In the middle stages of AD, the patient is unable to work, is easily lost and confused, and requires daily supervision. Language becomes impaired—first naming, then comprehension, and finally fluency. Word-finding difficulties and circumlocution can be evident in the early stages, even when formal testing demonstrates intact naming and fluency. *Apraxia* emerges, and patients have trouble performing learned sequential motor tasks. Visuospatial deficits begin to interfere with dressing, eating, or even walking, and patients fail to solve simple puzzles or copy geometric figures. Simple calculations and clock reading become difficult in parallel.

In the late stages, some persons remain ambulatory, wandering aimlessly. Loss of judgment and reasoning is inevitable. Delusions are common, usually simple, with common themes of theft, infidelity, or misidentification. Approximately 10% of AD patients develop *Capgras' syndrome*, believing that a caregiver has been replaced by an impostor. In contrast to dementia with Lewy bodies (DLB), where Capgras' syndrome is an early feature, in AD this syndrome emerges late. Disinhibition and uncharacteristic belligerence may occur and alternate with passivity and withdrawal. Sleep-wake patterns are disrupted, and nighttime wandering becomes disturbing to the household. Some patients develop a shuffling gait with generalized muscle rigidity associated with slowness and awkwardness of movement. Patients often look parkinsonian **(Chap. 449)** but rarely have a high-amplitude, low-frequency tremor at rest. There is a strong overlap between Parkinson's disease (PD) and AD, and some AD patients develop more classical PD features.

In the end stages, AD patients become rigid, mute, incontinent, and bedridden, and help is needed with eating, dressing, and toileting. Hyperactive tendon reflexes and myoclonic jerks (sudden brief contractions of various muscles or the whole body) may occur spontaneously or in response to physical or auditory stimulation. Often death results from malnutrition, secondary infections, pulmonary emboli, heart disease, or, most commonly, aspiration. The typical duration of AD is 8–10 years, but the course ranges from 1 to 25 years. For unknown reasons, some patients with AD show a steady decline in function while others have prolonged plateaus without major deterioration.

DIFFERENTIAL DIAGNOSIS

Early in the disease course, other etiologies of dementia should be excluded **(see Tables 35-1, 35-3, and 35-4)**. Neuroimaging studies (computed tomography [CT] and magnetic resonance imaging [MRI]) do not show a single specific pattern with AD and may be normal early in the disease. As AD progresses, more distributed but usually posterior-predominant cortical atrophy becomes apparent, along with atrophy of the medial temporal memory structures **(see Chap. 35, Fig. 35-1)**. The main purpose of imaging is to exclude other disorders, such as primary and secondary neoplasms, vascular dementia, diffuse white matter disease, and normal-pressure hydrocephalus (NPH). Imaging also helps to distinguish AD from other degenerative disorders, such as frontotemporal dementia (FTD) or Creutzfeldt-Jacob disease (CJD), which feature distinctive imaging patterns. Functional imaging studies, such as positron emission tomography (PET), reveal hypometabolism in the posterior temporal-parietal cortex in AD **(see Fig. 35-1)**. PET can also be used to detect the presence of fibrillar amyloid in the brain **(see Fig. 35-4)**, and amyloid PET positivity is becoming required for entry into treatment trials for AD. Barriers to interpretation continue, however, to limit the use of amyloid PET in routine clinical evaluation. Although amyloid binding with PET is typical for AD, many asymptomatic healthy older individuals show amyloid uptake, and the likelihood that these individuals will convert to clinical AD is still under study. Similarly, dementia due to a non-AD disorder can be the underlying etiology in a patient who is amyloid positive on imaging. Electroencephalogram (EEG) is normal or shows nonspecific slowing; prolonged EEG can be used to seek out intermittent nonconvulsive seizures. Routine spinal fluid examination is also normal. Cerebrospinal fluid (CSF) $A\beta_{42}$ level is reduced, whereas the tau protein is elevated, but the test characteristics of these assays still make interpretation challenging in individual patients. *Slowly progressive decline in memory and orientation, normal results on laboratory tests, and an MRI or CT scan showing only distributed or posteriorly predominant cortical and hippocampal atrophy are highly suggestive of AD.* A clinical diagnosis of AD reached after careful evaluation is confirmed at autopsy about 90% of the time, with misdiagnosed cases usually representing one of the other dementing disorders described later in this chapter, a mixture of AD with vascular pathology, or DLB.

Simple clinical clues are useful in the differential diagnosis. Early prominent gait disturbance with only mild memory loss suggests vascular dementia or, rarely, NPH (see below). Resting tremor with stooped posture, bradykinesia, and masked facies suggest PD **(Chap. 449)**. When dementia occurs after a well-established diagnosis of PD, PD dementia (PDD) is usually the correct diagnosis, but many patients with this diagnosis will show a mixture of AD and Lewy body disease at autopsy. The early appearance of parkinsonian features in association with fluctuating alertness, visual hallucinations, or delusional misidentification suggests DLB. Chronic alcoholism should prompt the search for vitamin deficiency. Loss of joint position and vibration sensibility accompanied by Babinski signs suggests vitamin B_{12} deficiency **(Chap. 456)**. Early onset of a focal seizure suggests a metastatic or primary brain neoplasm **(Chap. 118)**. Previous or ongoing depression raises suspicion for depression-related cognitive impairment, although AD can feature a depressive prodrome. A history of treatment for insomnia, anxiety, psychiatric disturbance, or epilepsy suggests chronic drug intoxication. Rapid progression over a few weeks or months associated with rigidity and myoclonus suggests CJD **(Chap. 453e)**. Prominent behavioral changes with intact navigation and focal anterior-predominant atrophy on brain imaging are typical of FTD. A positive family history of dementia suggests either one of the familial forms of AD or one of the other genetic disorders associated with dementia, such as FTD (see below), HD (see below), prion disease **(Chap. 453e)**, or rare hereditary ataxias **(Chap. 450)**.

EPIDEMIOLOGY

The most important risk factors for AD are old age and a positive family history. The prevalence of AD increases with each decade of adult life, reaching 20–40% of the population over the age of 85. A positive family history of dementia suggests a genetic contribution to AD, although autosomal dominant inheritance occurs in only 2% of patients. Female sex is a risk factor independent of the greater longevity of women, and women who carry an Apo ε4 allele are more susceptible than are male ε4 carriers. A history of head trauma with concussion increases the risk for AD. AD is more common in groups with low educational attainment, but education influences test-taking ability, and it is clear that AD can affect persons of all intellectual levels. One study found that the capacity to express complex written language in early adulthood correlated with a decreased risk for AD. Numerous environmental factors, including aluminum, mercury, and viruses, have been proposed as causes of AD, but rigorous studies have failed to demonstrate to a significant role for any of these exposures. Similarly, several studies suggest that the use of nonsteroidal anti-inflammatory agents is associated with a decreased risk of AD, but this risk has not been confirmed in large prospective studies. Vascular disease, and stroke in particular, seems to lower the threshold for the clinical expression of AD. Also, in many patients with AD, amyloid angiopathy can lead to microhemorrhages, large lobar hemorrhages, ischemic infarctions most often in the subcortical white matter, or in rare cases an inflammatory leukoencephalopathy. Diabetes increases the risk of AD threefold. Elevated homocysteine and cholesterol levels; hypertension; diminished serum levels of folic acid; low dietary intake of fruits, vegetables, and red wine; and low levels of exercise are all being explored as potential risk factors for AD.

PATHOLOGY

At autopsy, the earliest and most severe degeneration is usually found in the medial temporal lobe (entorhinal/perirhinal cortex and hippocampus), lateral temporal cortex, and nucleus basalis of Meynert. The characteristic microscopic findings are neuritic plaques and NFTs **(Fig. 448-1)**. These lesions may accumulate in small numbers during