TABLE 108-6 DIAGNOSTIC CRITERIA FOR PROBABLE ALZHEIMER'S DISEASE

Progressive functional decline and dementia established by clinical examination and mental status testing and confirmed by neuropsychological assessment
Insidious onset
Clear-cut history of worsening cognition by report or observation
Initial and most prominent cognitive deficits evident on history and examination in one of the following categories:
Amnestic presentation (plus at least one other domain)
Nonamnestic presentations (plus deficits in other domains): language, visuospatial, executive dysfunction
No evidence of vascular dementia, dementia with Lewy bodies, frontotemporal dementias, or other concurrent active neurologic or non-neurologic medical comorbidity or use of medication that could have a substantial effect on cognition

florbetapir F 18 (Amyvid), which binds to amyloid plaques, has been approved by the U.S. Food and Drug Administration (FDA) for use in the clinical diagnosis of AD. It can be positive in patients without clinical signs of dementia. Similarly, cerebrospinal fluid (CSF) assays for Aβ, tau, and phosphorylated tau protein loads have been commercialized as aids to diagnosis, but they are not universally used due to the invasive nature of the testing and the relatively good accuracy of the clinical diagnosis.

PET and CSF assays are in widespread use for stratification of subjects in emerging large-scale, prospective, randomized studies of individuals at risk for preclinical disease. Changes in brain morphometry are identifiable on structural imaging many years before onset of clinical symptoms.

Treatment

Although their benefits are modest, the cholinesterase-inhibiting drugs donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne) represent important advances. These drugs may be given in once-daily formulations. Rivastigmine is also available as a transdermal patch.

In clinical trials, cholinesterase inhibitors benefited less than 50% of patients. They have not been shown to prevent AD in patients with mild cognitive impairment (MCI), a condition in which the memory or another domain of cognition is impaired in the absence of meaningful dysfunction in daily life. Approximately 12% of patients with MCI go on to develop AD per year, with roughly two thirds of patients with MCI developing clinical AD within 5 years of symptom onset.

Gingko biloba has no role in the treatment or prevention of AD. The glutamate antagonist memantine (Namenda) has been shown to prolong daily function in patients with moderate to advanced AD.

Treatment strategies in clinical trials over the past decade have included decreasing Aβ peptide production by blocking α-secretase or β-secretase or upregulating cleavage of the amyloid precursor protein at the α-secretase site. Studies of active and passive immunization have been designed to lower brain Aβ levels. However, these approaches have failed to deliver on the promise of AD disease modification, necessitating a wide-reaching reassessment of current theories of disease pathogenesis.

There is an emerging concept of preclinical AD, with many biomarkers showing changes years before clinical manifestations. Several large, prospective, interventional studies targeting this population are getting underway or are planned on the inference that intervening later in the disease process (when symptoms of dementia have manifested) may be too late. Novel molecular and immunologic approaches continue to hold promise for disease-modifying treatments in the future.

Nursing services provide oversight of hygiene, nutrition, and medication compliance. Antipsychotics, antidepressants, and anxiolytics are useful for patients with behavioral disturbances, which are the most common cause of nursing home placement. Patients and families can be referred to a local Alzheimer's Association chapter for further information on available community support.

Prevention

There is no high or even moderate level of evidence that any intervention decreases the risk of AD. There is a low level of evidence that a Mediterranean diet, folic acid, HMG-CoA reductase inhibitors (i.e., statins), higher levels of education, light alcohol intake, cognitively engaging activities, and physical activity (particularly at high levels) may decrease the risk of AD.

There is a moderate level of scientific evidence that conjugated equine estrogen with methyl-progesterone increases the risk of AD. There is a low level of scientific evidence that some nonsteroidal anti-inflammatory drugs, depressive disorder, diabetes mellitus, hyperlipidemia in midlife, current tobacco use, traumatic brain injury, pesticide exposure, and relative social isolation increase the risk of AD.

Diffuse Lewy Body Disease

Lewy bodies are pathologic inclusions that are the hallmark of Parkinson's disease when they are restricted to the brain stem (see Chapter 114). Patients with diffuse Lewy body disease have clinical parkinsonism (i.e., slow movement, rigidity, and balance problems) combined with early and prominent dementia. Pathologically, Lewy bodies are found in the brain stem, limbic system, and cortex. Visual hallucinations and cognitive fluctuations are common, and patients are unusually sensitive to the adverse effects of neuroleptic medication.

Diffuse Lewy body disease may represent the second most common cause of dementia after AD. However, the common concurrence of the pathologic features of diffuse Lewy body disease with the classic neuritic plaques and neurofibrillary tangles of AD complicates the identification of the cause of dementia in a given patient.

Vascular Dementia

Approximately 10% to 20% of older patients with dementia have radiographic evidence of focal stroke on magnetic resonance imaging (MRI) or computed tomography (CT), combined with focal signs on the neurologic examination. When the dementia syndrome begins with a stroke and progression of the illness is stepwise (suggesting recurrent vascular events), the diagnosis of vascular dementia is likely.

Patients typically develop early incontinence, gait disturbances, and flattening of affect. A subcortical dementing process attributed to small vessel disease in the periventricular white matter has been referred to as *Binswanger's disease,* but it may be a radiographic finding rather than a true disease. Appropriate