

Review of Dementia

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Abstract

Elderly persons are at increased risk for developing dementia, and this risk increases with age. It is important to understand the following points: (a) how to diagnose dementia; (b) the etiology of the most common dementias (including Alzheimer's disease, ischemic vascular dementia, and diffuse Lewy body dementia); (c) some medical conditions which could contribute to symptoms of dementia; (d) the pathophysiology of Alzheimer's disease; and (e) management problems faced by caregivers for dementia patients. This review aims to educate clinicians to focus on caregivers' issues and the need for long-term planning.

Key Words: Dementia, elderly, Alzheimer's disease.

Introduction

DEMENTIA IS ALARMINGLY PREVALENT in the elderly population, affecting 5% of people over the age of 65 and up to 50% of people over the age of 85 (1). It is essential to diagnose dementia accurately, so that appropriate interventions can be implemented. Currently, the underdiagnosis rate of dementia in primary care settings is as high as 75% (2), which may be related to the wide range of symptoms, from mild to severe, and the multiplicity of possible etiologies. Several causes of dementia (e.g., hypothyroidism or dementia syndrome of major depression) are totally reversible, although the vast majority of dementias (e.g., Alzheimer's disease and vascular dementia) are not reversible. With the advent of new treatments to slow progression of Alzheimer's disease (AD) and medications to decrease the risk of vascular events in vascular dementia, it is important to make an

accurate diagnosis. Understanding the course of the dementing illnesses helps the clinician implement and monitor appropriate treatment for both the cognitive and behavioral aspects as well as undertake long-term planning with caregivers.

Diagnosing Dementia

Dementia vs. Mild Cognitive Impairment vs. Normal Aging

During an interview with a patient in whom memory impairment is suspected, it is important to review the clinical history and course of deterioration with both the patient and a knowledgeable informant (e.g., caregiver, family member) (3). Table 1 lists some helpful questions to ask. The history should include an assessment of:

- memory, language, orientation;
- activities of daily living;
- social, community, and intellectual functions;
- judgment;
- problem solving abilities;
- behavioral changes; and
- psychiatric symptoms.

Memory impairment is a necessary but not sufficient criterion for the diagnosis of demen-

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tia; *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV TR) (4) criteria for dementia require a person to manifest at least one additional cognitive deficit (Table 1): aphasia (loss of language abilities), apraxia (inability to carry out specific tasks), agnosia (inability to recognize objects or persons) or impairment of executive functioning (abstract reasoning, flexibility in problem solving, adapting to changed situations). Moreover, these deficits must result in impairment of social or occupational functioning and represent a significant decline from a person's previous level of functioning (4).

To a very limited extent, some cognitive changes observed in AD occur in normal aging. Neuropsychological testing reliably distinguishes among changes associated with normal aging, mild cognitive impairment (MCI) and early AD. Age- and education-corrected norms are an essential component of teasing out the benign from the pathological.

In contrast to dementia, MCI is defined as impairment in memory only, with other cognitive functions spared. MCI is a syndrome that in a subgroup represents the earliest stages of AD (5). Approximately 15% of patients with MCI will progress to AD within a year, or up to 70% in 4–5 years (6, 7), compared to a 1–2% conversion rate in age-matched normal controls (8). Several multicenter drug trials are underway to ascertain whether treatment can slow or halt disease progression in this high-risk group (9).

The Differential Diagnosis of Dementia

For all dementias, an evaluation should include a comprehensive history, a physical examination (including neurological evaluation), laboratory tests, cognitive testing (Table 2), and neuroimaging (to rule out vascular lesions, tumors, subdural hematomas and normal pressure hydrocephalus).

TABLE 1
Questions That Help Elicit a History of Cognitive Impairment

Questions to Ask Patient and Informant Separately	
Memory	Does s/he have difficulty remembering recent conversations? Is s/he frequently repetitive? Is s/he aware of current events? Does s/he misplace or lose things? Does s/he forget to turn off the stove?
Language/ Aphasia	Does s/he have difficulty finding the correct word? Is it sometimes difficult for others to understand him/her?
Orientation	Does s/he know where s/he is? The date/month/year? Does s/he forget upcoming holidays, birthdays, when to attend church, tax day, etc.?
Agnosia	Does s/he have difficulty recognizing people/places?
Activities of daily living	Does s/he have difficulty handling small sums of money? Does s/he have difficulty remembering short lists for shopping? Does s/he need assistance with eating, bathing, transfer in and out of bed, walking, toileting, grooming or dressing?
Apraxia	Does s/he have difficulty using once familiar objects (e.g., toaster)? Does s/he have difficulty performing simple tasks at home? (e.g., making coffee, setting table, operating the TV, vacuum, etc.)
Problem-solving abilities	Does s/he have difficulty relating to newspapers or TV?
Executive functioning	Is s/he still able to manage finances/ the check book/taxes?
Social, community and intellectual function	Has s/he lost special skills, interests or hobbies (e.g., reading, sewing, cards, gardening) for reasons other than physical? Does s/he engage in socially inappropriate behavior?
Judgment	Does s/he show problems in judgment? (e.g., letting a stranger into the house)

TABLE 2
Dementia Work-up

Assessments	Rationale
*Labs: CBC, SMA, b12, folate, RPR, TSH	R/o correctable causes of dementia
*Imaging: ct without contrast or MRI	R/o infarcts, mass lesions, tumors, hydrocephalus
Neurologic exam	Correlate imaging findings with clinical exam
Neuropsychological testing	Formal description of cognitive impairments
*MMSE: screening test of cognitive function	

* Mandatory

AD and vascular dementia are the most common illnesses in the differential diagnosis of a progressive, irreversible dementia. AD accounts for 55% of all dementias and vascular dementia for approximately 15% (Fig. 1). Other important etiologies for irreversible dementia include Lewy body dementia (10), frontotemporal dementia (11) and Parkinson’s disease (12). Table 3 lists multiple etiologies for dementia, many of which refer to medical conditions and are reversible (13). It is important to include HIV infection and AIDS dementia, which are not reversible and are found in the elderly (14). The majority of these diagnoses account for 5–10% of dementias.

Contrary to prior thinking, AD is a diagnosis of inclusion, not exclusion (15, 16). In part, this conclusion is based on the fact that comprehensive evaluations are accurate 90% of the time, as confirmed by postmortem findings (17, 18). There has been a growing interest in diffuse Lewy body dementia (DLBD), which is thought to be a variant of AD. It is clinically defined as a dementia with fluctuating levels of impairment, recurrent visual hallucinations and Parkinsonian features (e.g., cogwheeling [tremor superimposed on rigidity], resting tremor and bradykinesia) (10, 19).

Following AD, vascular dementia is the most common dementia in the geriatric population in the U.S. and Western Europe. The criteria

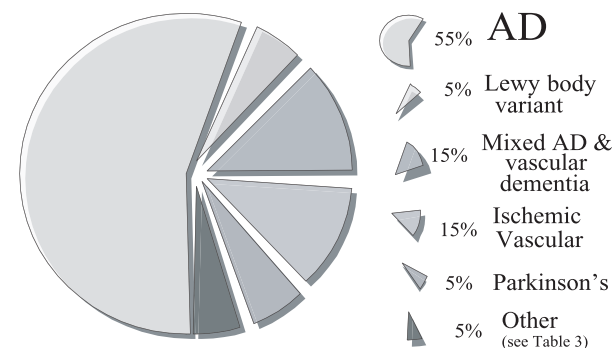


Fig. 1. Types of dementia in population 65+.

TABLE 3
Other Possible Etiologies of Dementia

Neurologic Processes	Metabolic
Corticobasal degeneration	HIV
Normal pressure hydrocephalus	Alcoholism
Traumatic brain injury	B12 or folate deficiency
Huntington’s disease	Thyroid disorder
Parkinson’s disease	
Primary progressive aphasia	Hypotensive
Brain tumor	Hypotoxic
Meningioma	CPR
Epilepsy	Intubation
Progressive supranuclear palsy	Hypoxic episode
	Anemia
Psychiatric Condition	Neoplastic
Major affective disorder	Cancer

ria for diagnosing ischemic vascular dementia require evidence of at least one infarct (cortical or thalamic) that has a temporal relationship to the onset of dementia (20). Scattered white matter changes are very nonspecific findings that are strongly associated with age and hypertension. Severe confluent white matter changes are consistent with the diagnosis of Binswanger’s disease (21), which is characterized by clinical features of dementia, incontinence and gait disturbance, similar to the triad of symptoms associated with normal pressure hydrocephalus.

Mixed dementia should be diagnosed when: (a) there is a preexisting diagnosis of AD that is complicated by a stroke, with a subsequent decline in cognitive functioning; or (b) an AD course develops after the evidence of a single stroke that caused a cognitive decline. Mixed dementia is not an appropriate diagnosis if there only is a presence of cardiovascular risk factors or TIAs.

Pathophysiology of Alzheimer’s Disease

The pathophysiology of AD includes the presence of neuritic plaques, tangles, neuronal

loss, and neurochemical abnormalities. Extracellular amyloid plaques are formed from cleavage of the amyloid precursor protein (APP), a transmembrane protein, to an amyloidogenic end product. APP is cleaved by secretases to form either a 1-40 or 42 base pair amyloidogenic product (β Amyloid or $A\beta$), or a soluble product of another length. There are 3 secretases, α , β and γ , which cleave APP at different points (Fig. 2). The non-amyloidogenic α secretase cleaves APP near the plasma membrane, releasing soluble APP into circulation. β and γ secretase cleave APP to form toxic amyloid (i.e., beta-amyloid [$A\beta$]). The amyloidogenic fragment, $A\beta$ 1-40, or the more amyloidogenic $A\beta$ 1-42 aggregate to form insoluble β -pleated sheet fibrils, which form the nidus of plaque. Amyloid-plaque-related neurotoxicity leads to cell death by attracting inflammatory products. Some plaque is seen in normal aging brain (22), but it is the density of the plaques and not the number that correlates with cognitive impairment and disease severity in AD.

Neurofibrillary tangles are the result of abnormal tau protein production. Tau is used to stabilize microtubules. When tau is abnormally hyperphosphorylated, it forms paired helical filaments, which distort the architecture of microtubules into tangles. These neurofibrillary tangles impede the delivery of neurotransmitters along the axons and contribute to cell death (23).

The neuronal loss is attributed to the neurotoxicity of plaques and tangles and to the degeneration of the cholinergic system. The nucleus basalis of Meynert (nbM), the site of central production of acetylcholine (ACh), has projections throughout the cortex and particularly to the temporoparietal association cortex and to the entorhinal cortex and hippocampus. Thus, the neuronal loss affects both cortical and sub-

cortical structures. Atrophy is demonstrated on imaging and autopsy. From early in the disease course, positron-emission tomography (PET) and single-photon emission computed tomography (SPECT) scans may show reduced metabolism in the hippocampus and entorhinal cortex. As the disease progresses, there is decreased blood flow in the medial temporal structures and the temporoparietal association cortex (24). These special imaging techniques, however, are not routinely used to make the diagnosis of AD.

Several neurotransmitters (acetylcholine, norepinephrine, dopamine) and neuropeptides (somatostatin, corticotropin-releasing factor) are involved in AD. Deficits in acetylcholine, norepinephrine, corticotropin-releasing factor and somatostatin are found in moderate-to-advanced cases of AD (25). In cases of rapidly progressive AD and in patients younger than 65 years old, norepinephrine and serotonin deficits are found as well (26). The cholinergic deficit has been found to correlate with symptom severity in AD (27).

Since AD is genetically heterogenous and genetic transmission accounts for only a small percentage of cases, genetic testing is not routinely done for making the diagnosis. Genes on chromosomes 21, 19, 14, and 1 have been implicated in AD (see Table 4). A point mutation in the amyloid precursor protein gene, on chromosome 21, is associated with familial early onset AD. In addition, Down syndrome patients universally show AD pathology by age 30 (28). A dose effect of extra $A\beta$ 1-42 burden is attributed to the additional chromosome.

The presenilin genes are transmitted as autosomal dominant with variable penetrance, and have been implicated in familial Alzheimer's disease. Presenilin 1 was mapped to chromosome 14, and presenilin 2 to chromosome 1. Presenilins are membrane-bound proteins of unclear function that may alter APP processing by promoting amyloidogenic $A\beta$. Presenilin 1 mutations account for approximately 50% of early onset familial AD. Presenilins may prove to be associated with the β and γ secretases (29). The β secretase, also called BACE (for beta-site APP-cleaving enzyme), has been cloned (30) and provides hope for the development of inhibitors to the production of amyloidogenic $A\beta$.

The apolipoprotein-epsilon (APOE) gene has been mapped to chromosome 19. ApoE is a cholesterol-carrying protein that may be involved in plaque metabolism. APOE genotype is related to plaque density and to increase in amyloid deposition in AD. There are 5 alleles of

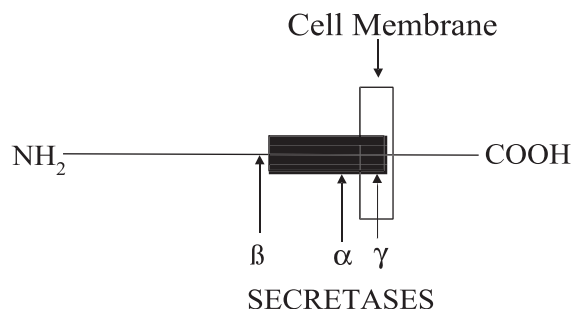


Fig. 2. Cleavage of amyloid precursor protein (APP) by secretases.

TABLE 4
Chromosomal Defects Producing AD

Chromosome	Gene Defect	Age of Onset	AB Phenotype
21	Amyloid precursor protein	50s	Increased production of A β (1-42)
19	APOE ϵ 4	60s	Increased density of A β plaques
14	Presenilin 1	40–50	Increased production of A β
1	Presenilin 2	50s	Increased production of A β

APOE, numbered ϵ 1 to ϵ 5. APOE ϵ 1 and ϵ 5 are rare alleles and have been implicated in hyperlipoproteinemia, but not in AD (31). APOE ϵ 2 allele may confer protection from amyloid deposition (32, 33). The APOE ϵ 3 allele, which does not seem to confer risk or benefit, is the most common allele, with 90% of the population inheriting one copy and 60% of Caucasians inheriting 2 copies (34). The APOE ϵ 4 allele is associated with increased risk of AD. Thirty percent of the general population inherits one copy of APOE ϵ 4 allele. On average, the frequency of APOE ϵ 4 in AD ranges from 25–50%. Some APOE ϵ 4 homozygotes have earlier onset, earlier mortality and a more severe course of AD (35–38). Because the absence of APOE ϵ 4 does not preclude AD and its presence does not invariably lead to AD, APOE testing cannot be used to definitively predict development of AD and is not recommended as a diagnostic test for AD.

Management of Alzheimer's Disease Involves Pharmacologic and Psychosocial Interventions

Pharmacologic Management

There are four FDA-approved treatments for AD, all of which are all acetyl cholinesterase inhibitors (AChE-Is). In general, studies with cholinesterase inhibitors show improvement in cognitive function from baseline of 6–12 months (or 1.5–3 MMSE points [39]) for patients with mild-to-moderate AD (40). The response is usually most pronounced in moderate AD (41). AChE-Is differ in terms of target enzymes (acetyl choline or butyl cholinesterase), allosteric modulation of the nicotinic receptor, half-life, and side effect profile (Table 5). Tacrine hydrochloride (Cognex) is no longer used because it was associated with increased hepatic enzymes and/or gastrointestinal intolerance in more than 50% of patients. Nausea and vomiting may accompany the use of rivastig-

mine tartrate (Exelon), due to its actions on the butyl cholinesterase in the gastrointestinal tract. Donepezil hydrochloride (Aricept) may increase arousal and disturb sleep more than the other medications. Caution should be used in stopping an AChE-Is, as there is often a marked decline in cognition and function when discontinued (40). The newest FDA-approved treatment for AD in this class is galantamine hydrobromide (Rеминyl), which inhibits acetyl cholinesterase and allosterically modulates the nicotinic receptor (42, 43). Galantamine has been studied in mixed Alzheimer's and vascular dementia, and was shown to be effective in maintaining cognition and behavior (44). There are no available studies comparing the effectiveness of one agent to the other. All agents show some improvement in cognition. The selection of a cholinesterase inhibitor should be based on ease of dose administration and tolerability.

Neuroprotective strategies are aimed at slowing disease progression in AD. The compounds studied to date include antioxidants, estrogen replacement therapy and anti-inflammatory agents. Use of antioxidants is based on their potential to reduce damage of excessive free radicals, as A β is known to cause oxidative stress in neurons (45). The most promising results were obtained in a clinical trial of patients with moderate-to-severe AD in which vitamin E 1000 IU bid was compared to 10 mg qd of selegiline (a monoamine oxidase type B [MAO-B] inhibitor, which has antioxidant and free-radical scavenging properties) and placebo. Treatment with vitamin E and/or selegiline slowed the progression of disease (46), but vitamin E is most widely recommended due to tolerability and lack of drug interactions.

Studies of estrogen replacement therapy looked promising in basic science, population studies and small clinical trials. In animal studies, estrogen was found to increase dendritic spines in hippocampal cells of ovariectomized rats (47) and to enhance learning (48). Large

TABLE 5
Acetylcholinesterase Inhibitors

	Donepezil	Rivastigmine	Galantamine
Features	Inhibits AChE	Inhibits BuChE and AChE	Allosteric modulation of nicotinic receptors Weak AChE inhibition
Dosing	5–10 mg qd	6–12 mg BID	12–16 mg BID
Medication-specific side effects*	Insomnia	Dizziness	Weight loss

*Side effects common to all: nausea, vomiting, diarrhea, myalgia, and anorexia.

population studies imply that estrogen may decrease risk of AD (49, 50). Patients to whom estrogen was administered with AChE-Is showed a more robust response to combination treatment in some small clinical trials (51, 52). These findings are in contrast to those of a multicenter, clinical trial of estrogen as a treatment for AD in which estrogen alone was equal to placebo for the treatment of cognitive disturbances in AD (53). Estrogen's effects may be most protective when used prior to the development of the disease.

Anti-inflammatory agents are used to target the central nervous system inflammatory response observed in AD. Population studies of patients with rheumatoid arthritis who are treated with NSAIDs show decreased risk of developing AD (54). Chronic use of NSAIDs (i.e., ibuprofen, naproxen) has been shown to delay the onset of AD in the general population (55). However, a multicenter trial of prednisone found no evidence of improvement nor slowed progress, as compared to placebo (56). An area of ongoing interest includes use of cyclooxygenase-2 (COX-2) inhibitors. COX-2 is upregulated *in vitro* in animal models and in the cortex of humans with AD (57).

New Directions for Treatment

New directions in treatment research look toward the protection of neurons. Degeneration of cholinergic cells from the excitatory neurotransmitter glutamate may be mitigated with memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist; this strategy may slow cognitive decline in AD (58, 59). Cholesterol-lowering statins, for example, may lower amyloid in the body, as cholesterol metabolism may be involved in the development of AD (60, 61). There is tremendous interest in anti-amyloid aggrega-

tive agents, which would also affect disease progression, and phase 1 trials are underway.

Plasma homocysteine has been evaluated as a risk factor for AD (62–64). Homocysteine may potentiate beta amyloid toxicity (65, 66), or vascular-related effects (67). Elevated homocysteine is an independent risk factor for AD (64). In fact, an increase in homocysteine of over 14 $\mu\text{mol/L}$ almost doubles the risk of AD. Clinically, it will be important to see if interventions aimed at decreasing plasma homocysteine (i.e., treatment with folic acid, pyridoxine and cobalamin) affect AD risk.

Animal models of inhibitors of the secretases target the presenilin gene, given the role in memory deposition (68) and the BACE1 gene, for which a specific inhibitor has not been identified. Immunization with A β 1-42 in transgenic mouse models increased clearance and prevented deposition of plaque (68). Vaccination with amyloid resulted in brain inflammation in recent human clinical trials, which were suspended.

In summary, the current evidence-based regimen for AD patients includes a cholinesterase inhibitor and vitamin E. It is important to continue treatment with the AChE-Is for the reasons discussed above. Before the onset of the illness, anti-inflammatory agents and estrogen replacement therapy may decrease relative risk. Preliminary findings (69) support the use of estrogen with an AChE-Is in women with AD. The use of agents targeting other neurotransmitter systems, amyloid degradation, and amyloid aggregation are currently under investigation.

Psychosocial Management

The psychosocial management of AD requires that there be a dialogue between the clinician, patient, family, loved ones and care-

givers. A session for diagnostic disclosure allows the clinician to review the results of the work-up and discuss treatment and prognosis. There is often pressure from families or caregiving friends to exclude the patient from this discussion. Interestingly, AD patients do not experience catastrophic reactions to the diagnosis (70). Understanding this fact and permitting patients to know their illness are of vital importance to family members. In deference to the patient and family concerned, as with any diagnostic disclosure, one should explore with the patient what he or she wishes to know. Discussion of the course of the illness and treatment options empowers the patient and their loved ones with options. Cognitive stimulation and memory enhancement programs have been found to be helpful (71).

Possible areas of concern to review with the family and loved ones include future planning and safety issues (e.g., driving, cooking, smoking, and firearms). Since AD patients will eventually lose the capacity to make financial, research and health care decisions, their inclusion in those discussions in the early-to-moderate stage of the illness is essential (72). Referral for legal assistance may be crucial for financial and estate planning, future needs and long-term care. It is also important to educate caregivers regarding changes in behavior, mood, agitation, and psychotic symptoms.

Caregivers of AD patients incur significant costs and burdens in the course of managing the illness. The spouse or eldest daughter often takes on the day-to-day caregiving of the patient. Paid home care is often used as a supplement to the unpaid care by family members (73). Studies of caregivers have found an increased risk for the emergence of psychopathology (e.g., substance abuse and depression) for the primary caregiver living with the AD patient in the community. Strategies for primary prevention of caregiver burnout include day centers for the patient, support groups, individual and family counseling, and paid care during the day or overnight. There is a wealth of information for patients and their loved ones, and physicians, available through the Alzheimer's Association (1-800-272-3900), <http://www.alz.org>, which provides pamphlets, books, videotapes and support groups.

Conclusion

Given the prevalence of dementia in the elderly and the availability of effective treat-

ments, it is essential for the clinician to be able to diagnose and manage these illnesses. A careful assessment, including a complete history, laboratory evaluation and neuroimaging, should lead to an accurate diagnosis of the dementia subtype. Particularly in patients with mild symptoms, the diagnosis can be difficult and may require serial cognitive or neuropsychological testing. AD, the most common cause of dementia, is caused by neurotransmitter deficits and accumulation of amyloid plaques and neurofibrillary tangles. The FDA-approved pharmacotherapy for AD employs cholinesterase inhibitors, and there is evidence supporting the use of vitamin E to slow disease progression. Other neuroprotective strategies are currently being studied.

Ongoing dialogues with the patient and caregivers about the diagnosis and management of the illness are likely to improve expectations for the patient and the caregiver.

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