DEGENERATIVE DISEASES

ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

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More than 4 million people in the United States have Alzheimer's disease (AD), the most common cause of dementia in the elderly. As our population ages, the number of AD patients may triple by the year 2020. The physician has a particularly important role in providing care for dementia patients and their families. If nursing home placement could be delayed for 1 month for each patient, it would result in an estimated savings of $5 billion, a major consideration in attempts to contain costs of health care. Appropriate management and utilization of services during the course of this disease can maximize patient and caregiver functioning as well as minimize behavioral difficulties and caregiver strain. This chapter provides specific recommendations for achieving this goal.

DIAGNOSIS

The first step in the treatment of patients with Alzheimer's disease and other dementias is to make a diagnosis. The routine workup for the evaluation of dementia is shown in Table 1.

Differential diagnosis depends primarily on the history, neurologic and physical examinations, and patterns of cognitive loss rather than on specific laboratory or radiologic tests since no biologic markers are available for the majority of primary dementing illnesses, including AD. Alzheimer's disease, however, is not a diagnosis of exclusion. The diagnosis is made when there is a dementia with a typical course of insidious onset; gradual progression; and absence of focal findings, significant extrapyramidal signs, or other illnesses that could account for the disorder. See National Institute of Neurologic Disease and Communicative Disorders-Alzheimer's Disease and Related Disorders Association criteria for more detail. Procedures such as lumbar punctures are necessary if the course is atypical, if there is an abrupt decline, or if systemic diseases including syphilis and malignancies are present. If depression or seizures are being considered as the etiology of the observed cognitive changes, an electroencephalogram may be helpful. Apolipoprotein E genotype is a susceptibility factor for AD, not a diagnostic test, and genotyping is not indicated for the clinical care of most patients.

Making a diagnosis within the best abilities of the clinician is crucial to permit the patient and family to frame appropriate short-term and long-term plans. Even if the physician is not certain of the specific category of primary dementing illness, use of terminology such as *dementia* and *similar to Alzheimer's disease* will support the individual's own quests for information from patient associations, reading materials, and the media. Families who hear that it is due to "getting old" or "hardening of the arteries" are unequipped to take advantage of available materials and support services as they await their next visit.

Should the patient be told of the diagnosis? Although many family members, as well as some physicians, may be uncomfortable with disclosure to the patient, the ethical principle of autonomy requires in most circumstances that the patient be aware of the diagnosis to the extent he or she is capable. Discussion of the diagnosis is best conducted in a multidisciplinary patient and family conference, allowing the patients' relatives to witness the patient's reaction (almost inevitably less catastrophic than anticipated) and the physician's management of questions that arise. Patients' insight and ability to comprehend the illness will vary considerably and must be handled on an individual basis. Even if the patient does not understand the specifics of the discussion, an approach that does not exclude the patient will encourage a sense of unity with his or her family and the health care team.

Frequency of Visits

The frequency of visits undoubtedly will vary depending on the needs of each patient and family. Most will benefit from a visit to the clinic every 3 to 4 months. More frequent evaluations are indicated when patients require medication adjustments or suffer severe affec-

Table 1 Workup for the Differential Diagnosis of Dementia

By the examiner
History, physical examination, hearing, vision
Mental status testing
Neurologic examination
Special tests
Blood for:
CBC, metabolic screen, thyroid
B_{12}, serology, HIV, if indicated
EEG
ECG
Brain imaging—CT or MRI
LP, if indicated
Psychometric testing, if indicated

CBC = complete blood cell count; HIV = human immunodeficiency virus; EEG = electroencephalography; ECG = electrocardiography; CT = computed tomography; MRI = magnetic resonance imaging; LP = lumbar puncture.

tive or behavioral disturbances, and when caregivers are unduly stressed. Conversely, biannual visits may suffice for the most stable patients provided that safety and education issues have been addressed. Telephone support is often required throughout the course of this illness.

Clinical Deterioration

Although patients with dementia gradually deteriorate, precipitous changes in clinical course require investigation, particularly for infections (urinary and pulmonary), subdural hematomas, and seizures. Additional factors that may contribute to abrupt alterations in mental status are new medications and dosage changes, crisis in the home environment, or new surroundings.

THERAPY

Treatment of Cognitive Loss

Currently, there is one FDA-approved compound for the treatment of the primary symptoms of Alzheimers disease. Tacrine (Cognex) is an acetylcholinesterase inhibitor, that can improve cognitive abilities in 30 to 40 percent of AD patients. Indeed, 5 to 10 percent of patients on tacrine show substantial improvement, although they never return to normal levels of cognition. The remaining subjects who respond to treatment have more modest clinical benefits including mild memory enhancement, increased social interaction, or heightened attention.

Tacrine dosage is titrated every 6 weeks (to a maximum of 160 mg per day) until satisfactory clinical improvement is noted or toxicity develops. Asymptomatic elevation of liver transaminases is the most frequent significant side effect, requiring monitoring of liver function tests (aspartate aminotransferase and alanine aminotransferase) every 2 weeks for several months. The *Physician's Desk Reference* and package insert provide detailed management instructions for adjusting dosage depending on transaminase elevations. When patients do not have observable clinical benefit from tacrine therapy, administration should be stopped.

Treatment of Associated Symptoms

Although in demented patients the focus is often on memory and cognitive loss, the syndrome also includes behavioral and affective disorders that disrupt the life of the patient and caregivers. Treating these symptoms with medications or behavioral management is generally more important for improving the lives of patient and family than attempts to improve the memory disorder. The clinician must help the caregiver generate strategies with the goal of limiting the problem behavior. Identifying unrealistic expectations on the part of the caregiver or family is essential.

Clinical research is sparse on the most effective strategies for managing the behavioral and affective symptoms of dementia and AD. Small doses of familiar medications can produce good results, but it may be very difficult to predict response in individual patients. The general clinical strategy is often reduced to successive medication attempts until there is an adequate clinical response. Behavioral problems change over time. The family (and physician) can generally be assured that today's problems are likely to give way to new issues. Dementia is a dynamic disorder.

Depression

More than one-third of all AD patients have significant depressive symptoms that may respond to antidepressant medications or counseling or both. Depression is particularly likely in the earlier stages of the illness and treatment can often improve cognitive and functional abilities. Some commonly used medications and dosages are shown in Table 2. Choice of drugs should be determined by individual patient profile and medical history. For example, the patient with sleep difficulties and agitation might benefit from a mildly sedating tricyclic antidepressant such as nortriptyline, whereas the depressed AD patient who is hypersomnolent may do better with a selective serotonergic reuptake inhibitor.

Delusions and Hallucinations

Paranoid delusions and visual or auditory hallucinations, which occur in more than one-third of AD patients, can be extremely disruptive for both the patient and family. However, management of these distressing symptoms can be very rewarding for the clinician. We primarily use low doses of neuroleptic medications, such as haloperidol, with careful monitoring for anticholinergic and extrapyramidal side effects. A subgroup of AD patients who also have diffuse cortical Lewy bodies (Lewy body variant of Alzheimer's disease) may have a

Table 2 Medications for Symptoms of Alzheimer's Disease

Symptom	*Drug*	*Starting Dose and Range*
Hallucinations or delusions	Neuroleptics:	
	Haloperidol (Haldol)	1 mg (0.5–2 mg)
	Fluphenazine (Prolixin)	1 mg (1–5 mg)
	Resperidone	1 mg (0.5–6 mg)
Agitation/ anxiety	Non-neuroleptics:	
	Buspirone	15 mg (15–30 mg)
	Lorazepam	1 mg (0.5–6 mg)
	Trazodone	100 mg (100–400 mg)
Depression	Nortriptyline (Pamelor)	30 mg (30–100 mg)
	Sertraline (Zoloft)	50 mg (50–200 mg)
	Paroxetine (Paxil)	20 mg (20–50 mg)
Insomnia	Zolpidem (Ambien)	5 mg (5–10 mg)
	Chloral hydrate	500 mg (500–1,000 mg)
	Lorazepam (Ativan)	1 mg (1–6 mg)

higher rate of delusions and hallucinations but are also likely to be hypersensitive to the extrapyramidal side effects of neuroleptic compounds and have unexplained falls.

Agitation and Sleep-Wake Cycle Disturbances

These frequent symptoms can be difficult to manage and generally require a combination of medical and behavioral strategies. If a patient also has depressive or psychotic symptoms, sedating compounds for treatment are likely to be useful for diminishing agitation. For the patient whose primary symptom is mild to moderate agitation, we generally try buspirone or benzodiazepine-related compounds such as lorazepam (Ativan). Sleep medications such as chloral hydrate or zolpidem (Ambien) may be helpful for some patients.

Behavioral Strategies

The most successful management of the associated symptoms of dementia combines behavioral and pharmacologic interventions. Behavioral difficulties are often triggered or exacerbated by environmental stimuli. For example, agitation or combativeness may be linked to caregiving strategies. Attempting to force patients usually results in resistance. Activities such as bathing and changing clothes are commonly cited by caregivers as circumstances that trigger agitation. Caregivers need help in identifying alternative approaches. Strategies as simple as changing the time of day of the activity, preceding the task with a favorite activity, limiting choices, or distraction during the task may solve the problem.

Sleep difficulties may be exacerbated by excessive daytime sleeping, presence of pain, or frequent bathroom visits. Limiting alcohol, caffeine, and fluids several hours before bedtime may improve nocturnal restlessness. Early bedtime promotes early awakening, especially in the elderly. It is imperative that caregivers and patients design synchronous sleep schedules to reduce night-time wandering and potential safety hazards.

Experimental Trials

A variety of compounds are under investigation for treatment of Alzheimer's disease. Table 3 lists the categories of investigational treatments by suggested mechanism of action. The design, length, and subject requirements for the research protocol will be influenced by the nature of the compound as well as the phase of the drug approval process. Drug trials may be financially supported by private industry or federal grant programs.

Patients may express interest in participating in experimental trials for the treatment of Alzheimer's disease. Trials can be located through the local Alzheimer's Association or closest teaching university. Study subjects, in general, should have no major medical illnesses or behavioral disturbances, be amenable to cognitive testing, and have scores on the Mini-Mental State Exam that fall in the mid-range (10 to 27).

COUNSELING

Education, Safety, and Referrals

A number of education and safety concerns need to be addressed with patients and families. Table 4 provides a checklist that can be utilized by the practitioner to document these discussions. Difficult issues such as revoking driving privileges and nursing home placement are made easier when the patient and family are given advance notice that these issues will be discussed at the next visit.

Assistance for families can be obtained through the national and local Alzheimer's Associations. These associations provide reading materials, telephone helplines, educational seminars, support groups, and financial assistance for day care. Available support services include home health aides, respite care, home-delivered meals, and transportation to and from doctor's appointments. Services may be provided free or have a sliding-scale fee. Families should also be referred to the Department of Aging as well as community and local religious organizations to inquire about services available in the area.

A case manager can assist families by providing a range of supportive services such as paying monthly bills or arranging for medication supervision. The plan of care will be tailored to the patient's medical, social, legal, and financial needs. This type of assistance is generally not covered by insurance. This service is particularly

Table 3 Experimental Compounds for the Treatment of Alzheimer's Disease

Cholinergic enhancers
Cholinesterase inhibitors
Muscarinic agonists
Cholinergic release enhancers
Additional agents
Serotonin receptor agonists
Cholinergic/adrenergic receptor activity
Anti-inflammatory compounds
Antioxidants
Estrogens

Table 4 Safety and Education Issues by Stage of Illness

Early/Mid Stages
Understanding diagnosis
Safety issues:
MedAlert bracelet
Driving
Smoking
Operating dangerous equipment
Wandering/supervision needs
Legal and financial planning
Advance directives
Day care
Late Stages
Nursing home placement
Autopsy

useful for family members who care for a patient at a distance or for patients who have no caregiver. Social workers may have much to offer when burdensome family circumstances, poor caregiver adaptation, or the need for extensive one-on-one counseling has been identified. Similarly, referral to psychiatry is helpful when fundamental approaches to managing psychiatric symptoms are not successful.

Genetics

Genetic counseling in AD is a complex issue that the clinician must address, particularly in families with more than one affected relative. Rarely, the clinician will encounter patients from large kindreds with multiple affected members in the same generation. Members of these families are likely to have a 50 percent risk of developing AD, often at an early age (presumed autosomal dominant inheritance). Examination of the pedigree for one of the known genetic mutations on chromosomes 21, 14, or 1 may be considered. These families are not common. Indeed, about 60 percent of all AD patients report no family history of dementia.

In general, a family history of dementia (one or more affected first-degree relatives) appears to increase the lifetime risk of developing dementia, but quantifying the excess risk is difficult. Estimates from the Eurodem meta-analyses report an estimated relative risk of 2.6 (CI 2.0 to 3.5) with one affected family member and 7.5 (CI 3.3 to 16.7) when two or more family members are affected.

Our general clinical approach is to acknowledge the increased genetic risk for the children of our patients, but also to reinforce that we cannot predict individual risk of developing AD even with additional procedures such as apolipoprotein E genotyping or positron emission tomography scanning. In the future, additional genetic and biologic markers are likely to be available for more adequate genetic counseling. More important, interventions to prevent or delay onset of disease are likely to be identified in the next decade.

SUGGESTED READING

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