function, naming, attention, fluency; abstract reasoning, short-term memory encoding and retrieval, and orientation.

In addition to the MoCA, patients with dementia should have tests of praxis (e.g., show how you would comb your hair; show how you would blow out a match) and neglect (e.g., testing of double-simultaneous extinction to visual, tactile, and auditory stimuli). Depending on the results of these screening procedures, more detailed neuropsychological studies can be pursued.

## Alzheimer's Disease

AD accounts for approximately 70% of dementia cases among older adults. Almost 5.3 million persons in the United States are affected, and this number may approach 18 million by 2050 as the population ages. AD places enormous burdens on the patient, family, and society. The annual direct and indirect expenditures are estimated to exceed $150 billion. The disease occurs in 32% to 47% of persons older than 80 years of age. Incidence at age 65 is one in 200 people per year. Incidence at age 80 is one case per 10 people per year. More than 50% of caregivers develop depression or major medical illness.

AD has many causes, but none is fully defined. All causes produce similar clinical and pathologic findings. The disease is characterized by the progressive loss of cortical neurons and the formation of amyloid plaques and intraneuronal neurofibrillary tangles. β-Amyloid (Aβ) is the major component of the plaques, and hyperphosphorylated tau protein is the major constituent of the neurofibrillary tangles. The process starts in the hippocampus and entorhinal cortex and spreads to involve diffuse areas of association cortex in the temporal, parietal, and frontal lobes. The relative deficiency of cortical acetylcholine (resulting from the loss of neurons in the nucleus basalis) provides the rationale for symptomatic treatment of the disease with centrally acting acetylcholinesterase inhibitors.

**TABLE 108-4 ELEMENTS OF THE MONTREAL COGNITIVE ASSESSMENT**

| COGNITIVE DOMAIN | ITEMS | SCORE |
|---|---|---|
| Visual-spatial or executive | Complete a trail-making task, copy a cube, draw a clock | 5 |
| Naming | Name three depicted animals | 3 |
| Attention | Recall 5 digits forward, 3 digits backward, maintain letter vigilance, subtract 7s serially | 6 |
| Language | Repeat two phrases, generate a list of words starting with a specific letter | 3 |
| Abstraction | Identify the similarity between nouns (train/bicycle; watch/ruler) | 2 |
| Delayed recall | Recall five words rehearsed twice previously (face, velvet, church, daisy, red) | 5 |
| Orientation | Identify the date, month, year, day, place, and city | 6 |
| Total possible score | | 30 |

From Nasreddine ZS, Phillips NA, Bedirian V, et al: The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, J Am Geriatr Soc 53:695–699, 2005.

### Pathogenesis

AD is often categorized as a young-onset, hereditary or familial form, which is rare and for which three specific genetic abnormalities have been determined, or as a common, sporadic form that typically occurs in persons older than 65 years of age (Table 108-5).

The autosomal dominant, early-onset forms of AD have in common abnormalities of Aβ production and processing, which have provided clues to the molecular pathogenesis of sporadic AD. Abnormal processing of amyloid precursor protein into the amyloidogenic peptide Aβ (1-42) is thought to be important in the pathogenesis of AD. It is thought to provoke downstream abnormalities of tau protein processing, with hyperphosphorylation of tau yielding intraneuronal tangles.

The apolipoprotein E (Apo E) gene *(APOE)* was found to be a susceptibility locus for sporadic AD in late-onset familial AD pedigrees. The gene is polymorphic (ε2, ε3, ε4), and first-degree relatives of AD patients, who inherit both ε4 alleles, have a more than 60% lifetime risk of developing AD. Apo E-ε4 interacts selectively with Aβ and with tau protein, but how Apo E-ε4 increases the risk of AD remains unknown.

### Clinical Features

AD begins gradually and affects memory, orientation, language, visuospatial processing, praxis, judgment, and insight. Depression is common early in AD, and psychosis with agitation and behavioral disinhibition often occur in advanced stages. Patients become dependent on others for all activities of daily living. The rate of progression of AD is varies but usually takes 5 to 15 years to progress from presentation to advanced illness.

Diagnostic criteria are outlined in Table 108-6. Although a definitive diagnosis of AD requires biopsy (rarely done) or autopsy confirmation, these diagnostic criteria establish the diagnosis with more than 85% specificity in moderately demented patients. The positron emission tomography (PET) ligand

**TABLE 108-5 FAMILIAL VERSUS SPORADIC ALZHEIMER'S DISEASE**

| CHROMOSOME AND GENE | AGE AT ONSET (YR) | % OF ALL FAD CASES | % OF ALL SAD CASES |
|---|---|---|---|
| **FAMILIAL ALZHEIMER'S DISEASE*** | | | |
| Chromosome 1, *PSEN2* (presenilin 2) | 40-80 | 5-10 | <0.5 |
| Chromosome 14, *PSEN1* (presenilin 1) | 30-60 | 70 | <1 |
| Chromosome 21, *APP* (amyloid-β precursor protein) | 35-65 | 5 | <0.5 |
| **SPORADIC ALZHEIMER'S DISEASE†** | | | |
| No single determinant gene‡ | Usually >60 | — | 98 |

*Familial Alzheimer's disease (FAD) has early onset and is autosomal dominant.
†Sporadic Alzheimer's disease (SAD) has late onset and may be polygenetic and/or environmental.
‡Apolipoprotein E-ε4 allele on chromosome 19 increases the risk compared with the ε2 or ε3 allele.