Alzheimer's disease (AD) is a neurodegenerative disease that causes dementia. There are many different causes of dementia, with AD being the most common (60-80% of all dementia).

AD is caused by changes to the brain that lead to damage and breakdown of the nerve cells (called neurons). Accumulation of specific proteins (beta-amyloid and tau) in the brain interfere with how the neurons function and communication, and can lead to the death of neurons. The presence of these proteins are also thought to cause an inflammatory response which contributes to this damage, and can ultimately lead to the brain wasting away. AD also impacts the brain's ability to use glucose, which is a primary source of energy for the brain's functions. Other types of changes in the brain have also been found, however there are still significant limitations in our understanding of the brain changes and progression of disease seen with AD. In most cases, these changes to the brain start years to decades before an individual may start showing symptoms.

There are different phases of AD, including:

- pre-clinical phase: this is when someone has brain changes consistent with AD but are not showing symptoms yet.
- mild cognitive impairment phase: this is when someone has brain changes consistent with AD and have started to develop some memory and/or other issues with cognitive function. These difficulties may be noticeable to the individual and their family, but may not be detected by others.
- dementia phase: this is when someone has brain changes consistent with AD and have noticeable cognitive changes. An individual will often progress from mild to severe dementia over a period of time that differs for everyone. The degree of dementia often represents the amount of changes to the brain.

The length of time someone spends in each of these phases is variable.

When an individual is suspected to have AD, the diagnosis is made based on a detailed review of the medical and family history, cognitive tests, ruling out other causes of dementia, and for some may involve specific lab tests and neuroimaging studies. These evaluations are done to look at and document cognitive, psychiatric, and other types of changes, and to rule out other potential causes that may have different treatments.

Categories of disease

AD is often separated into two categories – late-onset AD and early-onset AD. Late-onset AD

(LOAD) refers to those that develop dementia due to AD when they are 65 or older, and accounts for about 95% of AD. Early-onset AD (EOAD) refers to those that develop dementia due to AD before the age of 65, and accounts for less than 5% of AD. Both of these can present as sporadic cases (no family history) or familial cases (someone else in the family also has it). While most sporadic cases are late-onset AD and most familial cases are early-onset AD, there can be sporadic early-onset AD and familial late-onset AD. More than 75% of AD is considered sporadic, and about 15-25% of all AD is familial. Other causes of AD include Down syndrome, which accounts for about 1% of all AD.

Late-onset Alzheimer's Disease (LOAD)

The primary risk factors for late-onset AD are age and genetics. Overall, about 10-12% of those in the general population who are 65 and older have dementia due to AD, and more than 30% develop it by age 85. There are multiple genes that have been identified that increase the risk of AD. These genes are often called "susceptibility genes," which means changes in these genes may increase the risk to develop AD, but they do not cause AD on their own. The gene that has thus far been most strongly linked with AD is the *APOE* gene. The estimated heritability (amount of late-onset AD due to genetic susceptibility factors) is 60-80%.

Other risk factors that impact an individual's chance of developing AD include those that can be changed. Some factors that increase the risk for dementia that can be changed include:

- less education
- hypertension (or high blood pressure)
- hearing impairment
- smoking
- obesity
- depression
- physical inactivity
- diabetes
- low levels of social contact
- excessive alcohol consumption
- traumatic brain injuries
- air pollution

Modifying these risks may help prevent or delay 40% of all dementias.

In addition to the multiple genetic and environmental factors that can influence an individual's chance to develop AD, a family history of AD may also increase the risk. However, an individual does not have to have a family history of AD in order to develop it, and similarly a positive family history does not guarantee an individual will develop AD.

Early-onset Alzheimer's Disease (EOAD):

Early-onset AD is characterized by being diagnosed before the age of 65. There is also often a positive family history of AD, and many individuals with EOAD will have an underlying genetic cause for their early onset AD (90-100% heritability). The most well-known causes of early-onset AD are those inherited in an autosomal dominant pattern. About 1% of all AD and 10-15% of early-onset AD is caused by autosomal dominant AD.

Autosomal dominant AD is suspected when there are multiple individuals in the family across multiple generations who have with AD. The majority of autosomal dominant AD is due to pathogenic (harmful) variants in the genes presenillin 1 (*PSEN1*, 20-80%), amyloid-beta precursor (*APP*, 10-15%), and presenillin 2 (*PSEN2*, <5%). There are cases of early-onset AD with no family history (sporadic) but are caused by a pathogenic variant in one of these genes; this is called a de novo (or new) variant in the gene. These genes account for only about 5-10% of all early-onset AD. The remaining of early-onset AD are due to other or unknown causes. This means for the majority of those with early-onset AD, the specific cause may be not yet identified, or may be due to multiple genetic or other factors.

AD Genetic Testing

Genetic testing may be beneficial for those with a personal or family history of AD, particularly in those with early-onset AD and a family history of AD. For early-onset AD, genetic testing often involves sequencing and deletion/duplication analysis of the genes *APP*, *PSEN1*, and *PSEN2*. A positive result would indicate a pathogenic variant in one of these genes has been found and is the suspected cause of AD in that individual or family. A negative result would only indicate that the cause of AD is likely not due to one of these three genes. A negative result is common, as the cause of the majority of both early- and late-onset AD is unknown. While it is generally recommended that testing be done on an individual with AD, this is not always an option. Genetic counseling prior to and after testing is recommended.

Currently, genetic testing of the *APOE* gene is not routinely done outside of research studies because the predictive value (our ability to use the information from the testing to predict risks for someone) are variable and limited. Many people who have *APOE* test results that

say they have a higher risk for AD will not every develop AD. Similarly, many people who *APOE* test results say they have a lower risk for AD may actually develop AD. For those who do undergo genetic testing and receive a result regarding their *APOE* genes, genetic counseling is recommended.

Treatment/Management

There is no known treatment for AD. There are medications and therapies that may help some individuals with their cognitive functions, but none are able to slow or stop the progression of the disease. Medical management is focused on providing proper care through appropriate treatments, therapies, activities, or support services, managing other health conditions the individual may have, and providing support to the caregiver.

Resources:

General resources:

- Alzheimer's Disease Education and Referral Center (NIH)
- Alzheimer's association

Information about registries and clinical trials:

- Alzheimer's Prevention Registry
- DIAN Expanded Registry
- Alzheimer's Association Trial Match

References:

- Alzheimer's Association Report. 2020 Alzheimer's disease facts and figures. Alzheimer's Dement. 2020;16:391–460.
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