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# Alzheimer's disease

Alzheimer's disease (AD), Senile Dementia of the Alzheimer Type(SDAT) or simply Alzheimer's, and is the most common form of dementia.

It is a slowly progressive disease of the brain that is characterized by impairment of memory and eventually by disturbances in reasoning, planning, language, and perception. Many scientists believe that Alzheimer's disease results from an increase in the production or accumulation of a specific protein (beta-amyloid protein) in the brain that leads to nerve cell death.

The likelihood of having Alzheimer's disease increases substantially after the age of 70 and may affect around 50% of persons over the age of 85. Nonetheless, Alzheimer's disease is not a normal part of aging and is not something that inevitably happens in later life. For example, many people live to over 100 years of age and never develop Alzheimer's disease.

## EPIDEMIOLOGY

The prevalence of AD increases exponentially with age, affectingapproximately 7% of individuals aged 65 to 74 years, 53%aged 75 to 84, and 40% of persons aged 85 years and older. AD affects two times as many women as men, and family history of ADmay increase the risk of inheriting the disease by up to fourfold. Althoughgenetic inheritance is a significant factor in its transmission,other factors may contribute. Factors determining age of onset andrate of progression remain largely undefined.Survival following AD onset is estimated to be 3 to 20 years,with an average of 8 years after the onset of symptoms. Approximately100,000 individuals with AD die every year. AD is the eighthleading cause of death in United States.

## ETIOLOGY

The exact etiology of AD is unknown; however, several geneticand environmental causes have been explored as potential causesof AD.

## GENETICS

Genetic factors have been investigated in both early- and late-onsetAD. Almost all early-onset cases of AD can be attributedto alterations on chromosomes 1, 14, or 21. The majority andmost aggressive early-onset cases are attributed to mutations of anAlzheimer's gene located on chromosome 14, which produces a proteincalled presenilin 1. Similar in structure to presenilin 1 is a proteinproduced by a gene on chromosome 1 called presenilin 2. Both presenilin 1 and presenilin 2 encodefor membrane proteins that may be involved in amyloid precursorprotein (APP) processing. It has been suggested, but not proven, thatpresenilins are either ?-secretase or that presenilins affect ?–secretaseactivity. APP is encoded on chromosome 21. Only a small numberof early-onset familial AD cases have been associated with mutationsin the APP gene, resulting in overproduction of beta-amyloid protein(βAP).Genetic susceptibility to late-onset AD is thought to be primarilyinfluenced by the apolipoprotein E (apo E) genotype. The generesponsible for the production of apo E is located onchromosome19 in a region previously associated with late onset AD. Three majorsubtypes or alleles of apo E occur, and are termed apo E2, apo E3,and apo E4.

## ENVIRONMENTAL AND OTHER FACTORS

A number of environmental factors have been associated with anincreased risk of AD, including stroke, alcohol abuse, small headcircumference, repeated or severe head trauma, Down syndrome, andlower levels of education.In particular, traumatic head injury incombination with the apo E4 genotype has been associated with anincreased risk of AD.

## PATHOPHYSIOLOGY

- **STRUCTURAL CHANGES**

AD destroys neurons in the cortex and limbicstructures of the brain, particularly the basal forebrain, amygdala,hippocampus, and cerebral cortex.

These areas are responsible forhigher learning, memory, reasoning, behavior, and emotional control.Anatomically, four major alterations in brain structure are seen:

Cortical atrophy, degeneration of cholinergic and other neurons, presenceof neurofibrillary tangles (NFTs), and the accumulation ofneuritic plaques.

NFTs and neuritic plaques are consideredthe signature lesions of AD; without themADdoes not occur. Plaquesand tangles may also be present in other diseases, even in normal aging,but there is a much higher concentration of plaques and tangles inpatients with AD. To understand the causes of AD, researchers mustdiscern the circumstances in which these lesions lead to the clinicalpicture of AD.

- **INFLAMMATORY MEDIATORS**

Inflammatory mediators and other immune system constituents arepresent near areas of plaque formation, suggesting that the immunesystem plays an active role in the pathogenesis of AD. Althoughperhaps not the disease-initiating event, an immune response generatedagainst some brain insult could facilitate neuronal destruction.

Evidence supporting significant involvement of the immune systemincludes the increased presence of acute-phase proteins, such as*a*1-antichromotrypsin and *a*2-macroglobulin, both in the serum andwithin amyloid plaques of patients with AD.

Glial cells (microglialcells and astrocytes), cytokines (e.g., interleukin-1 and interleukin-6),and components of the classic complement cascade are also markedlyincreased in plaque-infested areas. These inflammatory mediatorsincrease βAP toxicity and aggregation. Chronic production of cytotoxicagents and free radicals by activated microglia can result inaccelerated neurodegeneration.

- **THE CHOLINERGIC SYSTEM**

Widespread cell destruction results in a variety ofneurotransmitter deficits. Most profoundly damaged are the cholinergicpathways, particularly a large system of neurons located at the baseof the forebrain in the nucleus basalis ofMeynert, a brain area believedto be involved in thought integration.

Axons of these cholinergicneurons project to the frontal cortex and hippocampus, areas stronglyassociated with memory and cognition.

The discovery of vast cholinergic cell loss led to the developmentof a cholinergic hypothesis linked to the pathophysiology of AD.

Thecholinergic hypothesis targeted cholinergic cell loss as the sourceof memory and cognitive impairment in AD. Therefore it was presumedthat increasing cholinergic function would improve symptomsof memory loss.

- **OTHER NEUROTRANSMITTER ABNORMALITIES**

Serotonergic neurons of the raphenuclei and noradrenergic cells of the locus ceruleus are lost, whilemonoamine oxidase type B activity is increased. Monoamine oxidasetype B is found predominantly in the brain and in platelets, andis responsible for metabolizing dopamine.

In addition, abnormalitiesappear in glutamate pathways of the cortex and limbic structures,where a loss of neurons leads to a focus on excitotoxicity models aspossible contributing factors to AD pathology.

If glutamate is allowed to remain in thesynapse for extended periods of time, it can destroy nerve cells. Toxiceffects are thought to be mediated through increased intracellular calciumand accumulation of intracellular free radicals.

- **CHOLESTEROL**

Some evidence suggests that cellular membranes containlipid rafts rich in cholesterol. These rafts are small conglomerates ofprotein and cholesterol that float within the cellular membrane ofthe lipid bilayer.

The APP in the lipid rafts is cleaved by *β*- and?-secretases to produce *β*-amyloid fragments that could eventuallyform amyloid plaques. It is theorized that cholesterol depletioncan inhibit the amyloidogenic pathway and prevent or slow down theplaque formation process.

In addition, the APP in the lipid rafts mayalter the shape of the membrane, which could promote further amyloidformation via a seeding-type mechanism.

The elevated cholesterol levels in brain neuronsmay alter membrane functioning and result in the cascade leading toplaque formation and AD.

- **ESTROGEN**

Estrogen is thought to be involved in promoting neuronal growth,and in preventing oxidative damage, which would benefit cells exposedto $\beta$AP.

Estrogen receptors are present in the brain, and aredistributed in a pattern consistent with areas destroyed in AD. Inthe hippocampus, cerebral cortex, and basal forebrain, estrogen receptorscolocalize with receptors for nerve growth factor on cholinergicnerve terminals.

The presence of estrogen increases the numberof nerve growth factor receptors. The ability of estrogen to interactwith nerve growth factor may explain estrogen's ability to promotesynaptic growth, stimulating axons and dendrites to sprout new terminals.

Estrogen mayalso increase NMDA receptor numbers in brain areas involved inrecording new memories. In addition to promoting growth, estrogenprevents cell damage by acting as an antioxidant.

## CLINICAL PRESENTATION

The onset ofADis almost imperceptible, without abrupt changesin cognition or function. Deficits occur progressively over time,affecting multiple areas of cognition.

For treatment and assessmentpurposes, it is helpful to divide Alzheimer's symptoms into twobasic categories: cognitive symptoms and noncognitive (behavioral)symptoms.

Cognitive symptoms are present throughout the illness,whereas behavioral symptoms are less predictable.

*Cognitive:*Memory loss (poor recall and losing items); aphasia (circumlocutionand anomia); apraxia; agnosia; disorientation (impairedperception of time and unable to recognize familiar people); impairedexecutive function

*Noncognitive:*Depression, psychotic symptoms (hallucinationsand delusions), behavioral disturbances (physical and verbal aggression,motor hyperactivity, uncooperativeness, wandering, repetitivemannerisms and activities, and combativeness)

*Functional:*Inability to care for self (dressing, bathing, toileting,and eating)

Stages of Cognitive Decline: The Global Deterioration Scale (GDS)

**Stage 1 Normal**

No subjective or objective change in intellectualfunctioning.

**Stage 2 Forgetfulness**

Complaints of losing things or forgetting names ofacquaintances.Does not interfere with job or socialfunctioning.Generally a component of normal aging.

### Stage 3 Early confusion

Cognitive decline causes interference with work and social functioning. Anomia, difficulty rememberingright word in conversation, and recall difficulties are present and noticed by family members. Memoryloss may cause anxiety for patient.

### Stage 4 Late confusion (early AD)

Patient can no longer manage finances or homemaking activities. Difficulty remembering recent events.Begins to withdraw from difficult tasks and to give up hobbies.May deny memory problems.

### Stage 5 Early dementia(moderate AD)

Patient can no longer survive without assistance. Frequently disoriented with regard to time (date, year,season). Difficulty selecting clothing. Recall for recent events is severely impaired; may forget somedetails of past life (e.g., school attended or occupation). Functioning may fluctuate from day to day.Patient generally denies problems. May become suspicious or tearful.Loses ability to drive safely.

### Stage 6 Middle dementia(moderately severe AD)

Patients need assistance with activities of daily living (e.g., bathing, dressing, and toileting). Patientsexperience difficulty interpreting their surroundings; may forget names of family and caregivers; forgetmost details of past life; have difficulty counting backward from 10. Agitation, paranoia, and delusionsare common.

### Stage 7 Late dementia

Patient loses ability to speak (may only grunt or scream), walk, and feed self. Incontinent of urine andfeces. Consciousness reduced to stupor or coma.

## DIAGNOSIS

## LABORATORY TESTS

_ Rule out vitamin B12 and folate deficiency

_ Rule out hypothyroidism with thyroid function tests

_ CT or MRI scans may aid diagnosis

A family member rather than the patient often first brings memorycomplaints to the attention of a primary care clinician. Up to 50%of patients who meet criteria for dementia are not given a diagnosisin the primary care setting, leading some to believe that an appropriatescreening tool may be helpful in aiding diagnosis and leading toearlier treatment.

At present the only way to definitively diagnose AD is throughdirect examination of brain tissue at autopsy or biopsy.

The NINCDS(National Institute of Neurological and Communicative Disordersand Stroke ) – ADRDA (Alzheimer's Disease and RelatedDisorders Association ) criteria remain the standard.

**NINCDS-ADRDA Criteria and Diagnostic Work-Upfor Probable Alzheimer's Disease**

I. History of progressive cognitive decline of insidious onset

_ In-depth interview of patient and caregivers

II. Deficits in at least two or more areas of functioning

III. No disturbance of consciousness

_ Confirmation with use of dementia rating scale (e.g., Mini-Mental Status Exam [MMSE] or Blessed Dementia Scale)

IV. Age between 40 and 90 years (usually >65 years)

V. No other explainable cause of symptoms

_ Normal laboratory tests including hematology, full chemistries, B12 and folate, thyroid function tests, Venereal Disease Research Lab test (to rule out venereal disease or syphilis)

_ Normal electrocardiogram and electroencephalogram

_ Normal physical exam, including thorough neurologic exam

_ Neuroimaging: CT or MRI scanning: No focal lesions signifying other possible causes of dementia are present. Abnormalities which are common, but not diagnostic for AD include general cerebral wasting, widening of sulci, widening of the ventricles, and lesions of white matter surrounding the ventricle deep in the brain.

Other recommendations from theAANinclude noncontrast computedtomography (CT) or magnetic resonance imaging (MRI) scanning,which can be useful neuroimaging tests for initial evaluation; screeningand treatment of depression, B12 deficiency, and hypothyroidismare also recommended.

Functional assessment can be obtained fromthe patient and caregiver using the functional activities questionnaire(FAQ).

Side effects are nausea and vomiting, Dizziness, Less common secondary effects include Insomnia, muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.

**Other Agents**

***Memantine.****(Brand-Admenta)*

Memantine, an NMDA-antagonist, is a novelagent for treating AD. By blocking NMDA receptors, excitotoxicreactions, which ultimately lead to cell death, may be prevented.

Memantine is likely to be used as monotherapy and also incombination with cholinesterase inhibitors, particularly in patientswith moderate to severe AD. Memantine should be initiated at5 mg once a day and increased weekly by 5 mg a day to the effectivedose of 10 mg twice daily.

The most frequent **adverse events** associated with memantine includeconstipation, confusion, dizziness, headache, coughing, andhypertension.

***Vitamin E***

Based on pathophysiologic theoriesinvolving free radicals, significant interest has evolved regardingthe use of antioxidants in the treatment of AD.

Vitamin E is oftenrecommended as adjunctive treatment for AD patients, and should be titratedto a maintenance dose of 1000 international units twice a day.

***Estrogen.***

Interest in estrogen use has increased over thelast decade. Most, but not all, epidemiologic studies show a lowerincidence of AD in women who took estrogen replacement therapypostmenopausally.

Showed increased risk in coronary heart disease, breast cancer, stroke,and pulmonary embolism. Benefits included reduced risk of colorectalcancer and hip fracture.

The effect of estrogen inADas a treatmentof cognition has not been established, and other health risks are alsoof concern; therefore estrogen should only be used in those patientswho have another medical reason for estrogen replacement therapy.

***Anti-Inflammatory Agents.***

Long-term usage of non-steroidal anti-inflammatory drug (NSAIDs) is associated with a reduced likelihood of developing AD.

NSAIDs can reduce inflammation related to amyloid plaques.

Epidemiologic studies havealso suggested a protective effect against AD in patients whohave taken nonsteroidal anti-inflammatory drugs (NSAIDs)Treatment for less than 2 years has been associated with a lowerrelative risk of AD; however, longer treatment duration lowered thisrisk further.

*Lipid-Lowering Agents.*

Interest in the potential protectiveeffects in AD patients of lipid-lowering agents, particularly the3-hydroxy-3-methylglutaryl-CoA (HMG-CoA)-reductase inhibitors,is growing based on recent epidemiologic studies.

Studies suggested that the incidence of AD is lower in patients whohave taken either a statin or another lipid-lowering agent, butnot in patients who were taking other cardiovascular medications.

Interestingly, pravastatin and lovastatin, but not simvastatin, were associatedwith a lower prevalence of AD.

For now these agents should be reserved forpatients who have other indications for their use.

*Ginkgo Biloba.*

Egb 761 is an extract of ginkgo biloba, isclaimed to improve memory. Although it is thought to be an antioxidantand to affect inflammation and neuromodulation, the mechanismsof the multiple compounds in Egb have not been elucidated.

Standardized doses of ginkgo ranged from 120 to 240 mg/day.

Nosignificant adverse events were reported; however, some case reportshave shown an association with hemorrhaging.

Until theseproducts are better standardized and their manufacturing and stabilitybetter assured, it is recommended that they be used with caution.

## 2.PHARMACOTHERAPY OF NONCOGNITIVE (BEHAVIOURAL) SYMPTOMS

The majority of patients with AD manifest noncognitive symptoms atsome point in the illness. These symptoms can be roughly dividedinto three categories: psychotic symptoms, inappropriate or disruptivebehavior, and depression.

Effective management of these problems isimportant because behavioral symptoms are distressing to both thepatient and the caregiver, necessitate increased caregiver supervisionand patience, and are a leading reason for nursing home placement.

Strategies for treatment of psychotic or behavioral symptomsshould include both environmental and pharmacologic interventions(e.g., antipsychotics, antidepressants, mood stabilizers, andanxiolytics).

| Drugs | Suggested Dosage | Indications |
|---|---|---|
| **inDementia (mg/day)** | | |
| **Antipsychotics** | | |
| Haloperidol | 0.5–4 mg | Psychosis: hallucinations, delusions, suspiciousness |
| Olanzapine | 2.5–10 mg | Disruptive behaviors: agitation, aggression |
| Quetiapine | 12.5–200 mg | |
| Risperidone | 0.25–2 mg | |
| **Antidepressants Depression:** | | |
| Citalopram | 10–20 mg | poor appetite, insomnia, hopelessness, |
| Fluoxetine | 5–20 mg | anhedonia, withdrawal, suicidal thoughts, agitation |
| Mirtazapine | 15–45 mg | |
| Paroxetine | 10–40 mg | |
| Sertraline | 50–200 mg | |
| Trazodone | 75–400 mg | |
| Venlafaxine | 37.5–150 mg | |
| **Anticonvulsants** | | Agitation or aggression |
| Carbamazepine | 100–1,000 mg | |
| **Others** | | |
| Buspirone | 10–45 mg | Disruptive behaviors |
| Oxazepam | 10–60 mg | Disruptive behaviours |
| Selegiline | 10 mg | Disruptive behaviors, agitation, anxiety, depression |

## Antipsychotics

Antipsychotic medications have traditionally been used to treat disruptivebehaviors and psychosis in AD patients. Symptoms respondingto antipsychotics include assaultiveness, extreme agitation, hyperexcitability,hallucinations, delusions, suspiciousness, hostility, anduncooperativeness; whereas withdrawal, apathy, cognitive deficits, wandering, and incontinence are not responsive.