Early Recognition of Alzheimer's Disease: What Is Consensual? What Is Controversial? What Is Practical?

P. Murali Doraiswamy, M.D.; David C. Steffens, M.D.; Suresh Pitchumoni; and Sara Tabrizi

Alzheimer's disease is often unrecognized or misdiagnosed in its early stages. Despite the lack of curative treatments, there are compelling reasons why early recognition of Alzheimer's disease may offer substantial benefits. Early evaluation and diagnosis may offer opportunities to enhance patient safety, allow families to plan for the future, provide family education and support, and initiate the best treatment before more substantial neuronal loss occurs. Barriers to early diagnosis include failure of family or physicians to recognize the existence or importance of cognitive/functional changes and/or misperceptions regarding diagnostic requirements and treatment capabilities. There is consensus that high diagnostic accuracy can be achieved clinically, even by nonspecialists, using established criteria and practice parameters. Population-based screening programs for the elderly, genetic testing, yield of routine neuroimaging studies, and the diagnostic value of certain molecular markers remain controversial. This review highlights practical issues related to the initial clinical evaluation and differential diagnosis of Alzheimer's disease. *(J Clin Psychiatry 1998;59[suppl 13]:6–18)*

Alzheimer's disease, a progressive neurodegenerative disorder, either alone or in combination with other illnesses accounts for 70% of all cases of dementia among the elderly in most industrialized nations.[1] In this article, we discuss (1) the importance of early diagnosis of Alzheimer's disease to desirable outcomes; (2) the extent of underrecognition of Alzheimer's disease and strategies to overcome potential barriers to early diagnosis; (3) the basic diagnostic evaluation and differential diagnosis of Alzheimer's disease; and (4) the current and future relevance of molecular and imaging biomarkers. In each area, we highlight issues that, in our view, are consensual, controversial, and/or are of practical relevance.

From the Department of Psychiatry and Behavioral Sciences (all authors), and the Center for the Study of Aging and Human Development, Duke University Medical Center, Durham, N.C. (Dr. Doraiswamy).

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Reprint requests to: P. Murali Doraiswamy, M.D., Director, Clinical Trials, Department of Psychiatry and Behavioral Sciences, Box 3018, Duke University Medical Center, Durham, NC 27710.

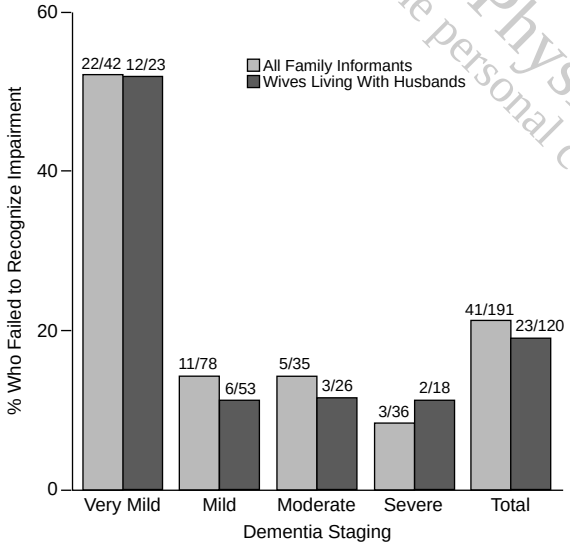
THE IMPORTANCE OF EARLY RECOGNITION

A key concept that has emerged from recent consensus conferences on Alzheimer's disease is the importance of early evaluation and accurate diagnosis to desirable outcome.[2] Despite the lack of curative treatments, there are several compelling reasons why early recognition of Alzheimer's disease may offer substantial benefits (Table 1). Dementia is frequently unrecognized by both families and physicians. Using results from a community survey of 3734 elderly Japanese-American men in the Honolulu-Asia Aging study, Ross et al.[3] found that unrecognized dementia was common in their population. Family informants failed to recognize a problem with memory in 21% of subjects subsequently identified to have dementia[3] (Figure 1). Surprisingly, even among subjects with more severe dementia, 13% of family informants failed to recognize a problem. Of the subjects found to have dementia as a result of screening, 53% had not received a prior medical evaluation for dementia. Overall, more than 60% of the subjects subsequently found to have dementia either were not recognized by their family informant to have a memory problem or were not evaluated by a physician for this problem[3] (Figure 2). In another study, Callahan et al.[4] screened elderly subjects being followed at a primary care practice for cognitive impairment. They reported that 76% of those found during screening to have moderate-to-severe cognitive impairment had no prior documentation of such impairment in their medical record. Although

Table 1. Advantages of Early Alzheimer's Disease Detection

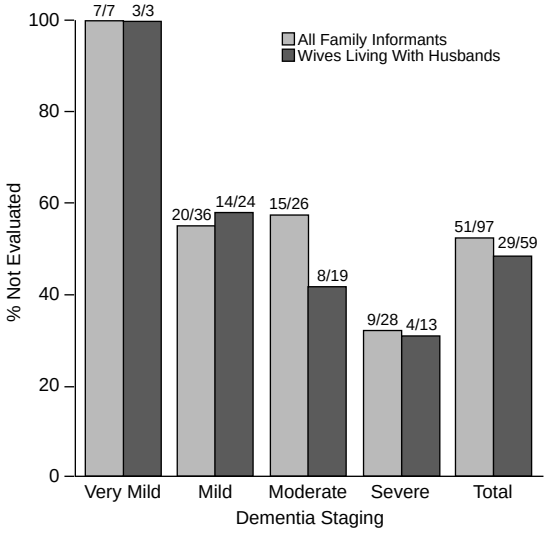
Advantages for the patient
Provides an answer to questions about failing cognition
Empowers patient to help make treatment decisions
Can begin to plan for the future
Begin treatment before more extensive neuronal loss occurs
Enhanced safety
Possible influence on Alzheimer's disease outcome
Advantages for the family
Answers questions about cognitive and functional decline
Blame the disease, not the patient, for personality changes
Plan for the future
Support systems and health care resources may decrease stress
Advantages for the clinician
Allows for tailoring of specific treatment plan
Allows for prediction of course
Opportunity to detect occult illnesses early
Advantages for society
Cognitive enhancement may provide cost savings and delay institutionalization
Driving accidents may be reduced
Possible enrollment in research studies of early Alzheimer's disease

Figure 1. Percentage of Family Informants Who Failed to Recognize Memory Impairment in Noninstitutionalized Men With Dementia by Dementia Severity*



*From reference 3, with permission. Clinical Dementia Rating [CDR]: very mild, CDR = 0.5; mild, CDR = 1; moderate, CDR = 2; severe, CDR = 3, 4, or 5 in the Honolulu-Asia Aging Study (1991–1993). Failure to recognize memory impairment was significantly higher in men with very mild vs. men with more severe forms of dementia for all family informants ($p < .001$) and for wives living with husbands ($p < .001$).

Figure 2. Percentage of Noninstitutionalized Men With Dementia in the Honolulu-Asia Aging Study (1991–1993) Who Failed to Receive Evaluation for a Memory Problem, Having Been Identified as Having Definite Memory Impairment by Their Family Informant, Depicted According to Dementia Severity*



*From reference 3, with permission. Clinical Dementia Rating [CDR]: very mild, CDR = 0.5; mild, CDR = 1; moderate, CDR = 2; severe, CDR = 3, 4, or 5. Failure to receive evaluation for memory impairment declined significantly with increased dementia severity for all family informants ($p = .004$) and for wives living with husbands ($p = .03$).

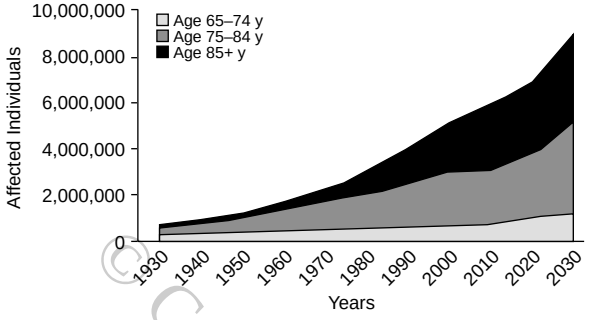
there may be cultural differences in attribution of symptoms to dementia, Ross et al.[3] projected from their data that there may be 1.8 million cases of dementia in the United States that are currently unrecognized and/or not receiving medical services.

Normal elderly subjects who have memory complaints but do not have dementia need to be reassured that their complaints are benign. This may be especially true for aging subjects with a family history of Alzheimer's disease, since many of them worry about their memory. If someone has a potentially reversible cause of cognitive impairment (i.e., delirium, toxicity, depression, hypothyroidism, subdural hematoma), early treatment is highly desirable. Patients with vascular dementia and alcohol dementia also usually benefit from early identification and appropriate therapy (i.e., risk factor modification).

If someone has Alzheimer's disease or another progressive dementia, one should not forget that that person has the same rights as patients with other curable or incurable medical illnesses (e.g., hypertension or cancer). These rights[5] include the right to know the diagnosis, the right to grieve, the right to plan for the future, the right to begin treatment before more extensive neuronal loss occurs, and the right to receive the latest, the best, and the most appropriate treatment. Such treatment may include approved therapies or the chance to participate in investigational trials. Would we deny a cancer patient the right to early assessment or treatment?

McCormick et al.[6] compared the symptoms reported by 154 Alzheimer's disease subjects, 92 nondemented subjects with minor memory complaints, and 129 cognitively intact patient controls in a health maintenance organization (HMO) population. Despite having similar comorbidity, Alzheimer's disease subjects tended to underreport physical symptoms such as gastrointestinal distress, joint

Figure 3. Projected Prevalence Rates for Alzheimer's Disease by Age Group*



*From reference 12, with permission.

pain, and vision problems. In 2 other studies,[7] previously unrecognized illnesses were found in nearly half of all dementia subjects. Although not all studies agree with these findings, physicians should be aware that elderly Alzheimer's disease subjects may be at raised risk for "occult" medical illnesses, perhaps due to the patients' lack of insight or difficulty expressing their symptoms accurately.

Early evaluation and diagnosis also offer opportunities to educate the family and patient. Patients with early Alzheimer's disease are usually worried and anxious about the changes they have noticed, and information about the disease will help them cope more easily. Perhaps the best such source of information written specifically for the person with Alzheimer's disease is a booklet called "Just for You" developed by Alzheimer Canada (telephone number for reprints: 1-416-925-3552).

Early assessment has advantages from a caregiving point of view as well. Until the diagnosis of Alzheimer's disease is made, health care providers usually cannot help caregivers in terms of education, assessment of caregiver needs, and referral to support groups and other health care resources. Early diagnosis may also offer opportunities to enhance patient safety both inside and outside of the home setting. Driving and operation of potentially dangerous machinery are 2 areas in which Alzheimer's disease subjects may be at greater risk for accidents.[8] In the recently developed American Psychiatric Association (APA) practice guidelines,[9] this issue is discussed in greater detail with respect to the various stages of Alzheimer's disease.

At present in the United States, Alzheimer's disease is the third most expensive disease to treat, with a social economic burden approaching $100 billion annually.[10] Nearly 50% of all patients in nursing homes are believed to have dementia, and the average Alzheimer's disease family is projected to spend more than $173,932 over the remainder of the patient's lifetime.[11] With the rapid rise in the older population, the prevalence of Alzheimer's disease is expected to double by the year 2030, with the largest increase occurring in those 85 years and older[12] (Figure 3). Given the progressive neurodegeneration that occurs in Alzheimer's disease, logic would dictate that the earlier we begin the most appropriate therapy, the more cognitive and functional abilities we can potentially preserve in a given patient. There are also economic data supporting the view that in moderately to severely demented home-dwelling patients, large savings in the costs for caring can be achieved even from disease interventions that produce small cognitive gains. For example, in a recent cross-sectional study of 64 home-dwelling Alzheimer's disease subjects,[10] prevention of a 2-point decline from a Mini-Mental State Examination (MMSE) score of 7 at baseline was estimated to save about $3700 annually, and a 2-point increase would save about $7100. In view of these data, and given the availability of safe and effective cognitive enhancement strategies, the argument that Alzheimer's disease families would be better off not knowing the diagnosis is unconvincing. A recently completed prospective cross-sectional health outcomes study of about 800 Alzheimer's disease subjects at different stages of severity and receiving care at different health care settings may yield additional insights into all of these issues.[13] Taken together, these data support the hypothesis that early evaluation and management would enhance the functional autonomy, safety, and quality of life of Alzheimer's disease subjects, as well as the caregiver's quality of life. Prospective studies comparing cases diagnosed and treated early versus those never diagnosed are needed to confirm this hypothesis.

SHOULD WE SCREEN FOR ALZHEIMER'S DISEASE?

In the context of Alzheimer's disease, the terms *screening* and *early recognition* currently refer to different objectives. Screening for Alzheimer's disease implies searching for all prevalent cases of Alzheimer's disease regardless of symptoms or severity in the general at-risk population. In the context of dementia, this refers to the application of a test to the general elderly population that can detect "true" cases with high sensitivity. Such a test should ideally separate dementia from normal aging without being confounded by the effects of age, gender, culture, educational level, or physical disabilities and detect both symptomatic and asymptomatic cases.

There is considerable interest in developing screening programs because both physicians and health policy makers recognize that there are several potential barriers to the timely recognition and diagnosis of dementia. For example, both families and physicians may fail to recognize the existence or importance of the cognitive or functional impairments in a patient. This may be especially true among patients of lower socioeconomic or educational status. Nonspecialist physicians may not be up to date in the skills necessary to evaluate dementia and/or may not have an interest in what they perceive as an incurable disease. They may also perceive mental status tests and dementia

Table 2. Trigger Symptoms That May Indicate Dementia*

Does the person have increased difficulty with any of the activities listed below?[a]

- *Learning and retaining new information.* Is more repetitive; has trouble remembering recent conversations, events, appointments; frequently misplaces objects.
- *Handling complex tasks.* Has trouble following a complex train of thought or performing tasks that require many steps such as balancing a checkbook or cooking a meal.
- *Reasoning ability.* Is unable to respond with a reasonable plan to problems at work or home, such as knowing what to do if the bathroom is flooded; shows uncharacteristic disregard for rules of social conduct.
- *Spatial ability and orientation.* Has trouble driving, organizing objects around the house, finding his or her way around familiar places.
- *Language.* Has increasing difficulty with finding the words to express what he or she wants to say and with following conversations.
- *Behavior.* Appears more passive and less responsive; is more irritable than usual; is more suspicious than usual; misinterprets visual or auditory stimuli.

In addition to a patient's failure to arrive at the right time for appointments, the clinician can look for a patient's difficulty discussing current events in an area of interest and changes in behavior or dress. It also may be helpful to follow up on areas of concern by asking the patient or family members relevant questions.

*Reproduced from reference 2, public document.
[a]Positive findings in any of these areas generally indicate the need for further assessment for the presence of dementia.

Table 3. Suggested Supplemental Mental Status Testing for Patients With Dementia*

Area	Test
Memory	Recalling name and address (eg, "John Brown, 42 Market Street, Chicago")
Language	Remembering 3 unusual words (eg, "tulip, umbrella, fear")
	Naming parts of objects (eg, "lab coat: lapel, sleeve, cuff; watch: hand, face, crystal")
	Following syntactically complex command (eg, "Before pointing to the door, point to the ceiling.")
	Word-list generation (eg, "In the next minute, tell me all the different kinds of animals you can think of.")
Praxis	Bimanual pantomime (eg, "Using both hands, show me how you would slice a loaf of bread.")
Visuospatial	Clock drawing (eg, "From memory, draw the face of a clock with the numbers, and mark the hands to say 10:35.")
Judgment and reasoning	Explaining similarities (eg, "How is an apple like a banana?" or "How is a canal different from a river?")
Attention and concentration	Reverse sequences (eg, "Please tell me the months of the year, starting with December and working backwards.")

*Adapted from reference 1, with permission.

workups as time consuming and having a lower priority than other medical assessments.

At a recent interactive symposium during the APA's annual meeting, 386 audience participants were asked to indicate their support for the implementation of guidelines to screen all individuals 75 years of age and older for Alzheimer's disease. The audience consisted primarily of psychiatrists, with 72% of them seeing 3 or more geriatric patients each week; 66.3% of participants indicated they would support or strongly support a screening program, 16.8% were neutral, and 16.8% disagreed (Doraiswamy PM. 1998. Unpublished data).

The Agency for Health Care Policy and Research (AHCPR) expert consensus panel[2] on the recognition of Alzheimer's disease reviewed a variety of cognitive and functional instruments and concluded that none of these instruments met their criteria for suitability as a screening instrument. Pending the development of a screening instrument, early recognition and public education are the 2 potential solutions to the issues discussed above.

EARLY RECOGNITION OF DEMENTIA

Early recognition currently refers to an increased awareness among health care providers for dementia and its presenting symptoms in their patients. A valuable treatise on this subject is the AHCPR Quick Reference Guide for Clinicians "Early Recognition and Initial Assessment of Alzheimer's Disease and Related Dementias."[2] The first step in recognizing dementia is determining whether there has been a progressive change in both memory and function.[14–16] The list of "trigger symptoms" compiled by the AHCPR (Table 2) provides a practical guide to the type of information needed to quickly recognize possible dementia and separate it from normal aging, low IQ, and minimal cognitive impairment. If patients do not report any of the trigger symptoms and dementia is suspected, then clinicians should seek corroborating information. A general statement about a medical workup for physical problems that may affect thinking may help convey to patients and families the clinician's concern about cognitive dysfunction without confronting them with suspicions about Alzheimer's disease and other dementias.

The presence of any of these trigger symptoms should warrant further evaluation for possible dementia in the form of mental and functional status testing. In practice, the easiest way to achieve a satisfactory mental status examination (MSE) is to administer the MMSE. Some supplemental tests of memory, language, visuospatial skills, attention, and praxis are listed in Table 3. Executive function, which may not be as well assessed by the MMSE, is manifest usually by perseverations, difficulty shifting tasks, and loss of abstracting ability.[16] The serial 7's item on the MMSE tests for executive dysfunction and can be used instead of the option to spell "world" backwards. Clock drawing is a useful test to supplement the MMSE.

The functional status exam (FSE) should obtain information about the patient's current and premorbid functioning from both the patient and the informant separately. The AHCPR has recommended the Functional Activities Questionnaire (FAQ)[17] as the FSE of choice for this population. In the authors' opinion, every elderly patient who is

seen for the first time should have a documented MMSE and FSE on record with follow-ups either every 6 months or annually. If significant abnormalities are found in both the MSE and the FSE, further evaluation for suspected dementia is warranted. If the MSE and the FSE are both normal, or if one is normal and the other abnormal, then one needs to use clinical judgment and/or evaluate further.

In some patients, dementia may present initially with noncognitive symptoms, such as personality changes, drinking problems, driving difficulties, or physical complaints. It should be noted that many highly educated subjects with very early Alzheimer's disease will have high MMSE scores (e.g., 26), whereas nondemented subjects with low educational level may occasionally score below 24. In a person with subjective memory complaints and a normal MSE and FSE, it may be prudent to follow up in 6 to 12 months,[2] since such complaints may be a form of preclinical dementia. Consultation with a neuropsychologist or specialist may be helpful in uncertain situations. The delayed recall measure appears to be the most sensitive cognitive indicator of early Alzheimer's disease.

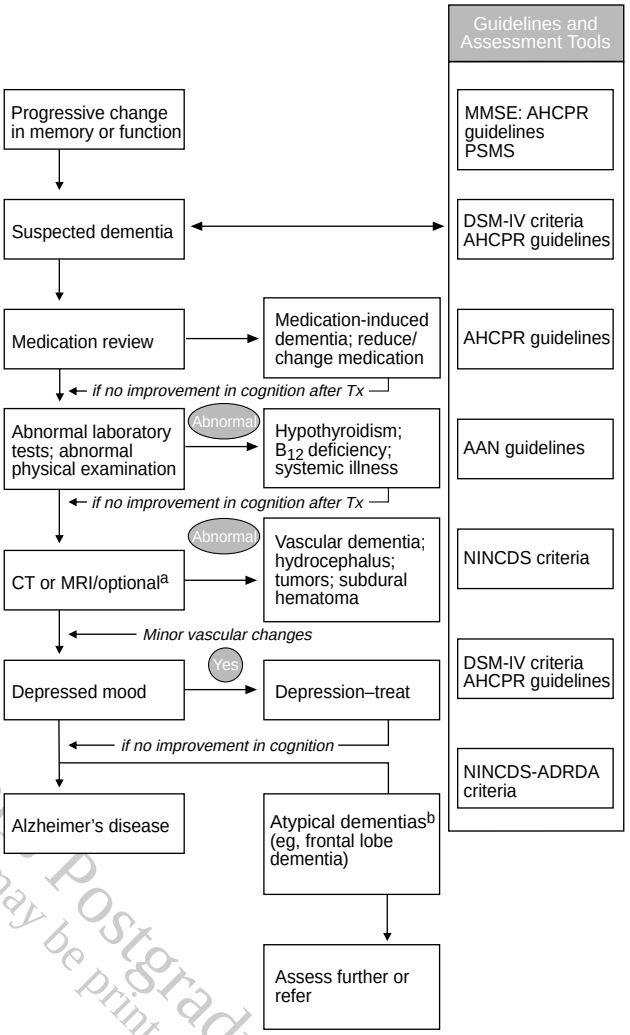
EVALUATION OF SUSPECTED DEMENTIA

Once a diagnosis of dementia has been established, physicians should remember that Alzheimer's disease is the cause of dementia in more than 50% of the cases. Although a diagnosis of Alzheimer's disease is based partially on excluding other causes of dementia, overreliance on this criteria creates uncertainty as to the extent of assessment and follow-up needed to rule out the many common and obscure causes of dementia. Even after ruling out the common reversible and irreversible dementias, many physicians in practice continue to label their Alzheimer's disease subjects as "senile dementia" or "organic brain syndrome" rather than committing themselves to a diagnosis of probable Alzheimer's disease. Hence, there is now emerging consensus that Alzheimer's disease should be viewed as a diagnosis of *inclusion*. Given the probability of Alzheimer's disease, even without any formal evaluation, a diagnosis of Alzheimer's disease would be correct 55% to 70% of the time in a subject with dementia. From both an ethical and prognostic point of view, physicians must try to establish and document a final diagnosis in every demented subject. The correct clinical diagnostic terms for Alzheimer's disease are *possible Alzheimer's disease*, *probable Alzheimer's disease*, or *primary degenerative dementia*, with a qualifier if the patient has additional symptoms such as depression or psychosis that warrant description.

In the initial evaluation of dementia, an algorithmic approach may offer practical convenience (Figure 4). The key elements of the differential diagnosis of dementia are to assess for depression, delirium, and potentially reversible causes of dementia.[12] Once these are excluded, the evaluation is focused on differentiating Alzheimer's disease from vascular dementia, frontotemporal lobe dementias, dementia with Lewy bodies, subcortical dementias, and some rapidly progressive dementias (Table 4).

The initial assessment should consist of a focused history (from patient and informant interviewed separately), review of medical record, MSE, FSE, a brief physical, and neurologic examination.[2] The history should inquire into

Figure 4. An Algorithm for the Evaluation of Suspected Alzheimer's Disease*



*From Cummings J, with permission. This algorithm is provided as an example of a systematic approach to the evaluation of suspected dementia and is not intended as a practice guideline or the only accepted approach for this purpose. Abbreviations: AAN = American Academy of Neurology, AHCPR = Agency for Health Care Policy and Research, MMSE = Mini-Mental State Examination, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association, PSMS = Physical Self-Maintenance Scale.
[a]It is required in patients with focal signs, rapid progression, and headache.
[b]This category will contain other conditions associated with dementias (e.g., frontotemporal degenerations, Creutzfeldt-Jakob disease, Parkinson's disease [and other movement disorders that present with dementia]) that should be considered when unusual clinical features are present or a rapidly progressive course is noted.

Table 4. Potentially Reversible Causes of Cognitive Impairment in the Elderly*

1. Deficiency states (eg, B_{12}, thiamine)
2. Infectious (eg, meningitis, encephalitis, vasculitis)
3. Depression, psychosis
4. Toxicity/delirium (medications, alcohol, heavy metals)
5. Hypothyroidism, parathyroid disease
6. Uremia or dialysis dementia
7. Anoxic (respiratory or cardiac anoxia)
8. Subdural hematoma
9. Hydrocephalus
10. Inflammatory (eg, sarcoidosis)
11. Malignancies

*Adapted from reference 16, with permission.

Table 5. Differentiating Dementia and Depression*

Alzheimer's Disease	Depression With Cognitive Disturbance
Cognitive deficits minimized	Cognitive deficits exaggerated
Impaired memory, executive function	Impaired motivation
"Indirect" symptoms of depression (eg, agitation, insomnia)	Mood complaints
Aphasia, apraxia	Language, motor skills intact

*From Small G, with permission.

Table 6. Differentiating Dementia and Delirium*

Symptom	Delirium	Alzheimer's Disease
Shortened digit span	Present	Absent until late
Memory	Impaired registration	Impaired recall and recognition
Hallucinations/illusions	Common	Uncommon
Language	Mild anomia	Anomia early, aphasia late
Onset	Abrupt	Insidious

*From Small G, with permission.

Table 7. Laboratory and Other Studies in the Workup of Suspected Dementia*

Laboratory Tests	Diagnostic Studies
Complete blood count	Electrocardiogram
Urinalysis	Chest x-ray
Serum electrolytes	Computerized tomography or magnetic resonance imaging, as indicated
Serum calcium	
Blood urea nitrogen and creatinine	
Liver function tests	
Thyroid function	
Serum B_{12}	
Syphilis serology	

*Modified from reference 18.

cognitive symptoms (onset, rate of progression, fluctuations, effect on functioning), past and present behavioral history, prescription and nonprescription drug use, alcohol and illicit drug use, medical illnesses and vascular risk factors, diet, lifestyle and hobbies, educational level, physical disabilities, family history of depression, dementia or movement disorder, as well as the informant's relationship with the patient. The physical examination should focus on occult illnesses, medical conditions that may affect cognition (e.g., metastatic cancer, infections, hypothyroidism), incontinence, disabilities (e.g., hearing), and preventive interventions (e.g., influenza vaccine). On the neurologic examination, laterality or asymmetry, early ataxia, sensory deficits, ophthalmoplegia, nystagmus, myoclonus, chorea, and other extrapyramidal signs should serve as red flags and raise the possibility of non–Alzheimer's disease dementias.

DEPRESSION, DELIRIUM, AND TOXICITY

The presence of depression or delirium can usually be determined by history and MSE. However, it is often difficult to make an absolute distinction between dementia and either of these 2 conditions. Tips for differentiating these conditions from Alzheimer's disease are outlined in Tables 5 and 6. The Confusion Assessment Method (CAM)[15] may also be helpful to assess for delirium. Medications are a common cause of toxicity. Although the list of possible culprits is large, anticholinergic drugs and benzodiazepines are 2 important drug classes that may impair cognition. In practice, one should review all medications and renew only those that are absolutely necessary.

An often overlooked cause of delirium or cognitive impairment in the elderly is surreptitious alcohol abuse, which may require corroborative information to detect. Cognitive impairment may persist for weeks or months after cessation of abuse. It should be noted that Alzheimer's disease can coexist with other conditions, and the presence of new-onset confusion in an Alzheimer's disease subject may signal infection, alcohol abuse, toxicity, or withdrawal symptoms. Persistent cognitive impairment after treating depression or toxicity may indicate an underlying dementia of another origin.

REQUIRED LABORATORY EVALUATION

The basic laboratory evaluation required for the assessment of dementia is listed in Table 7.[18] If hypothyroidism or a B_{12} deficiency is detected, one should reassess for Alzheimer's disease after a few months of replacement therapy. Continuing dementia may suggest a comorbid diagnosis of Alzheimer's disease. Other tests such as a lumbar puncture, while not required, may be useful in selected situations. However, the cost effectiveness and yield from laboratory testing remain controversial.[1]

NEUROIMAGING

Although the value of a major neuroimaging (computerized tomography [CT] or magnetic resonance imaging [MRI]) procedure in the workup of dementia remains controversial, it continues to be used routinely. Those who favor it[19] argue as follows: (1) neuroimaging contributes to increased diagnostic accuracy and may detect occult le-

Table 8. Neuroimaging in Alzheimer's Disease: Practical Tips

Not a substitute for history and examination
Choice of modality determined by presentation and suspected pathology/brain region to be examined
CT is appropriate for evaluating
Acute stroke, hematoma, or head trauma
Gross atrophy or hydrocephalus
Calcified lesions and skull lesions (very sensitive for both)
Patients with contraindications or claustrophobia for MRI
MRI is appropriate for evaluating
Pathology of the hippocampus, white matter, basal ganglia, thalamus, midbrain, pons, or cerebellum
Brain tumors or metastasis
Focal atrophy
Subacute and chronic infarctions, vascular lesions
Normal pressure hydrocephalus, small obstructions of the aqueductal system
Imaging may help diagnose atypical dementias, meningitis, hydrocephalus, tumor, stroke, focal lesions or atrophy, and hematomas
Imaging is particularly recommended in patients with atypical presentation, rapid deterioration, incontinence, ataxia, focal neurologic signs, and/or past head injury
Imaging may not differentiate Alzheimer's disease from normal aging, depression, or metabolic causes

sions not evident on clinical examination; (2) most physicians' clinical skills in diagnosing Alzheimer's disease are not sufficient to abandon imaging; (3) CT or MRI may identify potentially treatable causes of dementia missed by clinical evaluation; (4) the value of even a single case detected through imaging cannot be measured purely economically; (5) imaging protects against possible malpractice suits; and (6) MRI may allow for a positive diagnosis of Alzheimer's disease in the future. At a recent APA interactive symposium, 80% of 395 participants felt that every patient with suspected Alzheimer's disease should have at least 1 imaging study (Doraiswamy PM. 1998. Unpublished data). The argument against[20] routine neuroimaging is as follows: (1) it is not cost-effective and the yield is very low (< 5%), (2) it reflects an overreliance on technology and underreliance on clinical common sense, (3) it does not influence eventual outcome, (4) imaging may result in unwanted procedures (e.g., surgery) or cause distress to patients, (5) benign small vessel changes on MRI often result in an overdiagnosis of vascular dementia, and (6) MRI assessment of hippocampal atrophy is not sensitive or specific enough to offer clinical value at present.

Currently, most physicians continue to obtain at least 1 imaging study. Some practical tips for using imaging in Alzheimer's disease are presented in Table 8. The main objective is to detect tumors, subdural hematoma, strokes, hydrocephalus, and occult lesions. A secondary objective is to obtain clues that may help differentiate among the nonreversible dementias. In most situations, a CT is usually appropriate to rule out space-occupying lesions or significant strokes, whereas an MRI scan may be useful to rule out more subtle white matter, brain stem, vascular, or limbic lesions.

History of motor symptoms, new-onset amnesia, infection, or ischemia may increase the value of an MRI scan. CT or MR findings in typical Alzheimer's disease consist of cortical atrophy, more prominent in the temporal region, and corresponding ventricular enlargement (Figure 5). The degree of atrophy can vary widely from one subject to another and be influenced by nutrition, depression, and other variables. Ratings of atrophy on imaging studies either as consistent with age or in excess of normal aging can also vary from one radiologist to another. Hence, atrophy is consistent with dementia only if it occurs in the context of significant cognitive impairment, and likewise, the absence of atrophy or the presence of small vessel disease does not necessarily rule out a diagnosis of Alzheimer's disease.

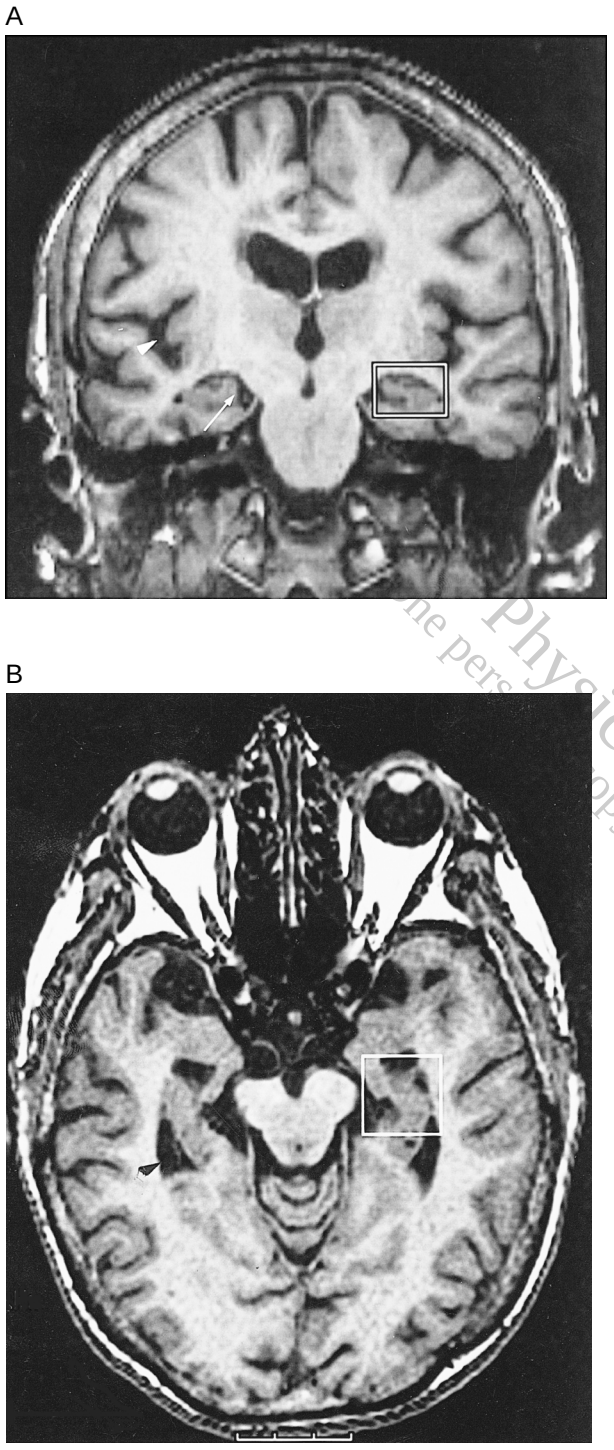
Positron emission tomography (PET) and single photon emission computed tomography (SPECT) typically demonstrate biparietal abnormalities in Alzheimer's disease. However, they are currently not required for the routine workup of Alzheimer's disease in general practice. PET and SPECT scans may have particular utility in detecting focal metabolic abnormalities and in differentiating specific types of nonreversible dementias[21] (Figure 6). The utility of PET in differentiating late-life depression from dementia is controversial, since both groups may sometimes demonstrate similar findings[22] (Figure 7). Electroencephalograms (EEGs) in Alzheimer's disease are normal or reveal diffuse slowing. An EEG may be indicated if there is a suspicion of Creutzfeldt-Jakob disease (slowing and periodic complexes) or seizures. Yet many clinicians, patients, and family members believe a workup is not complete without a brain scan, and it remains to be seen whether our reliance on imaging will change in the future.

VASCULAR DEMENTIA

Vascular dementia is believed to be the second most common cause of dementia accounting for 10% to 20% of all cases.[1] Diagnostic criteria for vascular dementia have been proposed but remain controversial.[23] Besides stroke, a number of other vascular etiologies (e.g., lupus, vasculitis, Binswanger disease, endocarditis, emboli, Lyme disease, neurosyphilis) can cause dementia. Hence, the preferred term currently is *vascular dementia* and not multiinfarct dementia.[1] Abrupt onset, stepwise deterioration, emotional incontinence, focal neurologic symptoms and signs (ataxia, incontinence, extensor plantar responses, rigidity, asymmetry of reflexes, unilateral drift, gait lateralization, visual field deficit) in the context of excess cerebrovascular risk factors (hypertension, hyperlipidemia, hypertriglyceridemia, history of atherosclerotic disease) point to the possibility of vascular dementia.

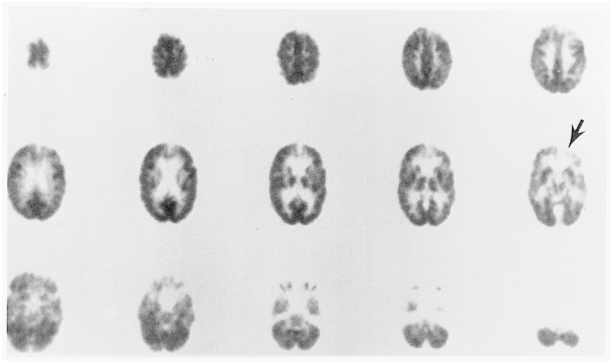
The Hachinski Ischemia Rating Scale[24] is a useful instrument in evaluating for vascular risk factors, focal signs, and the stepwise decline usually typical of vascular

Figure 5. (A) Coronal and (B) Axial MRI Scans in an Elderly Subject Who Volunteered for a Research Study on Mild Memory Complaints*



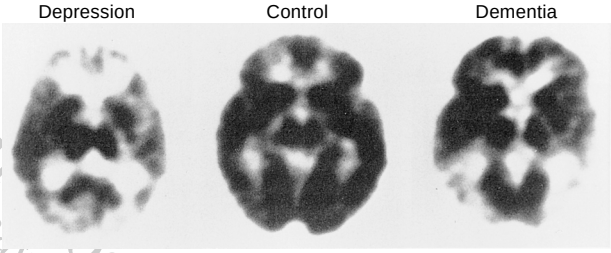
*On questioning, this 81-year-old woman denied difficulties in activities of daily living. The scan demonstrated hippocampal atrophy (arrow) and temporal sulcal enlargement (arrowheads). Her MMSE score was 23, and she had deficits on measures of delayed recall. Her APOE genotype was 4/4. Initially she was felt to have predementia. On follow-up 1 year later, her cognition and function worsened and she was diagnosed with probable Alzheimer's disease. The white boxes over the left hippocampus illustrate how the coronal and axial images correspond cross-sectionally.

Figure 6. FDG-PET Images of a 57-Year Old Man With a History of Alcohol Abuse and Prominent Personality Changes*



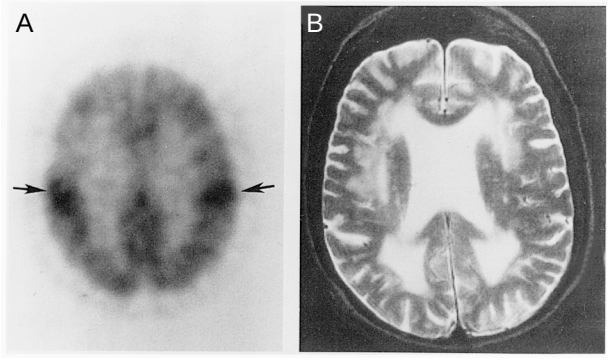
*From reference 21, with permission. An MRI showed prominent frontal atrophy. The patient had progressive memory problems and significant cognitive dysfunction. FDG-PET images show diminished FDG uptake in the frontal lobes (left greater than right) (arrow). This patient eventually had a biopsy performed in the left frontal lobe, which showed the classic neuropathologic changes of Pick's disease.

Figure 7. The Widespread Decline in rCMRglc in Subjects With Late-Life Major Depression (Comparable to Alzheimer's Disease) Compared With Controls*



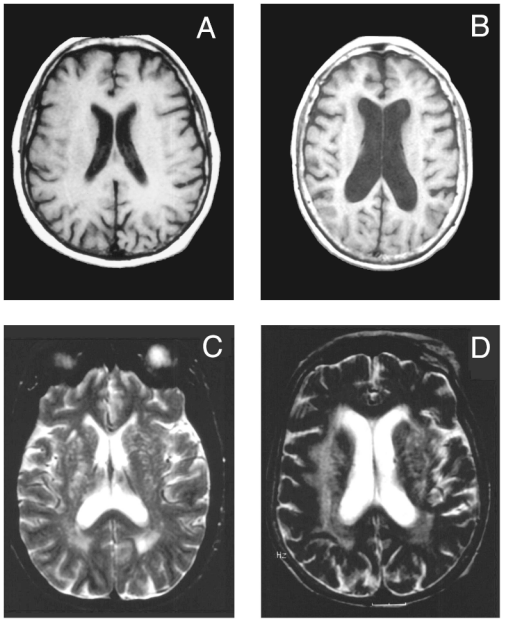
*From reference 22, with permission. Abbreviation: rCMRglc = resting cerebral metabolic rate of glucose uptake.

Figure 8. (A) FDG-PET and (B) T_2 MRI Images of a 67-Year-Old Woman With Stepwise Progressive Dementia*



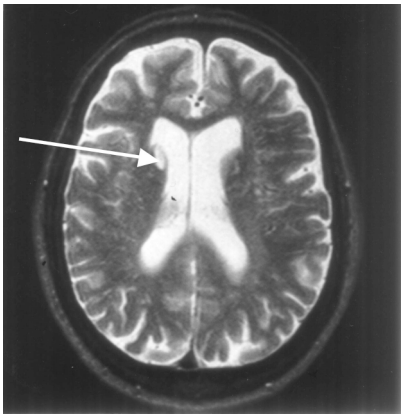
*From reference 21, with permission. (A) FDG-PET study shows inhomogeneous FDG uptake throughout the frontal and parietal areas. In this individual, the frontal reduction is more profound than the parietal. However, both are abnormal, with significant reduction. Note sparing of the motor sensory strip (arrows).
(B) T_2 MRI study of the same individual shows extensive white matter changes consistent with small vessel and vascular disease. In this individual, the clinical course was atypical for Alzheimer's disease because of steplike episodes of worsening. The FDG-PET study could be confused with that of Alzheimer's disease if the MRI study showing small vessel disease and clinical course was not known.

Figure 9. Spectrum of Structural Imaging Findings in Alzheimer's Disease*



*Axial T_1 weighted MRI scan in subjects with mild (A) and moderate (B) Alzheimer's disease. Ventricular enlargement and cortical atrophy is minimal in the subject with mild Alzheimer's disease but more prominent in the subject with moderate Alzheimer's disease. In early Alzheimer's disease, typically there is hippocampal atrophy, which may be detectable on coronal MRI scans. In the later stages, there is more widespread atrophy. The presence of temporal lobe or generalized atrophy beyond that expected for the subject's age supports a diagnosis of Alzheimer's disease, but the absence of such atrophy does not rule out a diagnosis of Alzheimer's disease. There is considerable variability among radiologists in rating atrophy as normal for age or abnormal for age. Axial T_2 weighted scan (C) in a subject with probable Alzheimer's disease, showing white matter hyperintensities (WMH) in the subcortical regions. This is sometimes also referred to as leukoariosis or small vessel disease. Occult WMH must be interpreted in the context of the clinical presentation and do not necessarily rule out a diagnosis of Alzheimer's disease or rule in a diagnosis of vascular dementia automatically. WMH are present in many subjects with Alzheimer's disease and can also occur in geriatric depression or as a normal part of aging. Panel D is an axial MRI scan depicting extensive cortical and subcortical WMH in a subject with a history of many transient ischemic attacks and multiple risk factors for stroke. Such a scan is more suggestive of vascular dementia.

Figure 10. Axial MRI Scan Demonstrating a Single Lacunar Infarct (arrow) in the Caudate Nucleus in an Elderly Subject With Depression*



*This person did not have vascular dementia, but exhibited apathy and psychomotor slowing.

Table 9. Typical Features of Alzheimer's Disease and Vascular Dementia

Feature	Alzheimer's Disease	Vascular Dementia
Onset	Insidious	Abrupt
Course	Slowly progressive	Stepwise, sudden deterioration
Clinical presentation	Short-term memory deficits followed by other cognitive deficits	Patchy cognitive deficits, with some areas affected early and others spared
Neurologic examination	Gait and motor disturbance develop only late in the course	Extensor plantar response, pseudobulbar palsy, gait abnormality, increased deep tendon reflex, and limb weakness may be present early
Neuroimaging	Cortical atrophy often present; may appear normal or with small vessel disease	Multiple vascular lesions of the cerebral cortex and subcortical structures
Incidence	Continues to increase with age	Onset may occur any time in later life, but becomes less common after age 75

dementia. MRI findings of clinically significant infarctions and PET findings of corresponding focal metabolic deficits can be helpful in the differential diagnosis[21] (Figure 8).

It has been suggested that excessive reliance on MRI findings has led to an overdiagnosis of vascular dementia. MRI findings of small vessel disease in the subcortical white matter (Figure 9) or a single lacunae in the basal ganglia (Figure 10) need to be interpreted in the context of the clinical presentation. Both can be found in normal aging as well as in subjects with Alzheimer's disease, and postmortem studies in Alzheimer's disease subjects have reported a vascular component to the disease. Table 9 lists the typical features of vascular dementia that may help to differentiate it from Alzheimer's disease.

ESTABLISHING THE DIAGNOSIS OF ALZHEIMER'S DISEASE

Typically, the patient with Alzheimer's disease initially experiences deficits in recent memory, followed by aphasia (language disturbance), apraxia (impairment in motor activities), and agnosia (failure to recognize familiar objects). The usual onset of symptoms is insidious and between the ages of 40 and 90 years, most often after age 65. The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable Alzheimer's disease[25] or the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

Table 10. NINCDS-ADRDA Criteria for Definite, Probable, and Possible Alzheimer's Disease*

Definite Alzheimer's Disease
Clinical criteria for probable Alzheimer's disease
Histopathologic evidence of Alzheimer's disease (autopsy or biopsy)
Probable Alzheimer's Disease
Dementia established by clinical examination and documented by mental status questionnaire
Dementia confirmed by neuropsychological testing
Deficits in 2 or more areas of cognition
Progressive worsening of memory and other cognitive functions
No disturbances of consciousness
Onset between ages 40 and 90
Absence of systemic or other brain diseases capable of producing a dementia syndrome
Possible Alzheimer's Disease
Atypical onset, presentation, or progression of a dementia syndrome without a known etiology
A systemic or other brain disease capable of producing dementia but not thought to be the cause of dementia is present
Gradually progressive decline in a single intellectual function in the absence of any other identifiable cause
Unlikely Alzheimer's Disease
Sudden onset
Focal neurologic signs
Seizures or gait disturbance early in the course of the illness

*Adapted from reference 25, with permission.
Abbreviation: NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association.

Table 11. DSM-IV Criteria for Dementia of the Alzheimer's Type*

A. The development of multiple cognitive deficits manifested by both
1. memory impairment (impaired ability to learn new information or to recall previously learned information)
2. one (or more) of the following cognitive disturbances:
a. aphasia (language disturbance)
b. apraxia (impaired ability to carry out motor activities despite intact motor function)
c. agnosia (failure to recognize or identify objects despite intact sensory function)
d. disturbance in executive functioning (ie, planning, organizing, sequencing, abstracting)
B. The cognitive deficits of Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing decline.
D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:
1. other central nervous system conditions that cause progressive deficits in memory and cognition (eg, cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)
2. systemic conditions that are known to cause dementia (eg, hypothyroidism, vitamin B_{12} or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection)
3. substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium.
F. The disturbance is not better accounted for by another Axis I disorder (eg, major depressive disorder, schizophrenia).

*Adapted from reference 26, with permission.

(DSM-IV) criteria[26] for dementia of the Alzheimer's type can be used to establish the clinical diagnosis (Tables 10 and 11). The primary difference between the 2 criteria is the requirement for social and occupational decline in the DSM-IV.

Deficits in executive function (problems with planning, organizing, and abstract thought) are also frequently seen in the early stages of the disease. Less common in the early stages of the illness are personality changes or increased irritability. Early on, individuals may have difficulty learning a new task, lose valuables, forget a short list of items at the store, have difficulty balancing a checkbook, or forget food cooking on the stove. Untreated, this early stage may last 1 to 3 years, with slow progression of symptoms being the hallmark.

Patients with moderate dementia may have difficulties carrying out simple food preparation, routine household chores, and may require reminders or assistance with self-care. Patients may experience visuospatial disturbance and may get lost in familiar places, even in their own home. Memory difficulties worsen, as do the other cognitive problems seen in earlier stages. In untreated patients, this middle stage of decline can be protracted, lasting 3 to 8 years. The MMSE usually declines by about 2 to 4 points each year but may decline faster in patients with comorbid medical conditions, psychosis, or parkinsonism.

In the last stage of dementia, self-care deficits progress to the point that patients are completely dependent on their caregivers. They become oblivious to their surroundings, fail to recognize close family members and friends, and may speak largely nonsense, mumble incomprehensibly, or be totally mute. Wandering and agitation can become very problematic and may lead to nursing home placement. Seizures and myoclonus may occur at this stage. Patients in the terminal phase are usually bedridden, require total care and constant supervision, and are prone to falls and other accidents. Death frequently results from accident or infection. Untreated, this final stage of dementia may last 1 to 3 years. Overall, the average duration from onset of symptoms to death is 8 to 10 years.

ATYPICAL PRESENTATIONS OF ALZHEIMER'S DISEASE

Alzheimer's disease may differ from the typical form of the illness in presentation, course, or associated clinical features. There are forms of the illness that are distinguished by the rapidity with which symptoms progress. Such cases are often of early onset (e.g., late 40s or early 50s) and may have a strong hereditary contribution. The illness is characterized by an inexorable progression of symptoms over 3 to 5 years. There are also forms of Alzheimer's disease in which the course is protracted, with slow progression up to 15 to 20 years.

Alzheimer's disease may also vary in the clinical features both at presentation and during the course of the illness. While short-term memory problems may be present initially, other symptoms may be much more disturbing

Table 12. Features That May Indicate a Non–Alzheimer's Dementia

Memory deficits may be less prominent at onset
Marked language deficits or fluctuating mental status
More marked behavioral abnormalities
Focal findings on examination, parkinsonian features, eye findings, etc
Rapid deterioration, abrupt onset

for the patient and family. A striking aphasia may develop early in the illness, which may leave the patient essentially mute. Other presentations may be characterized by prominent visuospatial disturbances, personality change, executive dysfunction, or apraxia.

NON–ALZHEIMER'S DISEASE DEMENTIAS

Table 12 lists some features that are suggestive of a non–Alzheimer's disease type of dementia. Two relevant primary dementias that may present to psychiatrists are dementia with Lewy bodies and frontotemporal dementia. Dementia with Lewy bodies has clinical features similar to Alzheimer's disease, but tends to have prominent visual hallucinations and parkinsonian features beginning early in the illness. The course may be slightly more rapid than in Alzheimer's disease. Patients are very sensitive to the extrapyramidal side effects of traditional antipsychotic medications, which are contraindicated in these patients. On neuropathology, in addition to changes typical for Alzheimer's disease, specimens also contain Lewy bodies in the cerebral cortex. Recent studies suggest that dementia with Lewy bodies may account for as many as 7% to 26% of dementia cases.[27] Table 13 lists consensus criteria[28] for dementia with Lewy bodies.

Frontotemporal dementia primarily involves the prefrontal and anterior temporal cortex (e.g., Pick's disease). An earlier age at onset and prominent psychiatric symptoms (e.g., apathy, disinhibition, excessive smoking or drinking, antisocial behavior) are usually key features. Diagnostic criteria have also been proposed for frontotemporal dementia.[29] Deficits in executive functioning and imaging evidence of frontal or anterior temporal abnormality assist with the diagnosis. Rapid progression of dementia (e.g., decline over few months) should also warrant a search for conditions such as Creutzfeldt-Jakob disease (EEG may be diagnostic) and malignancy. These and other dementias are discussed in greater detail elsewhere.[1]

APOLIPOPROTEIN (APOE) AND OTHER BIOMARKERS

A number of molecular and imaging biomarkers are under investigation for clinical use in Alzheimer's disease. APOE genotyping can increase or decrease the probability of a diagnosis of Alzheimer's disease and may help with differential diagnosis. APOE genotyping may be used as an adjunct to other diagnostic tests for Alzheimer's disease but not as the sole diagnostic test.[30,31] It is not currently recommended for use as a screening instrument or to predict future risk in asymptomatic subjects.[30] It should also be noted that experts disagree on the usefulness of APOE as a diagnostic test for Alzheimer's disease in demented patients.[30]

Table 13. Consensus Criteria for the Clinical Diagnosis of Probable and Possible Dementia With Lewy Bodies*

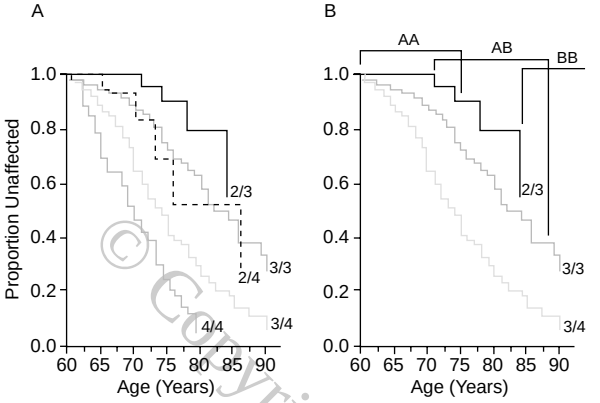
1. The central feature required for a diagnosis of dementia with Lewy bodies is progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent.
2. Two of the following core features are essential for a diagnosis of probable dementia with Lewy bodies, and one is essential for possible dementia with Lewy bodies:
   a. Fluctuating cognition with pronounced variations in attention and alertness
   b. Recurrent visual hallucinations that are typically well formed and detailed
   c. Spontaneous motor features of parkinsonism
3. Features supportive of the diagnosis are
   a. Repeated falls
   b. Syncope
   c. Transient loss of consciousness
   d. Neuroleptic sensitivity
   e. Systematized delusions
   f. Hallucinations in other modalities
4. A diagnosis of dementia with Lewy bodies is less likely in the presence of
   a. Stroke disease, evident as focal neurologic signs or on brain imaging
   b. Evidence on physical examination and investigation of any physical illness or other brain disorder sufficient to account for the clinical picture.

*Adapted from reference 28, with permission.

APOE is a polymorphic lipid transport protein found in the brain. The term *polymorphism* refers to the fact that its gene has 3 allelic forms, known as APOE ε2, ε3, and ε4, responsible for the 3 different APOE protein formations. APOE has been confirmed to be a major susceptibility gene for Alzheimer's disease, and each APOE genotype is associated with a different age at onset distribution and relative risk of Alzheimer's disease (Figure 11A).[32] The presence of 2 APOE ε4 alleles is associated with the earliest onset of Alzheimer's disease distribution. Figure 11B illustrates how discovery of a second major susceptibility polymorphism may allow for Alzheimer's disease prediction in the near future.[32] A number of other markers (e.g., tau, *Aβ42*, *p97* protein, mitochondrial mutations, pupil dilation test) are under investigation.

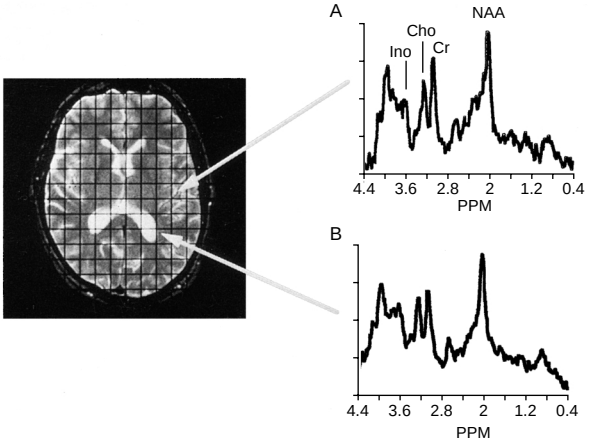
MR techniques to detect or monitor Alzheimer's disease clinically are also under investigation.[33] Hippocampal atrophy is a sensitive early marker of Alzheimer's disease and may have prognostic significance in subjects with memory complaints too mild for a dementia diagnosis. Functional imaging (SPECT and PET) may demonstrate

Figure 11. Age at Onset Distributions as a Function of APOE Genotype*



*From reference 32, with permission.
(A) Representation of proportion of each genotype remaining unaffected as a function of age. The median age at onset for ε4/ε4 represents ~2% of the population; ε3/ε4, 21%; ε3/ε3, 11%; and ε2/ε4, 5%. ε2/ε2 is not shown because it represents less than 0.5% and there was only a single control with that genotype. These data are not epidemiologic, but are derived from sporadic and familial Alzheimer's disease cases with family and case controls.
(B) The theoretical effect on subjects with the APOE-ε3/ε4, ε3/ε3, and ε2/ε3 genotype-specific age at onset distributions of a second hypothetical susceptibility gene. Using a hypothetical 2 allele system as a simple example, A/A is suggested to contribute to an earlier age at onset and β/β to a later age of onset. The effects could be independent or interactive, but will be weighted in the population by the relative allele frequency of A and β. A multi-allele system may provide even greater differentiation and prediction of age at onset ranges.[32]

Figure 12. Schematic Illustration of a Proton Magnetic Resonance Spectroscopy (MRS) Image With the 2 Arrows Depicting the Voxel Resolution With Which Chemical Information Can Be Obtained*



*From reference 34, with permission. MRS studies have consistently revealed reduced *N*-acetyl aspartate (NAA) concentrations in the Alzheimer's disease cortex consistent with the view that NAA may be a marker of neuronal integrity.

metabolic abnormalities in subjects at risk for Alzheimer's disease. Newer MR-based techniques, such as magnetic resonance spectroscopy (MRS) (Figure 12) and dynamic susceptibility contrast scans, can also demonstrate metabolic deficits in Alzheimer's disease without the need for radioactive tracers. *N*-acetyl aspartate (NAA) measured in vivo using MRS is a sensitive measure of neuronal integrity and is being investigated as an outcome measure in an antidementia trial. None of these newer imaging markers are recommended for routine clinical diagnostic use at present.

CONCLUSIONS

Increased awareness of trigger symptoms and public education may assist with the early recognition of dementia. Focused history, mental status examination, and functional assessment are critical in evaluating dementia. Laboratory assessments can be minimal in typical cases of Alzheimer's disease. Early recognition of Alzheimer's disease is important and may have a bearing on outcome.

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