Alzheimer’s disease

**Category:** Diseases and syndromes

**Definition**
Alzheimer’s disease is a progressive neurodegenerative disorder that causes a gradual, irreversible loss of memory, language, visual-spatial perceptions, and judgment. Approximately 5.5 million Americans have the disease, a number that is expected to increase to between 11 and 16 million by 2050 if means of preventing or effectively treating it are not discovered. The annual costs of caring for persons with Alzheimer’s disease and other dementias and costs to businesses for lost productivity from caregivers will be approximately $259 billion in 2017. The number of persons with Alzheimer’s disease and the associated economic burden is expected to rise dramatically as the baby boomer generation ages.

**Risk Factors**
Individual features and environmental influences may either cause a disease or increase the risk of developing that disease. Aging is a well-established risk factor for Alzheimer’s disease, and the rate of Alzheimer’s disease doubles every five years after age sixty-five. One in nine people age 65 and older (11 percent) has Alzheimer’s disease. About one-third of people age 85 and older (32 percent) have Alzheimer’s disease. In the United States, 3.2 million are women and 1.8 million are men, and the remaining are under age 65. Be that as it may, among US residents age 65 and older, the prevalence of all dementia diseases in the US declined from 11.6% in the year 2000 to 8.8% in 2012.

Alzheimer’s disease is a complex disorder, and many scientists believe that a combination of variations in some genes, possibly acting in conjunction with external factors, may increase the risk. Several genetic factors are known to cause Alzheimer’s disease, but they are extremely rare and account for a very small minority of cases. Persons with early onset Alzheimer’s disease (which develops before the age of sixty) who also have multiple family members with Alzheimer’s disease from at least three generations are considered to have familial early onset Alzheimer’s disease, which is very rare (less than 2 percent of all persons with the disease). Familial early-onset Alzheimer’s disease is caused by mutations in the gene for amyloid precursor protein (APP) gene and the presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes. Down syndrome (Trisomy 21) is another genetic disease associated with an increased risk for developing Alzheimer’s disease. Persons with Down syndrome have evidence of amyloid pathology at an early age, and those who live to their forties have a 50-50 chance of developing Alzheimer’s disease.

Risk factors for the much more common late onset Alzheimer’s disease (occurring after age sixty-five) are less clear-cut. Some scientists hypothesize that late-onset Alzheimer’s disease is caused by amyloid plaque accumulation in the brain or by enhanced degradation of the tau protein leading to development of neurofibrillary tangles. To date, no single factor has been identified that definitely causes late-onset Alzheimer’s disease. The risk of this form is increased (but not caused) by the presence of susceptibility genes. Persons without susceptibility genes can develop Alzheimer’s disease, however, just as individuals who carry a susceptibility gene may never develop the disease. The most thoroughly studied susceptibility gene for Alzheimer’s disease is apolipoprotein E (APOE) ε4. Individuals who carry one or more APOE ε4 alleles are at increased risk compared with noncarriers. Environmental factors that may increase the chance of Alzheimer’s disease include diabetes mellitus, hypercholesterolemia, hypertension, depression, traumatic brain injury, and a lower level of education.

**Etiology and Genetics**
The hallmark lesions in the brains of persons with Alzheimer’s disease are extracellular amyloid plaques and intraneuronal neurofibrillary tangles. Accumulation of the amyloid-beta (A-beta) peptide in the brain triggers a series of events that culminate in the development of Alzheimer’s disease. The A beta peptide is a sticky substance that forms clumps (or aggregates) called amyloid plaques that surround nerve cells. Amyloid plaques concentrate in the hippocampus and other brain regions that control memory and cognition. A-beta is produced by a series of steps that convert APP to neurotoxic forms of A-beta. APP is broken down by the beta-secretase and gamma-secretase enzymes, which results in the formation of toxic A-beta peptides that aggregate and form plaque. Another enzyme, alpha-secretase, is believed to protect against A-beta production. Accumulation of A-beta, either by overproduction or reduced clearance from the brain or both, leads to
Mutations in the APOE gene represent the most common genetic risk factor for late-onset Alzheimer’s disease. There are at least three forms of APOE alleles: 2, 3, and 4. Scientists believe that APOE may interrupt the normal breakdown of APP and alter A-beta production. The APOE 2 allele, which is rare and develops later in life, may protect individuals against Alzheimer’s disease. The APOE 3 allele is believed to play a neutral role in Alzheimer’s disease risk. The APOE 4 allele occurs in approximately 25 percent of all individuals. Persons who carry the APOE 4 allele have a two to fourfold increased risk of developing Alzheimer’s disease compared with noncarriers. Individuals with two copies of the APOE 4 allele are more than ten times more likely to develop Alzheimer’s disease than noncarriers. SORL1 and GRB associated binding protein 2 (GAB2) are other susceptibility genes that may increase the risk of developing Alzheimer’s disease. The SORL1 gene found on
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accompany advanced Alzheimer’s disease and may result in institutionalization. While survival following a diagnosis of Alzheimer’s disease has been reported to range from four to six years, patients may live for as long as twenty years after being diagnosed.

Screening and Diagnosis

In 1906, a German physician, Dr. Alois Alzheimer, reported on the rapid mental decline and death of his patient, Auguste Deter, and at autopsy described plaques and neurofibrillary tangles in her brain. Today, observation of plaques and tangles at autopsy remains the only way to definitively diagnose Alzheimer’s disease. Up until recently, a presumptive diagnosis of Alzheimer’s disease was based on clinical observation of symptoms and progressive deterioration. Recent research has shown that positron-emission scanning (PET scans) can be used to detect early signs of disease by imaging cellular level changes in the brain. This type of imaging may be useful for staging the disease, following the progression of disease and to help guide adjustments in treatment and interventions.

Early diagnosis of Alzheimer’s disease is essential to ensure that treatable causes of memory loss, cognitive impairment and other diseases, such as depression, drug interactions, nutritional deficiencies, or endocrine disorders are ruled out. The Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) multiphase study sponsored by the National Human Genome Research Institute (NHGRI) is investigating the impact of genetic testing and disclosure of APOE gene status to the adult children and siblings of persons with Alzheimer’s disease. Findings from the REVEAL study will help inform patients’ and clinicians’ decisions about genetic counseling and guide actions taken after learning about this status.

Treatment and Therapy

Despite a huge research effort, disease-modifying therapies that prevent, slow, or halt disease progression have yet to be identified. Currently, cholinesterase inhibitors and an N-methyl-D-aspartate (NMDA) receptor antagonist are approved for use. These drugs may possibly slow the rate of symptom development for some patients, but they do not significantly impact disease progression. Other drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), cholesterol lowering statins, ginko biloba, estrogen, and vitamin E have not been shown to be effective. Treatments that interfere with tau pathology, prevent
clumping of A-beta, or boost the immune response to A-beta are being actively studied in clinical trials.

The NIA Alzheimer’s Disease Prevention Initiative seeks to accelerate the rate of new drug discovery and development. The Alzheimer’s Association is a national organization that provides patient advocacy and funding for research of potential new therapies.

**Prevention and Outcomes**

Genetic counseling is useful for those rare persons with familial early-onset Alzheimer’s disease, but there is no consensus among experts about the benefits of testing other individuals. Issues of patient confidentiality remain germane to genetic testing for Alzheimer’s disease. If confidentiality is illegally compromised, patients may face employment, insurance, or other forms of discrimination if genetic testing becomes part of the medical record.

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**Further Reading**


Caroline Van Cauwenberghe MSc, Christine Van Broeckhoven PhD, DSc & Kristel Sleegers MD, PhD “The genetic landscape of Alzheimer disease: clinical implications and perspectives” *Genetics in Medicine* (2016)18,421–430 doi:10.1038/gim.2015.117 Received 04 June 2015 Accepted 07 July 2015 Published online 27 August 2015


Food and Drug Administration. “Head Injury Linked to Increased Risk of Alzheimer’s Disease.” *FDA Consumer*, January/February, 2001, 8. Discusses research that focuses on the link between head injuries and dementias, including Alzheimer’s disease.


Long Wu and Liqin Zhao, Ph.D., “ApoE2 and Alzheimer’s disease: time to take a closer look,” *Neural Regen Res.* 2016 Mar; 11(3): 412–413. doi:10.4103/1673-5374.179044


Amniocentesis

Category: Techniques and methodologies

Significance: Amniocentesis is the needle aspiration (withdrawal) of fluid from the amniotic sac (the fluid-filled sac surrounding a fetus developing in the uterus). Fetal cells in the fluid are then analyzed for chromosomal abnormalities such as Down syndrome (extra chromosome 21) or trisomy 18 (extra chromosome 18). Other analyses of the amniotic sac can be performed, depending on the clinical situation.

Key terms
- chromosome: an organized structure of DNA that contains genetic coding
- deoxyribonucleic acid (DNA): a nucleic acid that contains genetic instructions
- Down syndrome: a genetic disorder characterized by mental retardation and physical abnormalities
- genetic counseling: parental counseling to explain amniocentesis results
- prenatal diagnosis: the diagnosis of a genetic abnormality before birth
- triple test: a blood test that screens for genetic defects
- trisomy: an extra chromosome (such as trisomy 21)

Technique
Amniocentesis is most commonly done between the fourteenth and sixteenth week of pregnancy. Ultrasound is used to determine a safe location for insertion of a needle through the mother’s abdomen.