

ALZHEIMER'S DISEASE (AD)

“That’s part of getting old”
and
“That’s normal for my age”

These are common explanations of memory loss as a person gets older. However, the degree of memory problems considered to be part of “normal aging” is much less than previously believed. In fact, the most common cause of progressive memory loss in the elderly is Alzheimer’s Disease. Since there are now medications that may slow the decline, early recognition of symptoms is vital to beginning treatment and delaying the debilitating effects of Alzheimer’s Disease.

Demographics

Alzheimer’s Disease (AD) accounts for 50-70% of all cases of dementia. The incidence of AD rises exponentially with advancing age. Men and women are equally at risk. However, more women are affected since AD is a disease of the elderly and women have a longer average life span than men. Approximately 30% of individuals with AD have a family member with AD.

Symptoms

Usually appearing after the age of 60, the first symptom of AD is impaired memory formation, especially for recent events or newly learned information. Memory lapses may be very subtle at first, thus leading many people to discount the symptoms as a sign of getting old. A person will ask the same question or say the same thing repeatedly within a short period of time but without remembering the prior conversation. Important objects such as checkbooks or wallets may be misplaced and lost. In the kitchen, pots can be left on the stove resulting in burnt food or small fires. Also, ingredients may be left out of recipes.

As AD progresses, details or even the occurrence of recent events may be forgotten. Implicit and semantic memory, as well as long-term memory, remain relatively intact early, but decline in these forms of memory eventually develops.

While memory is a key feature, AD is also defined by problems in other cognitive areas that result in a decline from previous levels of functioning. The additional cognitive areas include visuospatial skills, language, abstraction, planning and organization.

Visuospatial problems may cause an individual to become disoriented or lost in familiar environments. Accidents or becoming lost while driving can occur. Inability to recognize familiar individuals may also develop.

Language problems such as impaired comprehension or decreased speech output may occur in the later stages of AD.

Declines in planning and organization often result in missed bill payments or other difficulties with handling finances.

Behavioral symptoms are also common in AD. Apathy or decreased motivation causes affected individuals to appear lazy and indifferent. Depressed mood is also common. In some cases, the onset of depression late in life may precede the cognitive symptoms of AD. Agitation including physical and verbal aggressiveness may develop. Delusions and hallucinations can appear at any stage of AD. In rare instances, patients may believe that familiar people have been replaced with imposters.

Comparison to Other Disorders

Mild Cognitive Impairment (MCI)

In contrast to AD where other cognitive skills are affected, Mild Cognitive Impairment is defined by deficits in memory that do not significantly impact daily functioning. Memory problems may be minimal to mild and hardly noticeable to the individual. Writing reminders and taking notes allow a person to compensate for memory difficulties. Other cognitive spheres are intact in MCI.

The relationship between MCI and AD remains a point of debate. Unlike AD where cognitive abilities gradually decline, the memory deficits in MCI may remain stable for years. However, some individuals with MCI develop cognitive deficits and functional impairment consistent with AD. Whether MCI is a disorder distinct from AD or a very early phase of AD is a topic of continuing investigation.

Frontotemporal Dementia (FTD)

Frontotemporal Dementia is often mistaken for Alzheimer's Disease (AD). The age of onset in Frontotemporal Dementia can begin as early as age 35, commonly in the 50's, and rarely after 75. In contrast, the frequency of AD increases with age especially after age 60.

While memory problems are an early symptom of AD, FTD presents with early and prominent changes in behavior or language. In FTD, an individual becomes disinhibited and socially inappropriate, whereas people with AD may be apathetic, but generally remain socially appropriate. Changes in behavior in AD reflect cognitive deficits rather than loss of socialization seen in FTD.

Another early symptom of FTD is language difficulty, while memory remains largely unaffected. This manifests as difficulty reading, writing, naming, using correct words,

and expressing thoughts fluently. Conversely, language abilities become impaired late in AD. The advanced stages of AD and FTD are similar with profound deficits in memory, language, and behavior.

Genetics

“Am I at risk for developing Alzheimer’s Disease (AD) because my mother has it?” is a question we often hear at the UCSF Memory and Aging Center.

Clearly, the greatest risk for Alzheimer’s Disease is age. If we live into our 90s, up to 50% of us may develop the disease. At the same time, however, 5-10% of AD is caused by genes that are transmitted through families. In these families, people usually show symptoms well before the age of 65 and even as early as in their 30s. This form of AD is called early-onset familial Alzheimer’s Disease (EOFAD). Additionally there are other genes that increase or decrease susceptibility to AD but do not cause the disease.

Genetic Predisposition to Alzheimer’s Disease

The underlying mechanism of AD is the accumulation of a protein called beta-amyloid in neurons. This leads to neuron death with subsequent atrophy of certain regions of the brain. Early evidence of a genetic etiology to AD came from individuals with Down syndrome, also known as trisomy 21 due to an extra third copy of chromosome 21. It was found that almost all individuals with Down syndrome over the age of 40 had pathologic features of AD.

Since then, three predisposition genes have been associated with EOFAD. They are presenilin 1 (PS1) on chromosome 14, presenilin 2 PS2 on chromosome 1, and the amyloid precursor protein gene (APP) on chromosome 21. All of these genes affect the processing of the amyloid precursor protein and the generation of toxic beta-amyloid which creates the plaques in AD. Mutations (alterations) in PS1 account for approximately 30-50% of patients under the age of 60 with a strong family history of Alzheimer’s Disease. More than 70 mutations have been found in this gene. APP and PS2 are much rarer than PS1. Presenilin 2 mutations cause less than 1% of familial Alzheimer’s Disease Mutations in this gene and are largely limited to people originating from the Volga river area of Germany.

All three of these predisposition genes are inherited as autosomal dominant genes which means that carriers of the genes have a 50% risk of passing the gene to their offspring. Likewise, other first degree relatives (parents and siblings) have a 50% chance of carrying the gene. Clinical testing is available for the PS1 gene, but because of the small number of families with mutations in PS2 and APP, testing for these genes is currently only done through research labs.

Increased Susceptibility to Alzheimer's Disease

Up to 20% of presenile AD seems to be due to the presence of certain susceptibility genes that cause the disease to occur earlier in life than it would without the gene. However, the mechanism for this earlier onset is not well understood. Of these genes, the one with the clearest association to AD is the APOE gene. APOE is found in 3 different forms, APOE 2, APOE 3, or APOE 4. Like all other genes, each cell contains 2 copies (alleles) of the APOE gene. These alleles can be the same form or different forms of APOE. APOE 3 is the most common form of the gene and is found in approximately 75% of the population. APOE 4 has been associated with an increased risk for developing Alzheimer's Disease. People with 2 copies of APOE 4 have a significant increased risk over the general population, and people with 1 copy have about a 3-fold increased risk. Unlike the predisposition genes, however, APOE is a susceptibility gene. Not everybody with APOE 4 develops Alzheimer's Disease. Similarly, people without APOE 4 can develop Alzheimer's Disease.

As stated above, carrying 1 copy of the gene increases susceptibility to Alzheimer's Disease. However, other genetic and environmental factors also influence susceptibility. Carrying an APOE4 gene does not predict that an individual will definitely develop Alzheimer's Disease. Therefore, until preventative treatment is available, presymptomatic testing for APOE is not recommended.

Much about the genetics of AD is yet to be discovered. Researchers expect that many more susceptibility and modifier (risk reducing) genes will be found. The discovery of more genes will bring with it better understanding of the mechanism of the disease and the possibility of improved treatment and prevention.

Evaluation

AD is a clinical diagnosis. The most accurate way to diagnose AD is through a careful evaluation by specially trained physicians. No single (or combination) laboratory or radiological test can provide a definitive diagnosis.

An evaluation should include an interview with the patient as well as a collateral source such as a relative, spouse, or close friend. The collateral source can provide examples of memory loss and functional decline in areas such as hobbies, household chores, personal hygiene, problem-solving, and community affairs.

Because other neurologic disorders may mimic AD, a physical examination by a neurologist should be performed. Neuropsychological tests provide quantitative measures of cognitive functions, and repeated testing may uncover otherwise imperceptible decline.

Laboratory tests may reveal treatable disorders that can cause memory difficulty. When appropriate treatment is initiated, the memory deficits may improve. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain often reveals atrophy of the parietal and medial temporal lobes. Generalized cerebral atrophy with posterior predominance may be also seen, especially in advanced AD. Since the utility of any diagnostic test depends upon the clinical context, the evaluation for memory problems should be directed by a healthcare professional.

Treatment

Currently, there are several medications approved for the management of AD. By inhibiting the breakdown of acetylcholine, these medications slow the rate of decline. Some individuals may experience a mild, temporary improvement in cognition soon after starting the medication. However, the duration of improvement and stability is highly variable. It appears that all individuals with AD will progress over the long-term despite treatment.

Non-pharmacological interventions are also beneficial in AD. An aerobic and weight-bearing exercise regimen may increase energy levels, reduce apathy, and improve the overall sense of well-being. Since lack of motivation can be significant in AD, a personal trainer may assist in compliance with the exercise program.

While other similar medications are being developed, another area of research is a vaccine that targets the beta-amyloid protein. Studies of the vaccine in mice have shown promise. However, trials in humans are in the early stages.

Caregivers

Being a caregiver for someone with AD can be physically and emotionally challenging. Often, the caregiver has to assume tasks such as household finances and cooking that were previously the responsibility of the affected individual. Also, progressive loss of memory can impair recognition of familiar individuals which leads to emotional detachment and separation.

- Fortunately, the effects of AD are balanced by the fact that:
- AD is generally known and receives much publicity
- There is increasing awareness of memory loss in the elderly and vigilance for AD within the medical community
- A wide range of support services exist for individuals with dementia and their caregivers