tests they take measures brain activity using special techniques, such as PET (short for *positron emission tomography*).

PET works on a simple principle. Brain activity, whether one is looking at a picture, working out a problem in algebra, or simply observing the surroundings, requires energy. Neurons produce energy through metabolism, a chain of biochemical reactions that uses large amounts of glucose (sugar) and oxygen. PET can track the flow of glucose and oxygen molecules in the bloodstream to the parts of the brain producing energy, thus revealing which areas are active.

By deciphering these patterns, Alzheimer's researchers can chart the progress of the disease. Glucose metabolism declines dramatically as neurons degenerate and die. Scientists are also using PET to learn how changes in brain activity match up with changes in skills, such as the ability to do arithmetic or to remember names of objects.



normal brain



Alzheimer's brain

PET scans show differences in brain activity between a normal brain and a brain affected by Alzheimer's disease. Blue and black denote inactive areas.

No one knows whether the decline in glucose metabolism causes neurons to degenerate or whether neuron degeneration causes metabolism to decline. In the effort to find out, scientists have examined glucose molecules at every step of the way from bloodstream to neuron.

While the glitch in glucose metabolism has yet to be pinpointed, its results are known to be devastating. Neurons depend wholly on glucose for their sustenance and when glucose metabolism falters, they suffer in various ways. For example, they cannot manufacture as much acetylcholine as normal cells, which may be one reason this neurotransmitter declines in Alzheimer's.

In addition, neurons having a problem with metabolism react abnormally to another neurotransmitter, called glutamate. When these neurons are stimulated by glutamate--even normal amounts of glutamate--their regular mechanisms go awry and they are flooded by calcium, with deadly consequences.

The Calcium Hypothesis

Calcium is an important substance in certain cells of the body, the so-called excitable cells in muscles and the nervous system. Neurons need calcium to transmit signals. Normally, the amount of calcium in a cell at any one time is carefully regulated; calcium channels allow in certain amounts of calcium at certain times.

Too much calcium can kill a cell, and some neuroscientists suspect that in the end, a rise in calcium levels may be precisely what is killing neurons in Alzheimer's disease.

According to one hypothesis, an abnormally high concentration of calcium inside a neuron is the final step in cell death. Several different series or cascades of biochemical events could lead up to this last, fatal step.

What events might these be? There are many theories. One possibility is that an increase in calcium channels could allow an excess of calcium into the cell. Another possibility is that a defect develops in the structures that store calcium inside the cell or those that pump it out of the cell.

Environmental Suspects

No one doubts that genetic and other biological factors are important in Alzheimer's disease, but environmental factors could also contribute to its development. The most studied of these are aluminum, zinc, foodborne poisons, and viruses.

Aluminum

One of the most publicized and controversial hypotheses in this area concerns aluminum, which became a suspect in Alzheimer's disease when researchers found traces of this metal in the brains of Alzheimer's patients. Many studies since then have either not been able to confirm this finding or have had questionable results.

Aluminum does turn up in higher amounts than normal in some autopsy studies of Alzheimer's patients, but not in all. Further doubt about the importance of aluminum stems from the possibility that the aluminum found in some studies did not all come from the brain tissues being studied. Instead, some could have come from the special substances used in the laboratory to study brain tissue.

Aluminum is a common element in the Earth's crust and is found in small amounts in numerous household products and in many foods. As a result, there have been fears that aluminum in the diet or absorbed in other ways could be a factor in Alzheimer's. One study found that people who used antiperspirants and antacids containing aluminum had a higher risk of developing Alzheimer's. Others have also reported an association between aluminum exposure and Alzheimer's disease.

On the other hand, various studies have found that groups of people exposed to high levels of aluminum do not have an increased risk. Moreover, aluminum in cooking utensils does not get into food and the aluminum that does occur naturally in some foods,

such as potatoes, is not absorbed well by the body. On the whole, scientists can say only that it is still uncertain whether exposure to aluminum plays a role in Alzheimer's disease.

Zinc

Zinc has been implicated in Alzheimer's disease in two ways. Some reports suggest that too little zinc is a problem, others that too much zinc is at fault. Too little zinc was suggested by autopsies that found low levels of zinc in the brains of Alzheimer's disease patients, especially in the hippocampus.

On the other hand, a recent study suggests that too much zinc might be the problem. In this laboratory experiment, zinc caused soluble beta amyloid from cerebrospinal fluid to form clumps similar to the plaques of Alzheimer's disease. Current experiments with zinc are pursuing this lead in laboratory tests that more closely mimic conditions in the brain.

Foodborne poisons

Toxins in foods have come under suspicion in a few cases of dementia. Two amino acids found in seeds of certain legumes in Africa, India, and Guam may cause neurological damage. Both enhance the action of the neurotransmitter glutamate, also implicated in Alzheimer's disease.

In Canada, an outbreak of a neurological disorder similar to Alzheimer's occurred among people who had eaten mussels contaminated with demoic acid. This chemical, like the legume amino acids, is a glutamate stimulator. While these toxins may not be a common cause of dementia, they could eventually shed some light on the mechanisms that lead to neuron degeneration.

The search for a virus

In some neurological diseases a virus is the culprit, lurking in the body for decades before a combination of circumstances stirs it to action. So for years researchers have sought a virus or other infectious agent in Alzheimer's disease.

This line of research has yielded little in the way of hard evidence so far, although one study in the late 1980's did provide some data that have kept the possibility alive. A larger investigation is now under way.

Alzheimer's Risk Factors and the Search for Causes

One tool in the search for causes of disease is the study of risk factors. Similarities among people with a certain disease may be risk factors, and they can provide clues to what is going wrong. For example, when a sizable group of Alzheimer's patients all come from the same family, epidemiologists suspect that a gene is at fault.

Epidemiologic studies also search for environmental causes of disease. However, so far, only two risk factors have been linked to Alzheimer's disease. Others are under investigation.

Known risk factors

- Age

  The risk of Alzheimer's rises exponentially with age, doubling in each decade after age 65.

- Family history/genetic disposition

  People with relatives who developed Alzheimer's disease are more likely to develop the disease themselves. So far, scientists have discovered three genes that help explain why family history is a risk factor.

Possible risk factors

- Head injury

  Some studies have found that Alzheimer's disease occurs more often among people who suffered traumatic head injuries earlier in life. A major survey of World War II veterans is now looking for more evidence to corroborate this finding.

- Gender

  Women may have a higher risk of the disease, although their higher rates may only reflect the effects of age--women have longer life spans on the average than men.

- Educational level

  Research suggests that the more years of formal education a person has, the less likely he or she is to develop Alzheimer's later in life. Thus lower educational levels may increase the risk.

A Disease With Many Causes?

The trails of clues that Alzheimer's leaves in its wake have so far not converged. When they do, some scientists think that this detective story will turn out to have a number of culprits. One theory suggests that several factors act in sequence or in combination to

cause Alzheimer's disease, even though no single factor is sufficient by itself. To explain this idea, scientists use the metaphor of a light that requires several switches.

There might, for example, be just two switches, such as a gene mutation and another event to trigger the gene. Or there might be several. According to this idea, called the AND gate theory, these events do not have to occur at the same time, but their effects would have to linger and eventually coincide to bring about Alzheimer's disease.

Quiz

CAUSES OF ALZHEIMER'S DISEASE

True and False

1. T F Neurotransmitters are responsible for passing "messages" between brain cells.

2. T F In Alzheimer's disease, brains cells are killed, but neurotransmitters are unaffected.

3. T F The build up of protein plaques in the brain is considered the hallmark of Alzheimer's disease.

4. T F The protein plaques of Alzheimer's disease are composed of a protein called beta amyloid.

Multiple Choice

5. Which of the following proteins are believed to play a role in Alzheimer's disease?
   a. Beta amyloid
   b. Tau
   c. Alz protein
   d. Both a and b

6. Which of the following statements is most correct regarding genes and Alzheimer's?
   a. All cases of Alzheimer's disease are hereditary.
   b. Persons with Alzheimer's are more likely to have a gene the produces a protein called apoE
   c. There is no link between genes and Alzheimer's disease.
   d. None of the above

7. Which of the following is not considered a possible risk factor for developing Alzheimer's disease?
   a. Age
   b. Family history
   c. Head injury
   d. Using aluminum pans

Bibliography

Causes of Alzheimer's Disease

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Date:	Location:
Instructor/Title/Signature:	
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Name (print)	Signature

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