Alzheimer Disease

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ALZHEIMER DISEASE (AD), THE most common cause of dementia in the elderly, is a progressive neurodegenerative disorder that gradually robs the patient of cognitive function and eventually causes death. We review the epidemiology, clinical features, pathophysiology, and treatment of AD.

Incidence, Prevalence, and Economic Impact

Alzheimer disease accounts for 60% to 70% of cases of progressive cognitive impairment in elderly patients. The total prevalence of AD in the United States is estimated at 2.3 million (range, 1.09-4.8 million).[1] The prevalence of AD doubles every 5 years after the age of 60 increasing from a prevalence of 1% among those 60- to 64-years-old to up to 40% of those aged 85 years and older.[2] The disease is more common among women than men by a ratio of 1.2 to 1.5.[3] The number of new cases per year is estimated at 360 000 equating to 980 new cases per day or 40 new cases every hour. The population of patients with AD will nearly quadruple in the next 50 years if the current trend continues.[1]

The direct costs for the care of patients in 1991 were calculated at US $20.6 billion and the total cost was calculated to be $76.3 billion.[4] Most direct costs of care for patients with AD are absorbed by the expense of nursing home care, approximately $47 000 per patient per year.[5]

Several risk factors for AD have been identified in epidemiologic studies in addition to age and female sex. The most potent risk factor is the presence of the apolipoprotein ε4 (*APOE* ε4) allele. Of its 3 forms—ε2, ε3, and ε4—only the ε4 allele increases the likelihood of developing AD. The lifetime risk of AD for an individual without the ε4 allele is approximately 9%; the lifetime risk of AD for an individual carrying at least 1 ε4 allele is 29%.[6] While representing a substantial risk of AD, the ε4 genotype is not sufficiently specific or sensitive for the diagnosis of AD to allow its use as a diagnostic test.[7] Moreover, the ε4 allele appears to increase the risk of AD more in white and Asian populations than in black and Hispanic populations. Other risk factors implicated in a variety of studies include head injury, low serum levels of folate and vitamin B_{12}, elevated plasma and total homocysteine levels, family history of AD or dementia, fewer years of formal education, lower income, and lower occupational status.[8-12] Conversely, higher levels of education, moderate levels of daily wine consumption, and higher levels of fish in the diet have been associated with a lower risk for AD.[13,14] Differences in the prevalence of AD among population groups worldwide suggest as yet undisclosed genetic or environmental effects on the prevalence of AD.[15]

Clinical Diagnosis

Available evidence suggests that mild dementia is rarely diagnosed and even moderately severe dementia is underrecognized in clinical practice.[16] The evidence-based review conducted by the American Academy of Neurology concluded that mental status screening instruments such as the Mini-Mental State Examination[17] are useful for detecting dementia and should be used in populations at increased risk for dementia such as elderly patients and those with complaints of memory impairment.[18] The specificity of the Mini-Mental State Examination is good (96%) but the sensitivity is poor (63%), indicating that by itself the test (using a standard cutoff score of 24) will leave a substantial proportion of cases of early dementia undetected. Asking patients and knowledgeable informants about abnormalities in learning and retaining new information, difficulty handling complex tasks, impaired reasoning ability, and changes in language or behavioral alterations may enhance detection of early stages of AD.[19]

The typical clinical syndrome of AD includes an amnestic type of memory defect with difficulty learning and recalling new information, progressive language disorder beginning with anomia and progressing to fluent aphasia, and disturbances of visuospatial skills manifested by environmental disorientation and difficulty copying figures in the course of mental status examination.[20] There are usually deficits in executive function (planning, insight, judgment) and the patient is typically unaware of memory or cognitive compromise. All cognitive deficits progressively worsen.

Neuropsychiatric symptoms are common in AD. Apathy is apparent early in the clinical course with diminished interest and reduced concern. Agitation becomes increasingly common as the illness advances and is a frequent precipitant of nursing home placement. Depressive symptoms are present in about 50% of patients and approximately 25% exhibit delusions.[21]

Motor systems abnormalities are absent in AD until the final few years of the disease; focal abnormalities, gait changes, or seizures occurring early in the clinical course of dementia make the diagnosis of AD unlikely.[22] Patients with AD usually survive 7 to 10 years after

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onset of symptoms[23] and typically die from bronchitis or pneumonia.[24]

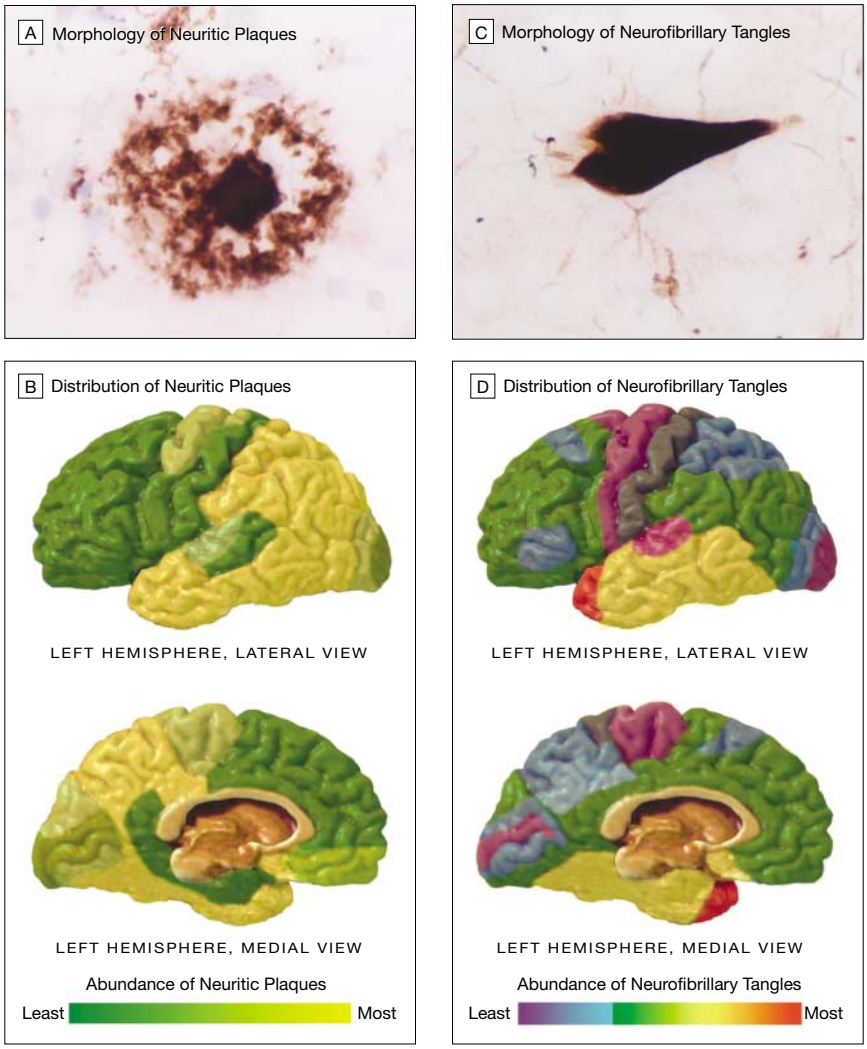
Assessment and diagnosis of AD require identifying the core clinical features and excluding other common causes of dementia in the elderly. Screening for thyroid dysfunction and vitamin B_{12} deficiency is recommended; syphilis is no longer sufficiently common to warrant routine screening in typical clinical circumstances.[25] Neuroimaging should be obtained to identify vascular contributions to the dementia syndrome and to identify other intracranial pathology. Functional imaging with positron emission tomography or single photon emission computed tomography are helpful particularly when clinical features are ambiguous.

Pathology

The current criteria for the pathologic diagnosis of AD require the presence of both neuritic plaques and neurofibrillary tangles in excess of the abundance anticipated for age-matched healthy controls (FIGURE 1).[26,27] Neuritic plaques consist of a central core of amyloid protein surrounded by astrocytes, microglia, and dystrophic neurites often containing paired helical filaments.[28] Neurofibrillary tangles are the second major histopathological feature of AD. They contain paired helical filaments of abnormally phosphorylated tau protein that occupy the cell body and extend into the dendrites.

In addition to the 2 major classic histopathologic features, AD also is characterized by reductions in synaptic density, loss of neurons, and granulovacuolar degeneration in hippocampal neurons.[29] Neuronal loss or atrophy in the nucleus basalis, locus ceruleus, and raphe nuclei of the brainstem leads to deficits in cholinergic, noradrenergic, and serotonergic transmitters, respectively.[29]

Figure 1. Morphology and Distribution of Neuritic Plaques and Neurofibrillary Tangles



A, Neuritic plaque (labeled with a monoclonal antibody for human amyloid peptide using diaminobenzidine combined with hematoxylin counterstain, ×2500 magnification). B, Distribution of neuritic plaques in the cerebral cortex. C, Neurofibrillary tangle (Gallyas silver stain; ×2500 magnification). D, Distribution of neurofibrillary tangles in the cerebral cortex.

Molecular Genetics and Pathogenesis

Mutations account for fewer than 5% of all cases of AD but have been of great value in the study of the pathogenesis of the disorder. Mutations in the amyloid precursor protein (*APP* gene, chromosome 21), presenilin 1 gene (chromosome 14), and the presenilin 2 gene (chromosome 1) produce an autosomal dominant pattern of inheritance with nearly complete penetrance.[30,31]

The amyloid protein that appears to be central to the pathogenesis of AD is derived from APP (FIGURE 2)[32] and is deposited in neuritic plaques. The accumulation of β-amyloid initiates a series of events contributing to cell death, including activation of cell death programs, oxidation of lipids and disruption of cell membranes, an inflammatory response, and possible tangle formation,[33] a close correlate of neuron loss. All of the identified mutations that cause AD result in increased production of β-amyloid protein.[32]

Head injury, educational level, and other risk and protective factors identified through epidemiologic studies may exert effects on the likelihood of developing AD through their impact on cerebral reserve—the ability of the brain to withstand the accumulating amy-

loid burden without evidencing dysfunction and cognitive impairment.[28]

Treatment

Treatments for AD include cholinesterase inhibitors; disease-modifying treatments; psychotropic agents; and psychosocial interventions and caregiver support. Treatment of AD must reflect the values and wishes of the patient and their family. Therapeutic strategies may also change in the course of the disease; for example, slowing of disease progression with vitamin E may be desirable early in the clinical course but not in patients with advanced disease.

Cholinesterase inhibitors are the only medications approved by the US Food and Drug Administration as treatment for AD. Sufficient evidence has accumulated for these to be recommended as standard therapy for AD.[34] Four inhibitors are currently available: tacrine, donepezil, rivastigmine, and galantamine. Tacrine is rarely used because it is hepatotoxic, a property not exhibited by other cholinesterase inhibitors. These agents have been shown to produce improvements in global function and cognition.[35-37] Secondary benefits may include reduction in behavioral disturbances, temporary stabilization of activities of daily living, delay of nursing home placement, and reduced demands on caregiver time.[38] The physician should seek evidence of changes in activities of daily living, behavior, or cognition to determine if the patient has benefited from treatment. Treatment responses include improvement, temporary stabilization, or amelioration of the rate of decline. Patients not responding to one agent in the class may respond to another. Discontinuation of treatment should be monitored; deterioration during withdrawal indicates therapeutic benefit and the medication should be reinstated.

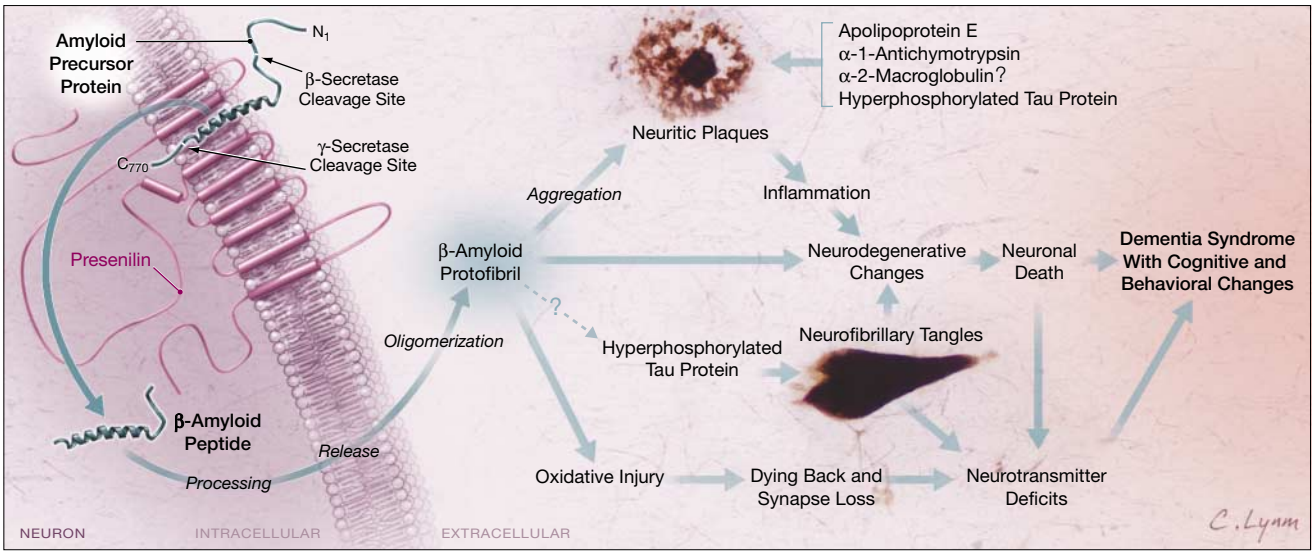
Vitamin E (2000 IU/d) and selegiline (10 mg/d) have been shown to reduce the rate of decline of functions in patients with AD. Combined therapy was not superior to either agent alone.[34,39] Evidence to support the use of other antioxidants, anti-inflammatory agents, or herbal medications such as ginkgo biloba is insufficient to recommend use as standard therapies.[34] Estrogen in standard doses has been shown not to improve cognition in postmenopausal women with AD.[40,41]

Reducing amyloid production, aggregation, or enhancing its removal are promising avenues of treatment that will address the basic pathophysiology of AD. Immunization, secretase inhibition, and other strategies to accomplish this are being studied.

Epidemiologic data suggest that nonsteroidal anti-inflammatory agents, hormonal treatments, histamine H2 blockers, antihypertensive agents, and statins may decrease the likelihood of developing AD.[42-44] Clinical trials of these compounds to test their roles in the treatment or prevention of AD are planned or under way.

Psychotropic medications play a critical role in the management of behavioral disturbances of patients with AD. Relatively few psychotropic compounds have been tested specifically in AD populations. Recent double-blind, placebo-controlled trials have established the efficacy of the atypical antipsychotics risperidone and olanzapine for the treatment of psychosis and agitation in patients with AD.[45,46] Anticonvulsants such as carbamazepine also have been shown to have antiagitation effects.[47] Depression responds to treatment with selective se-

Figure 2. Cascade of Events Associated With β-Amyloid Generation and Cell Death



Oligomerization of the β-amyloid peptide initiates oxidative injury, plaque formation (following β-amyloid aggregation), and possibly tangle formation (dashed line). Oxidative injury and inflammation contribute to membrane disruption, degeneration of the neuronal axon, and loss of synapses. Neurodegeneration ensues leading to cell death and neurotransmitter deficits. Apolipoprotein E, α-1-antichymotrypsin, and possibly α-2-macroglobulin contribute to plaque formation.

rotonin reuptake inhibitors or tricyclic antidepressants; there are fewer adverse effects with the former.[48,49]

Building an alliance with family caregivers is critical to success in the management of patients with AD. Family caregivers provide most of the care received by patients with AD over the course of their illness and are responsible for ensuring adherence to treatment regimens. Caregivers are prone to depression and physical illness as a result of the chronic stress associated with caregiving. Families benefit from short-term education programs and support groups.[34] The Alzheimer's Association is an important ally in identifying and providing community resources for patients with AD and their caregivers.[50]

Challenges

Dramatic progress has been made in understanding the pathogenesis of and developing therapy for AD. Advances so far have had no impact on the prevalence of the disorder and have had limited effects on the clinical course. An effective response to the public health challenge presented by AD requires united efforts in drug discovery, clinical trials of promising agents, implementation in health care delivery systems of programs for screening and treatment of patients with AD, and governmental and public policy initiatives that support patients with AD and their caregivers in all stages of the disease. Much has been achieved but much more remains to be done to prevent the losses of cognitive function, emotional integrity, enjoyment of life, and personal dignity associated with AD.

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