

## Essentials of the Proper Diagnoses of Mild Cognitive Impairment, Dementia, and Major Subtypes of Dementia

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Loss of cognitive function in the elderly population is a common condition encountered in general medical practice. Diagnostic criteria and approaches have become more refined and explicit in the past several years. Precise diagnosis is feasible clinically. In this article, the precursor state and major subtypes of dementia are considered. *Mild cognitive impairment* is the term given to patients with cognitive impairment that is detectable by clinical criteria but does not produce impairment in daily functioning. When daily functioning is impaired as a result of cognitive decline, *dementia* is the appropriate syndromic label. Specific causes of dementia tend to have distinctive clinical presentations: the anterograde amnesic syndrome of Alzheimer disease; the syndrome of dementia with cerebrovascular disease; the syndrome of Lewy body dementia with its distinctive constellation of extrapyramidal features, disordered arousal, and dementia; the behavioral-cognitive syndrome of frontotemporal dementia; the primary progressive aphasia; and the rapidly progressive dementias. Because dementia syndromes have distinctive natural histories, precise diagnosis leads to a better understanding of prognosis. As new treatments become available for Alzheimer disease, the most common of the

dementias, accurate diagnosis allows the appropriate patients to receive treatment.

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AD = Alzheimer disease; APOE = apolipoprotein E; CBD = corticobasal degeneration; CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid; CT = computed tomography; DCVD = dementia with cerebrovascular disease; DLB = dementia with Lewy bodies; DSM-III-R = *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; EEG = electroencephalography; FTD = frontotemporal dementia; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NAIM = nonvasculitic autoimmune inflammatory meningoencephalopathies; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association; PET = positron emission tomography; PPA = primary progressive aphasia; PSP = progressive supranuclear palsy; REM = rapid eye movement; SPECT = single-photon emission CT; STMS = Short Test of Mental Status; VaD = vascular dementia; WMH = white matter hyperintensities

It has been only 8 years since the diagnosis of dementia was reviewed in the *Mayo Clinic Proceedings*,<sup>1</sup> but since then, much research has been directed at defining the different clinical entities classified as *dementias*. Some diagnoses were virtually unknown before the mid-1990s (such as mild cognitive impairment [MCI] and dementia with Lewy bodies [DLB]), and some diagnoses have undergone considerable evolution (such as Creutzfeldt-Jakob disease [CJD], vascular dementia [VaD], and frontotemporal dementia [FTD]). Although the amount of new information is vast, the progress of the past few years can be put into a framework to help clarify the diagnostic approach to dementia for primary care physicians and general neurologists.

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### EPIDEMIOLOGY OF DEMENTIA

Dementing illness is common in elderly persons. Prevalence studies suggest that approximately 3 million individuals in the United States have dementia,<sup>2-10</sup> translating into an overall prevalence rate of about 6% to 8% among individuals older than 65 years. Prevalence increases with advancing age. Among individuals older than 85 years, the prevalence rate is more than 30%.<sup>10</sup> The incidence rate of dementia, in contrast, is about 1% per year<sup>9,11-17</sup> and increases with advancing age. Alzheimer disease (AD) is present in about 2 million Americans.<sup>18,19</sup> Except for advancing age, a family history of AD, and cardiovascular disease,<sup>6</sup> no environmental or health-behavioral factors strikingly increase the risk of AD. However, debates are ongoing about the risk of AD and the possible roles of low education, head injury, and female sex.

Because most patients with the principal subtypes of dementia have relatively long survival,<sup>20-23</sup> the prevalence rate of dementia greatly exceeds its incidence rate. Survival studies show clearly that dementia decreases survival rates compared with rates for individuals without dementia. Even so, from the onset of symptoms to death, median

survival is about 6 years. The vast majority of dementia is progressive and leads eventually to total disability.

As the elderly population increases in the United States and elsewhere, timely diagnosis has never been more important. Currently, no laboratory markers exist for pre-symptomatic testing for dementia or for its major subtypes. Thus, we are forced to wait until individuals become symptomatic. Most individuals with dementia are not recognized in clinical practice.<sup>24,25</sup> Although the consequences are real, failure to diagnose dementia has not resulted in the withholding of proven preventive therapies; unfortunately, no such therapies exist. However, prospects for more potent arrestive and preventive therapies for AD are now moving from the laboratory to the clinic. We can reasonably expect that by the time this review needs to be updated, such therapies may exist. Therefore, now is the time to begin improving the detection rate of dementia (by definition, symptomatic cases).

#### MEMORY IN TYPICAL AGING

It is hard to talk about dementia and its most common symptom of memory loss without putting them in the context of typical aging. Considerable confusion exists about what constitutes normal memory and normal forgetfulness in late life. The myth that forgetfulness is an inevitable consequence of aging exerts a powerful effect on the views of lay people and physicians alike. Memory function as measured by delayed recall of newly learned material is not substantially decreased for most older people.<sup>26-28</sup> Studies have shown that when individuals destined to develop dementia in a few years are excluded from the group called "normal elderly," there are few decrements with age in functions such as delayed recall.<sup>29,30</sup> Elderly persons experience a type of memory loss manifested by digit span testing—their rote memory declines.<sup>31</sup> However, in terms of information that they are allowed time to acquire, they experience no more memory loss over time of newly learned material than do young people. The consistent story from neuropsychology and experimental psychology is that typical aging per se does not degrade memory—disease does.

Unfortunately, memory is one function that fails in all of us—young and old—every day. Although it is extremely rare for most people to misspell common words, fail to compute a simple sum, or confuse a grammatical convention, memory is capricious and unreliable, even in the best of us. Extremely few of us have photographic memories for every face, name, street name, or fact. Consequently, memory failures are common. There are 2 divergent consequences of the ubiquitous nature of everyday forgetfulness. First, because forgetfulness is so common, it is easy for observers to overlook genuine memory lapses in incipient

dementia. Second, the regularity of forgetfulness in everyday life can provide ample but misleading evidence to someone with normal brain function who may fear developing AD.

However, as genuine loss of memory function due to incipient neurologic disease develops, concomitant loss of self-appreciation often occurs. Some individuals with incipient memory loss are aware of their declining abilities, but most patients with evolving dementia never acknowledge that they have memory dysfunction. It becomes obvious over time to observers that persons with incipient dementia routinely forget recent events and conversations and repeat themselves. Behind the forgetfulness that appears benign may be more serious mistakes such as forgotten bills, missed appointments, improperly taken medications, and misdirected travels.

Patients who present with self-reported memory loss often have additional motivating issues that drive their fears, such as a family history of dementia, history of depression, major psychosocial stressor, or medical illness. Such patients typically report retrieval lapses such as forgetting someone's name only to recall it later or word-finding problems during conversations. They may experience brief periods of geographic confusion in familiar places and may forget certain highly routinized activities that are virtually automatic, such as locking their front door or taking their pills. These individuals cannot be dismissed simply because their concern implies that their memory must be normal. Sometimes individuals with incipient dementia can sense that their memory abilities are declining. Ideally, a knowledgeable informant should be interviewed because genuine memory failure should be evident to those who are close to the patient. Also, a mental status examination should be performed. In individuals with self-reported complaints of memory loss, bedside testing of memory will likely be insufficient to prove or disprove their concern. If there is a possibility that the complaint is valid, psychometric testing is necessary. In individuals whose informants concur that memory loss is evident and whose mental status examination or psychometric assessments reveal poor learning and memory, MCI or dementia should be considered. In contrast, it is gratifying to note that many individuals with self-initiated evaluations for memory dysfunction prove to have normal cognitive function with neuropsychological evaluations. In many instances, neuropsychological test results can both reassure patients that they are normal and provide them with insight into their concerns.

#### DEFINITION OF DEMENTIA

Two key principles underlie the concept of dementia: (1) the affected person has experienced a decline from some

Table 1. Diagnostic Criteria for Dementia\*

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- A. On the basis of evidence from a patient's history and mental status examination, dementia is characterized by the presence of at least 2 of the following impairments<sup>34</sup>
1. Impaired learning and impaired retention of new or recently acquired information (impaired short-term memory)<sup>32</sup>
  2. Impaired handling of complex tasks
  3. Impaired reasoning ability (impaired abstract thinking)<sup>32</sup>
  4. Impaired spatial ability and orientation (constructional difficulty and agnosia)<sup>32</sup>
  5. Impaired language (aphasia)<sup>32</sup>
- B. The cognitive impairments in A notably interfere with work or usual social activities or relationships with others<sup>32,33</sup>
- C. The cognitive impairments in A represent a notable decline from a previous level of functioning
- D. The impairments in A do not occur exclusively during the course of delirium<sup>32,33</sup>
- E. The impairments in A are not better explained by a major psychiatric diagnosis<sup>32,33</sup>
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\*Diagnostic criteria for dementia associated with the common dementing illnesses, not just Alzheimer disease, are derived from several sources.<sup>32-35</sup>

previously higher level of functioning and (2) the dementia "significantly interferes with work or usual social activities...."<sup>32</sup> These principles, embodied in the diagnosis of dementia (Table 1<sup>32-35</sup>), may be transparent in some patients, but the insidious nature of the onset of dementia often blurs the meaning of "previously higher level of functioning" for family members and often for their physicians. Elderly persons often have comorbid conditions that limit their independence and may obscure emerging cognitive decline. The diverse ways in which marital and child-parent relationships develop and evolve may keep functional decline from surfacing. Although there are circumstances that decrease the sensitivity of family informants for recognizing decline and interference with usual activities, the presence of these features is the ultimate validation of the impact of dementia on the patient.

Cognitive dysfunction that is demonstrable on mental status examination or neuropsychological assessment is the other mainstay of the definition of dementia (Table 1). Deficits should be apparent in more than one cognitive domain. The core domains are as follows: (1) the ability to learn, retain, and retrieve newly acquired information (recent memory); (2) the ability to comprehend and express verbal information (language); (3) the ability to manipulate and synthesize nonverbal, geographic, or graphic information (visuospatial function); and (4) the ability to perform abstract reasoning, solve problems, plan for future events, mentally manipulate more than one idea at a time, maintain mental focus in the face of distraction, or shift mental effort easily (executive function).

Diagnostic criteria for dementia published in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-*

*III-R*)<sup>32</sup> can be applied reliably<sup>36-38</sup> and have been used widely in research. We corrected (in Table 1) 2 flaws in the *DSM-III-R* formulation. One misstatement, also corrected in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*,<sup>33</sup> was that "long-term memory," presumably referring to recall of events from the remote past, is impaired in dementia. In fact, in mild dementia due to AD, this function is likely to be preserved. *DSM-IV* requires deficits in "short-term memory," which includes deficits in new learning and in retention of newly acquired information. Second, the dementia definition in *DSM-III-R* that requires a memory deficit is based on the dominant presentation in AD as an anterograde amnesic syndrome. For some non-AD dementias, in which language dysfunction, visuospatial dysfunction, or executive dysfunction predominate, *DSM-III-R* definitions fail to help diagnose dementia. The modifications of *DSM-III-R* and *DSM-IV* dementia definitions presented in Table 1 create a flexible dementia definition that captures the major symptoms of the main dementia subtypes. The menu of cognitive domains is similar to that of *DSM-III-R* but uses the language of the Agency for Health Care Policy and Research work group on dementia.<sup>34</sup>

This definition of dementia includes individuals with neurologic disorders that result in cognitive impairment and functional loss that do not progressively worsen after the initial insult, such as a head injury or an episode of anoxic encephalopathy. The phenomena that this definition of dementia excludes are delirium, lifelong static encephalopathies, and major psychiatric disorders.

#### MILD COGNITIVE IMPAIRMENT

Clinicians have shown that they readily recognize a large intermediate zone between a cognitively normal elderly person and one with clear dementia.<sup>38</sup> The intermediate zone between these 2 states usually is referred to as *mild cognitive impairment*.<sup>39</sup> Other terms that have been used to define the range of cognitive and functional status that occurs between normal and demented include *cognitively impaired not demented*, *possible dementia prodrome*, *age-associated memory impairment*, and *age-associated cognitive impairment*. In this category are individuals who are not normal because of deficits in at least 1 cognitive domain (usually recent memory) but who appear to function independently in daily affairs. With the increased awareness of memory problems that years of publicity about AD has produced, more elderly individuals with MCI are presenting to physicians.

In studies of the preclinical manifestations of AD, impaired performance on delayed recall has consistently been the most common initial cognitive change.<sup>40,41</sup> Consequently, the most frequently encountered form of MCI is

the amnesic type. It is defined by subjective and objective memory impairment with other cognitive functions and activities of daily living preserved.<sup>39,42</sup> Less common variants of MCI present with localized impairment of other cognitive domains. These presentations probably signal non-AD clinical syndromes (discussed subsequently). The definition of the most common MCI subtype, the amnesic form, used in the Alzheimer's Disease Research Center at the Mayo Clinic in Rochester, Minn, is given in Table 2.

Mild cognitive impairment is a clinical diagnosis that involves judgments about whether the patient is impaired in more than 1 cognitive domain. Controversy surrounds how much impairment in nonmemory cognitive domains, especially in the executive function, should be allowed for a diagnosis of MCI. Given the variations in premorbid abilities, no rigid cutoff score will work for all patients. Clinicians should know that the more impaired a patient with MCI is, the more likely the patient is to develop AD.<sup>39,42,43</sup> Likewise, the more impaired a patient is who has a cognitive domain deficit other than memory, the more likely the patient is to have difficulties in daily functioning and to be diagnosed as having dementia. Certainty about the integrity of functional status is another aspect of the diagnosis that requires clinical judgment. Some patients with MCI may no longer be able to perform their jobs but may live independently in a retirement setting. They may be able to manage their own checkbook but not be as capable of managing an investment portfolio.

Psychometric testing usually is critical to verify a memory disturbance and the absence of other important cognitive deficits. Bedside testing may lack the sensitivity to draw conclusions. However, results of psychometric testing must be interpreted in the context of the patient's educational and occupational background. Because MCI represents a change from normal functioning, patients with MCI should undergo the same screening laboratory studies that other patients with dementia undergo. In a patient with MCI, magnetic resonance imaging (MRI) can predict future AD,<sup>44-46</sup> but MRI does not establish or refute the clinical diagnosis of MCI.

The likelihood of individuals with MCI developing dementia is 5 to 10 times that of cognitively healthy individuals.<sup>39</sup> Clearly, the rationale for making a diagnosis of MCI is to call attention to the increased risk of dementia associated with memory impairment, but patients should be assured that they do not have dementia at that point. Because many individuals with MCI who will eventually have dementia will not have dementia for several years, receiving a diagnosis of MCI has advantages to receiving a diagnosis of AD while the individuals are so highly functioning. A diagnosis of MCI means patients are still capable of func-

Table 2. **Diagnostic Criteria for Amnesic Mild Cognitive Impairment<sup>39</sup>**

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| A. The presence of a new memory complaint, preferably corroborated by an informant                     |
| B. Objective evidence of impairment of short-term memory (for age)                                     |
| C. Normal general cognitive functions  |
| D. No substantial interference with work, usual social activities, or other activities of daily living |
| E. No dementia, according to criteria in Table 1   |

tioning independently in most situations. Furthermore, not all individuals with MCI will have progression to dementia. Some patients presenting with MCI may have longstanding inefficiencies in their memory functions that do not foretell subsequent deterioration.

In contrast, patients with MCI often have the pathology of early AD at autopsy.<sup>47,48</sup> On the basis of these observations, some neurologists believe that patients with MCI should be told they probably have AD. These neurologists believe that if there is sufficient memory dysfunction to warrant a diagnostic label other than "normal," the patient must have sufficient impairment in daily functioning to be diagnosed as having dementia.

Our view is that MCI is a logical clinical construct that fills an important gap. Deficits in a single cognitive domain can occur in the absence of impairment in daily functioning, as evaluated by an informant of average acuity. Furthermore, we have found that patients and families can grasp the difference between future risk of dementia and existing isolated impairment of recent memory.

It is beyond the scope of this review to consider therapies in detail, but for now, no data are available on the benefits of current therapies for AD in MCI.

#### SYNDROMES IN THE DEMENTIA CONSTELLATION

Not all dementing illnesses are alike. Patients with prominent memory disorders pose different challenges to family caregivers than patients with the combination of cognitive slowing and parkinsonism. Thorough characterization of a dementia syndrome substantially aids in management, even if characterization of a pure syndrome is not always possible. Syndromic overlap is common in dementia. The frequent combination of depression and dementia is one example. The behavioral changes of FTD and a profound anterograde amnesia indistinguishable from that in AD may appear together. More than 1 underlying pathology should be expected. Multiple neuropathologies may be present; overlap is common among AD, dementia with cerebrovascular disease (DCVD), and DLB.<sup>49,50</sup> A diagnosis of dementia starts with the intention of identifying a single syndrome but often concludes with the realization that elements of more than 1 syndrome are present.

**Table 3. Diagnostic Criteria for the Anterograde Amnesic Syndrome of Alzheimer Disease\***

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- A. On the basis of evidence from a patient's history and mental status examination, Alzheimer disease is characterized by the presence of major impairments in learning and in retaining new information and at least 1 of the following impairments<sup>33,34</sup>
1. Impaired handling of complex tasks
  2. Impaired reasoning ability
  3. Impaired spatial ability and orientation
  4. Impaired language
- B. The impairments in A notably interfere with work or usual social activities or relationships with others<sup>32,33</sup>
- C. The impairments in A represent a notable decline from a previous level of functioning<sup>33,61</sup>
- D. The impairments in A are insidious at onset and progressive<sup>32,33,61</sup>
- E. The impairments in A do not occur exclusively during the course of delirium<sup>32,33,61</sup>
- F. The impairments in A are not better explained by a major psychiatric diagnosis<sup>32,33,61</sup>
- G. The impairments in A are not better explained by a systemic disease or another brain disease<sup>32,33,61</sup>
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\*Two criteria from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association<sup>61</sup> have been dropped: the age limitation and the requirement for psychometric test confirmation.

A word about terminology: it is helpful to keep clinical syndromes and pathological causes of dementia separate because of the overlap of syndromes and pathology. Unfortunately, the current diagnostic labels actually blend the two in ways that are sometimes unclear. Clinicians first need accurate syndromic labels, and then they can decide what pathological causes are possible. We have used names for clinical syndromes that purposely are meant to convey meaning about syndromes.

### The Anterograde Amnesic Syndrome of AD

Alzheimer disease is the most common pathologic cause of dementia in elderly persons; AD unassociated with any other pathology ("pure AD") makes up between 50% and 60% of most unbiased autopsy samples and up to 80% if AD occurs in conjunction with other pathologic lesions.<sup>49-60</sup> Although autopsy is still considered the gold standard for diagnosis, experience over the past 20 years has shown that the clinical diagnosis of AD is accurate. Both the *DSM-IV*<sup>33</sup> and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)<sup>61</sup> definitions have equal validity; in Table 3, diagnostic criteria for the anterograde amnesic syndrome of AD are based on the 2 definitions. For semantic clarity, the name *anterograde amnesic syndrome of AD* captures the highlights of the clinical syndrome, but the term *probable AD* used by the NINCDS-ADRDA or just *AD* is used here to designate the clinical syndrome in which the pathology is usually that of neuritic

plaques and neurofibrillary tangles in a characteristic regional distribution.

Pervasive forgetfulness is the most common manifestation of typical AD. Repeating questions and statements is probably the most common initial observation of family members. Forgetting to pay bills, taking medications incorrectly, and having problems with time orientation are other common observations in early AD. Some patients may experience notable geographic disorientation, word-finding and name-finding difficulties, and lapses in judgment and problem-solving abilities, in addition to the excessive forgetfulness.

Because of concerns about the specificity of behavioral and personality changes for AD, they are not included in the core definition of AD. Nonetheless, the behavioral symptoms of AD are common and clinically relevant.<sup>62</sup> Personality changes may antedate the more obvious memory changes but may be evident only in retrospect. Apathy, loss of interest in previous pastimes and activities, and loss of initiative are all part of the insidious changes in a person who is developing AD. Insight is usually lost early in the process.<sup>63,64</sup> However, insight is not invariably absent, and preserved insight should not be considered a strike against a diagnosis of AD. Some patients with AD can have prominent depression either spontaneously or as a result of their sense of declining function.

Patients with AD vary considerably in the extent of language deficits and visuospatial deficits. Sometimes, anomia<sup>65</sup> or visual agnosia<sup>66-69</sup> can be nearly as prominent as the anterograde amnesia in AD.

The specificity and sensitivity of the NINCDS-ADRDA definition of probable AD are generally good, with sensitivity better than specificity in most studies.<sup>49-60</sup> The definition has reduced specificity because patients with non-AD dementing illnesses whose clinical syndrome is also that of anterograde amnesia are common. Reasons for less-than-perfect sensitivity include the existence of rarer presentations of AD pathology such as in the visual variant of AD<sup>67,68</sup> in which memory can be preserved.

Several biomarkers for AD have been tested, but none have reached the threshold of accuracy and utility to be recommended for routine use. The critical issue is whether a diagnostic test provides genuine additive value to diagnostic accuracy beyond what is provided by the clinical diagnosis. Computed tomography (CT) and MRI are required for diagnostic purposes to eliminate brain structural lesions, but only MRI is being considered for diagnosing AD specifically. Magnetic resonance imaging for detecting hippocampal atrophy differentiates patients with AD from healthy patients.<sup>70-76</sup> The sensitivity of hippocampal atrophy for diagnosing AD has been in the 80% to 90% range, but the specificity is generally lower.<sup>77</sup> These values were derived from studies utilizing automated volumetric tech-

niques that are not clinically available. Qualitative ratings of hippocampal atrophy or visual assessments of atrophy are undoubtedly less precise. Single-photon emission computed tomography (SPECT) also can differentiate patients with AD from healthy patients or patients with other dementias; however, available studies show that SPECT is not much better than the clinical diagnosis alone.<sup>78</sup> Two recent studies with positron emission tomography (PET) touted its diagnostic accuracy,<sup>79,80</sup> but the cost and availability of PET preclude any recommendations for routine use in evaluating dementia.<sup>81</sup>

The diagnostic accuracy of measuring cerebrospinal fluid (CSF)  $\beta$ -amyloid (A $\beta$ ) protein and tau protein for AD has been studied extensively.<sup>82-85</sup> Determination of apolipoprotein E (*APOE*) genotype, easily performed on peripheral blood samples, has some additive diagnostic value.<sup>55</sup> However, the additive values of CSF markers and *APOE* genotyping beyond clinical diagnoses do not justify their routine use.<sup>81</sup> Because the ability to clinically diagnose AD is good, proving that a biomarker is superior will be extremely challenging. Perhaps in the future, as we place more emphasis on early diagnosis of the pathological basis for MCI (most of which will be AD), biomarkers used alone or in combination could have a more important role.

The prognosis of AD is that of inexorable decline, but the duration of the disease exceeds 6 years in most studies.<sup>20-23,86,87</sup> Almost all patients with AD require 24-hour care as they enter the severe stage of the illness; however, in contrast to a decade ago, more of this care is being delivered in alternative, less institutional settings than traditional nursing homes.

Alzheimer disease has a genetic component,<sup>88-90</sup> which is a large topic in itself that cannot be reviewed in detail. For most patients with AD, autosomal dominant inheritance with high penetrance is an extreme rarity.<sup>91</sup> The appearance of autosomal dominant AD is generally at a young age, approximately 30 to 50 years. In contrast, the *APOE* e4 allele, present in 14% to 19% of the population, strongly influences risk of AD from approximately age 60 to 80 years.<sup>92</sup> The incomplete penetrance of AD in *APOE* e4 carriers, even homozygotes, critically decreases the value of *APOE* genotyping in asymptomatic at-risk individuals.<sup>93-95</sup>

The management and treatment of AD are also beyond the scope of this review; however, effective treatments for AD exist. Several cholinesterase inhibitors—donepezil,<sup>96</sup> rivastigmine,<sup>97</sup> and galantamine<sup>98</sup>—have proven efficacy in AD, as does vitamin E.<sup>99</sup> However, agents that substantially affect the progression of AD are needed.

### Dementia Due to Cerebrovascular Disease

Uncertainty surrounds the relative contribution of cerebrovascular disease to dementia.<sup>100</sup> The label of *vascular*

Table 4. Diagnostic Criteria for Dementia With Cerebrovascular Disease\*

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- A. On the basis of evidence from a patient's history and mental status examination, dementia with cerebrovascular disease is characterized by the presence of at least 2 of the following impairments<sup>34</sup>
    - 1. Impaired learning and impaired retention of new information
    - 2. Impaired handling of complex tasks
    - 3. Impaired reasoning ability
    - 4. Impaired spatial ability and orientation
    - 5. Impaired language
  - B. The impairments in A notably interfere with work or usual social activities or relationships with others<sup>32</sup>
  - C. The impairments in A represent a notable decline from a previous level of functioning<sup>33</sup>
  - D. Clinically important dementia with cerebrovascular disease is characterized by either of the following
    - 1. Onset of listed impairments or dramatic worsening of an existing listed impairment that occurred within 3 months of a stroke<sup>105</sup>; *stroke* is defined as a focal neurologic deficit of acute onset, in which symptoms and signs persist for more than 24 hours
    - 2. Presence on neuroimaging of bilateral brain infarctions that involve cortical or subcortical gray matter structures<sup>105</sup>
  - E. The impairments in A do not occur exclusively during the course of delirium<sup>32</sup>
- 

\*Diagnostic criteria for dementia with cerebrovascular disease are based on observations in the Mayo Clinic Alzheimer's Disease Patient Registry,<sup>104</sup> the distillation of several published criteria,<sup>32,105</sup> and other sources.<sup>33,34</sup>

*dementia* has been criticized for failing to capture the full impact of cerebrovascular disease in dementia.<sup>101</sup> Cerebrovascular pathology can produce a clinical syndrome of MCI, emphasizing the heterogeneity of patients with MCI and of patients with dementia due to cerebrovascular disease. We discuss individuals with dementia according to the definition given in Table 1. We use the term *dementia with cerebrovascular disease* to include both "pure" VaD and dementias in which some vascular pathology is combined with other etiologies, usually AD.

Diagnostic criteria for VaD generally have been unsuccessful in predicting pathological findings.<sup>49,52-54,102,103</sup> Diagnostic criteria for DCVD (Table 4<sup>32-34,104,105</sup>) that require a causal link between a clinical stroke and dementia *or* bilateral supratentorial gray matter region infarctions have the best sensitivity for the pathological finding of substantial vascular disease in our clinicopathological experience<sup>104</sup> without a drastic loss of specificity. By including imaging-confirmed cerebral infarctions in the criteria for DCVD, we acknowledge that clinically silent cerebral infarctions occur that could be etiologically related to dementia. Rather than requiring that both features be present, as some criteria do,<sup>105</sup> which results in low sensitivity, our criteria allow diagnosis of DCVD if either feature is present (Table 4). Our definition of DCVD does not distinguish between pathologically pure VaD and VaD combined with AD. Lacking a biomarker for AD that can be applied antemortem, features of cerebrovascular disease cannot logically be used to exclude another disease, in this case AD.

Population-based incidence studies (which used various diagnostic criteria) from several European countries estimated that 17% of patients with dementia had clinically diagnosed VaD.<sup>106</sup> The prevalence of clinically diagnosed VaD is about one fifth that of AD.<sup>2,3,5,8,10</sup> Dementia clinics report lower rates,<sup>54,107</sup> almost certainly because of selection biases against patients who experience a stroke and then dementia. Seemingly, the patient and family recognize the cause-and-effect relationship of stroke to dementia and are more comfortable with the label *stroke* than *dementia*. There are few autopsy studies that are not subject to the underrepresentation of stroke patients. In one such study, Holmes et al<sup>49</sup> reported that 11% of their population-based series had pure VaD, and another 20% had a combination of AD and VaD. Therefore, in a primary care setting, between 1 in 10 and 1 in 5 patients with dementia will have a substantial cerebrovascular component.

The clinical syndrome of DCVD is best appreciated when dementia has its onset or dramatic worsening in association with a typical stroke or clear imaging evidence of cerebral infarctions. The most obvious manner in which a stroke produces clinical deficits in cognition or behavior is via the mechanism of infarction. The deficits that occur as a result of cerebrovascular disease should be of sudden onset, although nondominant hemispheric lesions or other lesions might escape immediate attention. A number of brain regions, if affected by single cerebral infarctions, produce characteristic cognitive and behavioral deficits. Some stroke-related syndromes include the clinical phenotype of anterograde amnesia that is identical to that of AD. Perhaps more commonly, excessive forgetfulness may not be an initial major manifestation of DCVD. Impaired judgment, personality changes, frank aphasia, or visuospatial disturbances may predominate either alone or in combination, as in FTD; however, DCVD cannot be diagnosed on the basis of the pattern of cognitive deficits.<sup>108</sup>

A subset of DCVD patients appear to have an illness characterized by insidious onset and gradual progression without overt strokes and sudden declines in cognition. Whether such patients had clinical strokes with acute manifestations that were missed is unknown. Severe white matter disease has been advanced as a mechanism for insidious progression, but this disease usually belies the presence of multiple subcortical or cortical infarctions.<sup>109</sup> Microinfarctions appear to be associated with dementia<sup>110</sup>; such pathology need not occur with overt strokes. Some patients with dementia with lacunar infarctions on MRI lacked AD pathology but had hippocampal cell loss that appeared to be vascular in origin.<sup>111</sup>

It is common in healthy elderly persons to observe one, but rarely more, cerebral infarction on neuroimaging.<sup>112-114</sup> Our data from the Mayo Clinic Alzheimer's Disease Pa-

tient Registry<sup>115</sup> suggest that clinically silent unilateral cerebral infarctions alone seem to correlate poorly with exclusive vascular pathology at autopsy and therefore should not be assumed to be etiologically related to dementia.

Persistent controversy surrounds the relevance and role of MRI-confirmed white matter hyperintensities (WMH) in dementia. White matter hyperintensities are found more frequently in individuals with hypertension and other vascular risk factors<sup>116,117</sup> and are associated with an increased risk of future stroke<sup>118</sup> and with reductions in cognitive function.<sup>117,119</sup> However, WMH also are found in patients with an exclusively AD pathology.<sup>120,121</sup> Unless it is extensive, WMH is a nonspecific marker for cerebrovascular disease. Leukoencephalopathy due to cerebrovascular disease should be considered mainly when WMH is severe.<sup>109</sup> In contrast, the presence of mild to moderate WMH should not lead to overestimation of cerebrovascular disease as causally related to dementia; WMH may be a marker for cerebrovascular pathology, but WMH alone is *not* synonymous with DCVD.

Other than neuroimaging with MRI or CT, no diagnostic tests or biomarkers exist for DCVD. Ironically, the kind of biomarker that would increase confidence in a diagnosis of DCVD would be one that had good negative predictive value for AD (a test that if negative would rule out AD with high accuracy). As noted previously, such a biomarker does not exist. Hence, the diagnosis of DCVD sometimes may be doubly uncertain: once because of uncertainty about whether the cerebrovascular disease is sufficient to contribute to cognitive impairment and then again because of the uncertainty about the role of AD in the cognitive impairment.

The prognosis of DCVD is worse than that of AD. On the basis of work from the Mayo Clinic Alzheimer's Disease Patient Registry,<sup>104</sup> patients with dementia temporally related to stroke had a notably worse prognosis than did patients with AD. Whereas the median survival of patients with AD was 6 years, patients who had dementia with onset or worsening in conjunction with a clinical stroke had a median survival of only 3 years.

Patients with DCVD appear to benefit from treatment with cholinesterase inhibitors.<sup>122</sup> Also, if patients with DCVD have untreated vascular risk factors, such as hypertension or diabetes mellitus, those should be addressed. The role of antiplatelet drugs for DCVD is unknown at this time.

#### **Dementia Associated With Parkinsonism: Dementia With Lewy Bodies**

Parkinsonism is common in the elderly population.<sup>123</sup> Dementia is now recognized as a frequent accompaniment of Parkinson disease in older persons. In the past 15 years,

increasing awareness of the unique syndrome of dementia and parkinsonism associated with Lewy body pathology has led to the designation of a syndrome known as *dementia with Lewy bodies*.<sup>124</sup> We prefer the clinical designation of *dementia with parkinsonism* to maintain the distinction between clinical diagnoses and pathologic ones. However, the field has embraced the term *dementia with Lewy bodies*; therefore, we use it here.

The pathological basis of DLB involves a combination of Lewy bodies and AD pathological features.<sup>125</sup> Lewy body pathology is present at autopsy in 10% to 20% of patients with dementia, usually associated with some degree of AD. When spontaneous parkinsonism precedes dementia by several years, Lewy body pathology in limbic and neocortical regions predominates.<sup>126</sup> When dementia precedes or occurs simultaneously with parkinsonism, Lewy body pathology still may be the most common pathologic finding, but other conditions such as pure AD or progressive supranuclear palsy (PSP) may be observed.<sup>127</sup> Several clinicopathological studies have shown imperfect sensitivity and specificity of previously published diagnostic criteria for DLB.<sup>49,128-132</sup>

Our criteria for DLB (Table 5) differ from previously published criteria<sup>124</sup> by emphasizing the motor and arousal disturbances unique to Lewy body pathology. Patients with dementia who exhibit either some of the motor manifestations of parkinsonism or one of the arousal-sleep disorder manifestations require different management strategies than do typical patients with AD.

The motor manifestations include the gait and balance problems typical of parkinsonism, along with rigidity and bradykinesia. Patients with DLB have an increased risk of falling. Rest tremor is relatively uncommon, although a more symmetrical postural tremor often is present. It is diagnostically unimportant whether the motor symptoms precede or follow the cognitive disorder temporally.<sup>126</sup>

The cognitive disorder in DLB may be characterized by prominent anterograde amnesia<sup>133-135</sup> and may be indistinguishable from AD. However, the most common patterns of cognitive deficits in DLB are distinct from those in AD. Patients with DLB may have slightly better confrontational naming and verbal memory function than do typical patients with AD but have worse executive function and visuospatial functions. Patients with DLB are typically more apathetic than are patients with AD. Dementia with Lewy bodies can be suspected but not diagnosed confidently on the basis of this latter type of cognitive profile alone.

Many major manifestations of DLB originate in disordered arousal. Patients with DLB often have excessive daytime sleepiness and periods of reduced attention and concentration. The concept of fluctuations in DLB includes both sleepiness and altered arousal. Further study is needed

**Table 5. Diagnostic Criteria for Dementia With Lewy Bodies\***

- 
- A. On the basis of evidence from a patient's history and mental status examination, dementia with Lewy bodies is characterized by the presence of at least 2 of the following impairments<sup>34</sup>
    - 1. Impaired learning and impaired retention of new information
    - 2. Impaired handling of complex tasks
    - 3. Impaired reasoning ability
    - 4. Impaired spatial ability and orientation
    - 5. Impaired language
  - B. The impairments in A notably interfere with work or usual social activities or relationships with others<sup>32</sup>
  - C. The impairments in A represent a notable decline from a previous level of functioning<sup>33</sup>
  - D. Dementia with Lewy bodies is characterized by the presence of at least 2 of the following symptoms<sup>124</sup>
    - 1. Parkinsonism (muscular rigidity, resting tremor, bradykinesia, postural instability, parkinsonian gait disorder)
    - 2. Prominent, fully formed visual hallucinations
    - 3. Substantial fluctuations in alertness or cognition
    - 4. Rapid eye movement sleep behavior disorder<sup>133</sup>
  - E. The impairments in A do not occur exclusively during the course of delirium<sup>32</sup>
  - F. The impairments in A are not better explained by a major psychiatric diagnosis<sup>33</sup>
  - G. The impairments in A are not better explained by a systemic disease or another brain disease<sup>61</sup>
- 

\*Diagnostic criteria for dementia with Lewy bodies is based on the Consortium on Dementia with Lewy Bodies<sup>124</sup> but contain several important modifications (see text for further discussion). No limitations are based on the temporal relationship between onset of dementia and onset of parkinsonism. Rapid eye movement sleep behavior disorder is an additional characteristic diagnostic feature.

to determine whether fluctuations result from degeneration in the neuronal networks involved in arousal and thereby cause hypersomnia or a narcoleptic-like state, or from other sleep disorders such as obstructive sleep apnea and periodic limb movement disorder. Rapid eye movement (REM) sleep behavior disorder is often a precursor of DLB and is present in about half of patients with DLB.<sup>136,137</sup> A REM sleep disorder in the setting of a dementia may be diagnostic for DLB.<sup>138</sup> In addition, patients with DLB experience prominent, fully formed visual hallucinations. Visual hallucinations might indicate the intrusion of sleep phenomena into wakefulness, another manifestation of a REM sleep dyscontrol problem in DLB. Thus, both REM sleep behavior disorder and visual hallucinations are included in the definition of DLB given in Table 5.

No characteristic laboratory tests exist to help define DLB. Magnetic resonance imaging tends to show less hippocampal atrophy than is seen in AD, but the differences between AD and DLB are insufficient to be of diagnostic value.<sup>139</sup>

The prognosis of DLB appears to be somewhat worse than that of AD. Although the differences have not been dramatic, patients with DLB appear to have a faster progression and shorter survival.<sup>134,140</sup> However, some patients

Table 6. Diagnostic Criteria for Frontotemporal Dementia

- A. On the basis of evidence from a patient's history and mental status examination, FTD is characterized by early manifestations<sup>149</sup> of either of the following impairments
1. Decline in regulation of personal or social interpersonal conduct (characterized by loss of empathy for the feelings of others; socially inappropriate behaviors that are rude, caustic, irresponsible, or sexually explicit; mental rigidity; inflexibility in interpersonal relationships or emotional blunting; decline in personal hygiene and grooming; altered dietary habits)<sup>149</sup>
  2. Impaired reasoning or impaired handling of complex tasks out of proportion to impairments of recent memory or to spatial abilities\*
- B. The impairments in A notably interfere with work or usual social activities or relationships with others<sup>32,33,149</sup>
- C. The impairments in A represent a notable decline from a previous level of functioning<sup>33</sup>
- D. The impairments in A are of gradual onset and progressive<sup>149</sup>
- E. The impairments in A do not occur exclusively during the course of delirium<sup>32,33,149</sup>
- F. The impairments in A are not better explained by a major psychiatric diagnosis<sup>33</sup>
- G. The impairments in A are not better explained by a systemic disease or another brain disease<sup>32,33,149</sup>

\*Prior criteria chose to avoid a requirement for neuropsychological testing to diagnose frontotemporal dementia (FTD); however, on the basis of our own clinical experience and the literature,<sup>150-152</sup> cognitive assessment by a skilled neuropsychologist is necessary for diagnosing FTD.

with DLB experience considerable improvement and more gradual progression with appropriate pharmacological management of their cognitive impairment, neuropsychiatric features, motor dysfunction, autonomic dysfunction, and sleep disorders.

Treatment of DLB might involve several strategies, such as treatments for Parkinson disease if the patient has gait and balance difficulties, treatments for REM sleep behavior disorder, or treatments for cognitive dysfunction using cholinesterase inhibitors.<sup>141</sup>

Other neurodegenerative diseases can have dementia and extrapyramidal signs as their main manifestations: after DLB, PSP is the next most common. The cognitive deficits of PSP<sup>142-145</sup> are usually milder than those of AD or DLB. The cognitive and behavioral profiles of PSP include apathy, slowing of cognitive processing, and memory deficits. The motor abnormalities that occur in PSP, such as prominent parkinsonian signs, gait and balance disorder, and various brainstem abnormalities, may sometimes overshadow the dementia. The motor findings are usually distinctive enough to distinguish PSP from AD and DLB on clinical grounds.<sup>146</sup> Corticobasal degeneration (CBD) is another disorder that can present with dementia and a movement disorder.<sup>147</sup> No laboratory tests can help diagnose PSP or CBD.

### Cognitive-Behavioral Syndrome of FTD

*Cognitive-behavioral syndrome of frontotemporal dementia, or frontotemporal dementia, is a clinical syn-*

drome usually associated with one of several non-AD pathologies; FTD is uncommon in ordinary clinical practice.<sup>50,54,148</sup> Diagnostic criteria proposed by a recent work group<sup>149</sup> (Table 6<sup>32,33,149-152</sup>) were built on prior criteria<sup>153,154</sup> that were subjected to validation work.<sup>155</sup> The rarity of FTD has made determination of sensitivity and specificity difficult. There are no systematic studies of misdiagnosis of FTD; however, in our clinical experience, FTD has been difficult for primary care physicians, neurologists, and psychiatrists to diagnose.

The presentation of FTD is often dramatic, suggesting a psychiatric disorder. The principal manifestations are changes in personality, comportment, and judgment.<sup>153,154</sup> Personality changes may range from apathy to euphoria. Loss of initiative, loss of ability to follow through on tasks, and loss of interest in prior pastimes occur. Individuals with FTD begin to lose empathy for the feelings of others. They may make rude or off-color comments to family or strangers. They also can have dramatic lapses in judgment. Development of obsessional behaviors is common, such as eating the same meal day after day or seeking out letters of the alphabet on signs or other objects that the patient encounters.

Most patients with FTD perform poorly on psychometric tests of executive function.<sup>150,151</sup> Tests such as verbal fluency, Trailmaking, the Stroop test, and the Wisconsin Card Sorting Test are the commonly used laboratory measures of executive function. Another key clinical element of FTD is the relative preservation of memory. On formal testing of delayed recall, patients with FTD may score in the normal range. Also, patients with FTD typically have preservation of visuospatial functions. Psychometric testing is highly valuable when FTD is being considered because bedside testing of executive function is inadequate. Normal performance on psychometric testing does not necessarily rule out FTD, especially early in its course. Some patients who present with predominantly behavioral and personality manifestations may have only equivocal deficits on neuropsychological tests of executive function.

Neuroimaging is useful in confirming a diagnosis of FTD. Focal prefrontal or anterior temporal atrophy on CT or MRI, if present, is probably confirmatory of FTD, but atrophy is not always present. Because of temporal bone artifacts with CT, MRI is preferred for diagnosing FTD. Functional imaging with SPECT<sup>156-158</sup> or PET<sup>159</sup> has diagnostic value for increasing confidence in the clinical diagnosis. One report on CSF testing to distinguish FTD from AD<sup>160</sup> is intriguing but has not been replicated. No other types of diagnostic testing are useful for diagnosing FTD. Genetic testing for mutations in the *tau* gene is inappropriate for clinical use at this time except in instances with proven multigenerational FTD.<sup>161,162</sup>

The neuropathological basis for most FTD involves 1 of 3 non-AD pathologies that are referred to as *frontotemporal lobar degenerations*<sup>149</sup>: (1) a Pick body–positive, tau-positive, frontotemporally predominant degenerative dementia, (2) a tau-positive CBD, and (3) a degenerative disorder with frontotemporal predominance that is tau-negative and lacks other distinctive histology. Rarely will AD cause FTD.<sup>163</sup>

The prognosis of FTD is variable. In our experience, the typical course from onset to severe dementia can be as short as 3 or 4 years in some patients and, much more rarely, as long as a decade.

Currently, no primary treatments exist for FTD. Prospects for therapeutic interventions have brightened with the development of transgenic mouse models of the tauopathies,<sup>164</sup> but no large-scale efficacy trials are scheduled for 2003.

**Progressive Aphasia**

Nonfluent primary progressive aphasia (PPA) may not actually represent a dementia because its manifestations may be exclusively in the language domain.<sup>165</sup> In PPA, there is labored speech, impaired articulation, reduced number of words per utterance, and anomia.<sup>165-168</sup> Comprehension may be preserved. In the early stages of PPA, patients should be functionally independent except for limitations imposed by speaking difficulties.<sup>165</sup> Patients with PPA without dementia can be characterized by the diagnostic criteria in Table 7. If a patient with prominent expressive language deficits also has other cognitive deficits that interfere with daily activities, a diagnosis such as AD with prominent language disturbances or FTD might be more appropriate. Some patients with nonfluent PPA do not develop dementia, whereas others do.

Patients with a less common progressive aphasic disorder, sometimes referred to as *semantic dementia*, exhibit fluent speech, grossly impaired understanding of word meaning, prominent anomia, and often an element of disinhibition.<sup>169</sup>

Neuropsychological testing may be helpful in clarifying the extent of cognitive difficulty outside of the language domain; MRI or CT usually reveals asymmetrical atrophy of the left hemisphere, usually in a perisylvian distribution. Most patients with nonfluent PPA or semantic dementia have one of the pathologies associated with frontotemporal lobar degeneration.

**Rapidly Progressive Dementias**

**Creutzfeldt-Jakob Disease.**—Creutzfeldt-Jakob disease, the most common of the rapidly progressive dementias, should be suspected in any patient with a dementing illness of subacute onset (weeks to months). It is often accompanied by other motor manifestations such as cer-

**Table 7. Diagnostic Criteria for Primary Progressive Aphasia\***

- A. On the basis of evidence from a patient’s history and mental status examination, PPA is characterized predominantly by early manifestations of impaired expressive language or severe naming difficulty (nonfluent PPA)<sup>165</sup>
- B. The impairments in A are not accompanied by major impairment of learning and retaining new information
- C. If the listed impairments notably interfere with work or usual social activities or relationships with others, that interference must be attributable to the language impairment<sup>165</sup>
- D. The impairments in A represent a notable decline from a previous level of functioning<sup>33,165</sup>
- E. The impairments in A are of gradual onset and progressive<sup>165</sup>
- F. The impairments in A do not occur exclusively during the course of delirium<sup>32,33,165</sup>
- G. The impairments in A are not better explained by a major psychiatric diagnosis<sup>32,33,165</sup>
- H. The impairments in A are not better explained by a systemic disease or another brain disease<sup>32,33,165</sup>

\*The concept of primary progressive aphasia (PPA) without dementia is presented.

ebellar, extrapyramidal, or extraocular syndromes. World Health Organization criteria for the diagnosis of CJD are given in Table 8.<sup>170</sup> A closely related version of these criteria has excellent sensitivity and specificity.<sup>171</sup>

The differential diagnosis of a rapidly progressive dementia is given in Table 9. Most diagnoses listed in Table 9 can be established by laboratory testing.

Clinically, CJD usually begins with cognitive impairment or changes in behavior or personality.<sup>172</sup> Depression or agitation may be the initial presentation. The cognitive profile is not particularly distinct because any of the major cognitive domains—memory, language, visuospatial function, or executive function—may constitute the major presenting symptoms. The motor signs and symptoms may be present at the outset or appear shortly after the cognitive

**Table 8. Diagnostic Criteria for CJD<sup>170</sup>**

- Probable Creutzfeldt-Jakob disease (CJD)
  - A. Progressive dementia (dementia criteria from Table 1)
  - B. Presence of at least 2 of the following
    1. Myoclonus
    2. Extraocular or cerebellar disturbance
    3. Pyramidal/extrapyramidal dysfunction
    4. Akinetic mutism
  - C. Presence of at least 1 of the following
    1. Electroencephalogram typical for CJD, regardless of clinical duration of the disease
    2. Positive 14-3-3 assay for cerebrospinal fluid
- Possible CJD
  - A. Progressive dementia
  - B. Electroencephalogram atypical or inconclusive for CJD
  - C. Duration of symptoms <2 y
  - D. Presence of at least 2 of the following
    1. Myoclonus
    2. Extraocular or cerebellar disturbance
    3. Pyramidal/extrapyramidal dysfunction
    4. Akinetic mutism

Table 9. **Rapidly Progressive Dementias and Subacute Confusional States**

Potentially reversible conditions
Autoimmune/inflammatory encephalopathies
Toxic disturbances
Medication misuse, overuse, adverse effects
Alcohol-related, including intoxication, withdrawal syndromes, Wernicke-Korsakoff syndrome
Metabolic disturbances
Thyroid, vitamin B <sub>12</sub> -related, electrolyte, hepatic, renal, and calcium-based disturbances
Depressive disorders
Acute stroke
Atherosclerotic
Vasculitic (reversible only if detected early)
Brain structural lesions
Neoplasms, primary and metastatic
Chronic subdural hematomas
Normal-pressure hydrocephalus
Subacute/chronic meningitis or encephalitis
Fatal, irreversible conditions
Creutzfeldt-Jakob disease
Paraneoplastic limbic encephalitis

ones. Seizures and myoclonus are less common at outset but occur relatively frequently as the illness progresses.

The laboratory has been of considerable value in confirming the diagnosis of CJD. Electroencephalography (EEG) may be the least sensitive and specific. Recent work with the CSF markers 14-3-3 protein and neuron-specific enolase have shown excellent sensitivity and specificity. Laboratory studies are included in the diagnostic criteria (Table 8). A large German national surveillance study of CJD reported a sensitivity of 94%, specificity of 93%, and positive predictive value of 95% for a 14-3-3 assay in CSF.<sup>173</sup> Quantitation of the 14-3-3 protein may yield more information than the simple determination of present or absent.<sup>174</sup> However, other acute neurologic conditions such as stroke, viral encephalitis, or paraneoplastic neurologic disorders can provide false-positive results.<sup>173,175-177</sup> A negative 14-3-3 immunoassay does not rule out CJD.<sup>178</sup> Additional use of neuron-specific enolase does not appear to substantially improve diagnostic accuracy.<sup>179</sup> An MRI finding of gray matter abnormalities on diffusion imaging also has been shown to have good sensitivity and specificity.<sup>180</sup>

Although beyond the scope of this review, recent work in experimental prion systems suggests that compounds similar to the antimalarial drug quinacrine<sup>181</sup> may prevent the pathological aggregation of prion protein; clinical trials are planned. To see a grim disorder such as CJD being studied in therapeutic trials for the first time is exciting.

**Nonvasculitic Autoimmune Inflammatory Meningoencephalopathies.**—One poorly understood group of disorders known as nonvasculitic autoimmune inflammatory meningoencephalopathies (NAIM)<sup>182</sup> is important because these rapidly progressive dementias respond to treatment.

Examples in this category include so-called Hashimoto encephalopathy and Sjögren-associated encephalopathy. Because of the rapid course and prominent myoclonus, patients with these dementias often are misdiagnosed as having CJD, but their encephalopathy typically responds dramatically to a course of high-dose corticosteroids. Patients with NAIM often have normal thyroid function studies, a normal erythrocyte sedimentation rate, normal CSF results, and normal MRI studies; however, their EEGs are always abnormal. Because few features and findings can accurately predict who has treatable NAIM and who has currently incurable CJD, a course of high-dose corticosteroids should be considered in anyone with a rapidly progressive encephalopathy unless the characteristic MRI, EEG, and CSF findings of CJD are present.

## MENTAL STATUS ASSESSMENTS AND FUNCTIONAL ASSESSMENTS

To diagnose dementia, a physician must obtain a thorough patient history and assess function, administer and interpret mental status examinations, and perform a neurologic examination.

### History-taking and Assessment of Function

Obtaining a complete medical history of the patient is necessary. Many systemic illnesses may affect brain function. From the perspective of the differential diagnosis of dementia due to primary neurologic diseases, evidence needs to be sought for cerebrovascular events, prior serious head trauma, evolving difficulties with sleep, gait, or balance, or other neurologic symptoms.

When possible, the examining physician should interview a knowledgeable informant who can provide information about the evolution and current status of decline in a patient's daily activities. For assessing function in mild dementia, the questionnaire listing common activities of daily living<sup>183</sup> (Table 10) is both brief and focused. Assessment of daily functioning is a clinical skill that requires considerable effort and judgment by the physician. Making judgments about whether a behavior such as turning over management of one's checkbook to one's spouse constitutes a symptom of dementia rather than a dynamic of this particular couple's relationship may not always be straightforward. Other challenges in obtaining information about function include its time-consuming nature and the need to conduct such an interview separately from the patient. The latter is not a trivial issue because spouse informants often purposely downplay dysfunction if they are forced to discuss it in front of the patient. In addition, describing the patient's shortcomings in front of the patient often leads to either tearfulness or anger, both of which can be avoided easily by interviewing the spouse informant separately.

### Administration and Interpretation of Mental Status Examinations

A brief mental status examination by a primary care physician or collaborating medical care team member is the most valuable method to detect or confirm dementia. Several brief mental status examinations have been validated and are used extensively. The Mini-Mental State Examination (MMSE)<sup>184</sup> is widely used and covers the domains of orientation, learning, language, and constructions. Its validity against neuropathological diagnoses has been proved. In the context of the diagnosis of mild dementia, the MMSE is somewhat insensitive. Other tests have been devised to improve sensitivity for mild dementia. In the Department of Neurology at the Mayo Clinic in Rochester, Minn, we use a mental status examination known as the Short Test of Mental Status (STMS) developed by our late colleague Emre Kokmen.<sup>185,186</sup> The STMS is similar to the MMSE but has added features that we believe increase its sensitivity. It tests recall of 4 rather than 3 words, uses verbal similarities and calculations, and uses clock drawing, tasks that are more likely to detect milder impairment than the MMSE. Like the MMSE, the STMS has applicability over nearly the entire range of cognitive performance in dementia and has utility for analyzing neurocognitive disorders other than dementia. It takes 5 to 10 minutes to administer, depending on the patient's level and speed of performance.

Mental status testing is subject to variations in the attention and cooperation of the participant; therefore, the examiner must be attuned to the participant's performance beyond the item scores and total score. Furthermore, educational and occupational background and whether English is a first language are important considerations in interpreting responses. Thus, analysis of mental status performance is much more involved than noting the test's total score.

### Performance of Neurologic Examination

The number of neurologic diseases having dementia as a component is large, but many of these disorders have distinctive physical examination findings. In practice, in evaluating dementia in elderly persons, the 2 most common neurologic examination patterns that are important to recognize are those of parkinsonism (extrapyramidal signs) and cerebrovascular disease (lateralized or focal neurologic signs that could be due to strokes). A focused neurologic examination of cranial nerves, reflexes, motor system, and coordination and a brief sensory examination can be accomplished in less than 10 minutes unless there are multiple abnormalities.

Some physical findings loosely associated with degenerative neurologic disease, such as the palmomental reflex, snout reflex, or glabellar tap reflex, have virtually no speci-

Table 10. Assessment of Daily Activities\*

Recalling recent events and conversations
Keeping track of personal items (eg, keys, wallet, purse, glasses)
Writing checks, paying bills, balancing a checkbook
Assembling tax records, business affairs, or papers
Shopping alone for clothes, household necessities, or groceries
Playing a game of skill, working on a hobby
Heating water, making a cup of coffee, turning off stove
Preparing a balanced meal
Keeping track of current events
Paying attention to, understanding, discussing a TV show, book, or magazine
Remembering appointments, family occasions, holidays, medications
Traveling out of the neighborhood, driving, arranging to take buses

\*Some items drawn from reference 183.

ficity for dementia because they become more prevalent in healthy persons with advancing age.<sup>187,188</sup>

### Integration of Mental Status Testing and Informant's Assessments

Ultimately, the clinician must integrate information from the patient's medical history, the assessment of functional status, the mental status examination, and the neurologic examination into a coherent diagnosis. A flowchart involving 4 diagnostic choices is shown in Figure 1. In the usual situation, the functional assessment and the mental status examination will be concordant. Either both will indicate that the person does not have dementia, or both will indicate dysfunction of the same degree.

In some instances, the 2 principal sources of information are discordant. Sometimes, the informant may be worried about cognitive deficits, but the mental status examination is normal. This could occur in several circumstances, probably most commonly in MCI because the bedside mental status examination lacks sufficient sensitivity to detect deficits. Psychometric testing should confirm or refute MCI. Another common cause of discordant information is depression; this mood disorder can induce a level of functional impairment extremely inconsistent with the patient's ability to perform in a one-on-one interview with an empathic physician. Other possibilities include FTD, notorious for causing grossly disturbed behavior while sparing orientation, language functions, and memory. The least likely explanation for a divergence of history and examination is malfeasance of the informant. In almost all discrepant situations, neuropsychological testing is necessary to make a correct diagnosis.

When the informant's reports indicate normal function, but the mental status examination is abnormal, the clinician is faced with different possibilities. Could the abnormal performance on mental status testing be the result of medication effects, acute illness, or another immediate medical or psychiatric condition? Is the patient a

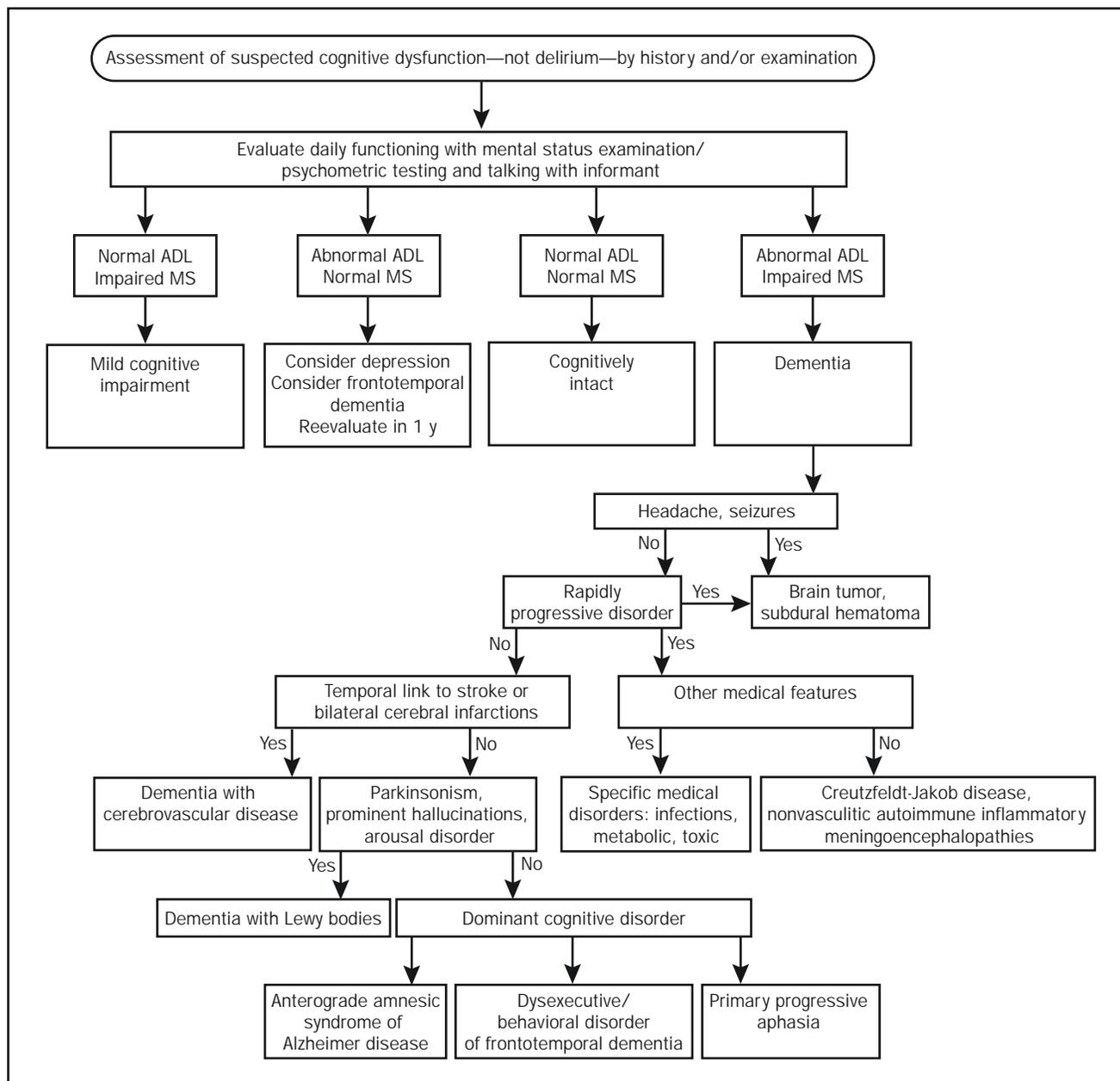


Figure 1. A hierarchical approach to diagnosing mild cognitive impairment, dementia, and the major subtypes of dementia. The sequence of decisions reflects a hierarchy of importance of diagnostic information: features appearing earlier in the decision tree suggest diagnoses regardless of features assessed later. ADL = activities of daily living necessary for independent life, including complex activities such as managing finances; MS = mental status, assessed through bedside mental status testing or formal neuropsychological evaluations.

native English speaker with an educational attainment sufficient to be tested by routine standards of normal vs abnormal function? If none of these alternatives are likely, the physician should consider whether the informant is either unaware of the patient's daily activities, is in denial of the impairment, or is somewhat impaired himself or herself (especially with elderly spouses). Seek-

ing another informant, such as an adult child or sibling of the patient, can often reconcile the problem. Alternatively, having the patient return in a week or even the next day for another interview and examination may resolve the confusion.

When there is no informant, the mental status assessment can be the sole basis for making a diagnosis.

Table 11. Laboratory Diagnostic Evaluation of Dementia in the Elderly Population\*

Test	Intended diagnosis	Use	Comments
Psychometric	All dementias, especially MCI, FTD	In appropriate clinical context	Virtually required for MCI, mild AD, FTD; may be essential if medicolegal complications are possible
CBC, electrolyte panel, calcium, SUN, creatinine, glucose	Common metabolic disorders	Routinely	Not intended to be dementia-specific, but part of routine screening for any elderly person
Vitamin B <sub>12</sub>	Vitamin B <sub>12</sub> deficiency	Routinely	Common disorder in elderly persons; may be associated with cognitive impairment
Thyrotropin	Hypothyroidism	Routinely	Common disorder in elderly persons; may be associated with cognitive impairment
MRI or CT	Brain structural lesions; CJD	Routinely	Needed only at initial diagnosis or after a rapid clinical change; perfusion MRI for CJD
PET or SPECT	AD, FTD	For added diagnostic certainty in selected instances	Marginal additive value over clinical diagnosis for AD, perhaps more helpful in FTD
EEG	CJD	When CJD is suspected	Not useful routinely, but required as part of diagnosis of CJD
APOE genotyping	AD	Rarely	Marginal additive value over clinical diagnoses
Routine CSF examination	Meningitis, encephalitis, meningeal cancer, other infections	In rapidly progressive dementias	None
CSF examination for 14-3-3 protein or neuron-specific enolase	CJD	When CJD is suspected	Highly sensitive and specific, if acute infections, stroke, and neoplastic diseases are excluded by other means
CSF examination for β-amyloid and tau	AD	Rarely	Marginal additive value over clinical diagnoses

\*AD = Alzheimer disease; APOE = apolipoprotein E; CBC = complete blood cell count; CJD = Creutzfeldt-Jakob disease; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalography; FTD = frontotemporal dementia; MCI = mild cognitive impairment; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single-photon emission CT; SUN = serum urea nitrogen.

**LABORATORY EVALUATIONS**

The American Academy of Neurology has published recommendations about the appropriate laboratory assessment of dementia.<sup>81,189</sup> The updated recommendations, with our editorial comments, are listed in Table 11. Blood work is focused on common medical problems in elderly persons. A CT study without contrast is recommended as the standard to detect brain tumors or subdural hematomas. Although such lesions are likely to present with seizures, headaches, or focal neurologic signs or symptoms, that is not always the case.<sup>190,191</sup> An MRI with coronal imaging and an imaging sequence adequate for white matter may provide a fuller view of the cerebrovascular status of the brain and of the hippocampus—the brain region affected early in the course of AD.

Studies such as carotid ultrasonography, EEG, and 24-hour urinary collections for heavy metals lack rationale for routine use. These tests should be reserved for patients with specific indications for these assessments. For certain diagnoses, such as CJD, specific biomarkers should be assessed.

**NEUROPSYCHOLOGICAL TESTING**

The role of neuropsychological testing undoubtedly varies, depending on the expertise of the ordering physician in assessing cognition. Primary care physicians may find neuropsychological testing to be particularly necessary in

patients with mild cognitive deficits, in patients whose depression and cognitive dysfunction coincide and are difficult to distinguish, in patients with extremely high or low educational attainment, and in patients in whom FTD or DLB is suspected. Neuropsychological testing otherwise is not required for diagnosing dementia or its subtypes. However, for patients in whom establishing a diagnosis may be challenging, neuropsychological testing should be an integral part of the dementia evaluation.

**HIERARCHICAL APPROACH TO DIAGNOSING DEMENTIA**

In clinical practice, patients with dementia are almost always brought to medical attention by complaints of family members, friends, or caregivers of the patient, and less commonly by complaints of the patients themselves. Cognitive assessments are done infrequently for general geriatric screening at this time; therefore, it is still uncommon for dementia to be diagnosed on the basis of an abnormal mental status examination alone. However, if the evaluation of a patient with suspected dementia were initiated by the finding of an abnormal mental status examination, the process of attaining a diagnosis still would involve gathering information from an informant and integrating that information with the mental status examination.

When all the information from the patient’s medical history, informant interview, mental status examination,

and neurologic examination is assembled for diagnostic purposes, there is a hierarchy in the assignment of diagnoses (Figure 1). Some features have high specificity and, if present, point to one diagnosis and make others unlikely. These include the rapidity of symptom onset, certain vascular features, extrapyramidal features, and certain cognitive or behavioral presentations. For example, if the patient had a stroke followed by dementia within 3 months, the diagnosis will certainly include DCVD as a prominent element. If a patient exhibits profuse visual hallucinations, a prominent disorder of gait and balance, and a REM sleep behavior disorder, DLB will be the diagnosis. The flowchart presented in Figure 1 should be used only for dementia in elderly persons. Moreover, people are so complex and individual that there certainly will be circumstances in which the hierarchy for diagnosing dementia will not be useful. However, for most patients, the hierarchical approach to assessing cognitive dysfunction in patients with dementia (Figure 1) will increase diagnostic confidence.

### PROGRESS AND FUTURE DIRECTIONS IN THE DIAGNOSIS OF DEMENTIA

In the past 20 years, our understanding of dementia has advanced remarkably. As primary care physicians see more patients with dementia and as more of these physicians are trained to perform mental status examinations, confidence and success in diagnosing dementia should increase. In the next decade, the focus may shift to earlier diagnosis and identification of individuals without dementia who are at risk of AD or other specific dementing illnesses. The highly likely development of effective preventive or arrestive therapies in the next 20 years will substantially increase the need for early, accurate clinical diagnosis.

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The Symposium on Geriatrics will continue in the November issue.