

The Diagnostic Evaluation of a Patient With Dementia

Douglas Galasko, MBBCh

ABSTRACT

Purpose of Review: This review outlines a practical approach to the history, mental state, neurologic examination, and laboratory tests in the diagnosis of dementia.

Recent Findings: Proposed new diagnostic criteria for Alzheimer disease recognize that nonamnesic presentations with symptoms that predominantly affect language, visuospatial abilities, or executive function may occur, particularly with onset before the age of 65. New criteria assign greater likelihood to diagnosis if progressive cognitive decline is documented through serial assessment, or if biomarkers are supportive. In patients aged 80 or older, more than one cause of dementia is often present, for example, Alzheimer disease plus vascular dementia. Clinical diagnostic criteria for non-Alzheimer dementias are evolving, particularly in areas such as frontotemporal dementia. Imaging and CSF biomarkers have been proposed in recent diagnostic criteria for Alzheimer disease. Although biomarkers can provide a higher level of certainty that Alzheimer pathology may or may not be present, biomarkers for non-Alzheimer dementias are lacking.

Summary: The availability of biomarkers does not replace or diminish the need for a thorough clinical evaluation. A structured clinical approach helps to define the diagnosis and collects information essential for establishing a comprehensive care plan for patients with dementia and their families.

Continuum (Minneapolis Minn) 2013;19(2):397–410.

INTRODUCTION

Dementia is defined as an acquired decline of cognitive abilities sufficient to result in social or occupational impairment. The usual presentation is the gradual onset and progressive loss of memory and other cognitive abilities occurring in elderly people; the prevalence rises from about 1% to 2% at age 65 to 10% to 15% at age 80, and may be as high as 40% by age 90. When someone younger develops significant cognitive decline or behavioral changes, the diagnosis of dementia may often be delayed because of a lower index of suspicion or a less typical clinical presentation. Recently revised criteria for

the diagnosis of Alzheimer disease (AD) have improved the clinical description of variants such as progressive aphasia or posterior cortical atrophy, and although they indicate that biomarkers may improve diagnostic accuracy, they also emphasize the importance of the clinical evaluation.¹

The key goals of a clinical evaluation are to establish whether dementia is present; to characterize the impaired areas of cognition, the severity of impairment, and functional consequences; and to determine the likely etiology. However, it is worth framing the evaluation more broadly. With the serious implications of dementia for the patient

Address correspondence to Dr Douglas Galasko, Department of Neurosciences, UC San Diego, 9500 Gilman Drive 0948, La Jolla, CA 92093

Relationship Disclosure:

Dr Galasko serves as a consultant for Elan Corporation and serves on the data and safety monitoring boards of Elan Corporation and Janssen Pharmaceuticals, Inc.

Dr Galasko serves as an editor-in-chief of *Alzheimer's Research and Therapy*.

Unlabeled Use of Products/Investigational Use Disclosure:

Dr Galasko reports no disclosure.

© 2013, American Academy of Neurology.

KEY POINT

- It is useful to determine the patient's degree of insight into problems, because this will influence his or her acceptance of elements of a care plan.

and family, the evaluation must collect enough information to allow the clinician to discuss the diagnosis and its immediate and long-term implications, and formulate a comprehensive overall care plan.

The evaluation of dementia is best staged over two clinic visits. The first visit should allow enough time to obtain a detailed history and examination, interview family members (often separately from the patient), and order diagnostic tests. The second visit usually consists of a conference with the patient and family members, for which the goals are to present and discuss the diagnosis and etiologic factors; review medical treatment options; develop a plan for overall management, including issues such as driving, financial matters, medications, and legal issues (eg, durable power of attorney for health care); exchange information about social and community resources; and, when relevant, discuss research options. Some clinicians who perform detailed cognitive or neuropsychological assessments themselves may divide the evaluation into three visits.

THE HISTORY
Initiating the Visit

Many patients with dementia lack insight into their deficits and tend to deny the existence of a problem. Patients with AD will often make excuses for their memory problems, for example, saying they do not do particular activities anymore or do not remember things because “that isn’t important.” It is useful to determine the patient’s degree of insight into problems, because this will influence his or her acceptance of elements of a care plan. Early in the course of AD, patients may have striking preservation of social and interpersonal skills, and a superficial conversation may show no obvious signs of impairment other than the

shallow content of their speech. Patients will often steer conversation toward experiences that they are able to recall in detail. On the other hand, when patients provide a rich and detailed account of their memory lapses, this usually indicates their awareness of age-associated cognitive changes or may raise the possibility of anxiety or depression. The key to obtaining an accurate history is to interview a knowledgeable informant. This is often best done when the patient is not present in order to avoid arguments or distress when the caregiver describes problems. A separate interview with one or more family members may be particularly important when the patient is referred against his or her will or is resistant to the evaluation. Some patients may be sensitive to or alarmed by the use of the words “Alzheimer disease,” and discussing the problem as “memory loss” or in other general terms (eg, “This is a checkup of how well you’re doing”) can smooth over the initial clinical encounter.

It is helpful to characterize the nature of the onset and the early symptoms in detail. AD and other neurodegenerative causes of dementia are characterized by a gradual onset of cognitive decline, whereas in vascular dementia the onset may be more abrupt. The course of AD is also gradual and relatively slow, measured over years. In early or mild stages, patients may have occasional lapses, but over time these become more frequent in AD and other neurodegenerative causes of dementia. Vascular dementia may show a stepwise decline; a history of stroke or strokelike episodes increases the confidence of this diagnosis but is not essential. Some events may accelerate the symptoms of dementia—for example, patients with AD may decline after undergoing major surgical procedures or become delirious after a medical illness such as

pneumonia. This should not be taken as evidence of cerebrovascular pathology. Rapid cognitive decline with a subacute course over weeks or months raises a different set of diagnostic concerns.

Characterizing Cognition

The informant interview should characterize the patient's cognition, behavior, and function to develop a detailed clinical picture and to help in diagnosis and staging. Although the cognitive history will generally focus on memory skills, some patients may present with other areas of impairment, such as language, executive function (ie, judgment, planning, and reasoning) or visuospatial abilities. Patients with frontotemporal dementia (FTD) typically have striking changes in behavior or personality, with relatively preserved memory and visuospatial abilities. Since history taking should be detailed and may involve interviewing the informant separately from the patient, it may be helpful to have the informant complete a questionnaire or a series of rating scales about these symptoms while the patient is undergoing the examination.

Symptoms that point to a major memory problem include asking questions repeatedly; forgetting details of conversations, appointments, and plans; not paying bills on time; and not recalling the details of TV shows or movies. These types of problems need to be distinguished from complaints that are usually blamed on memory but reflect age-associated cognitive changes. In particular, difficulty finding words or recalling people's names is related to problems with retrieval rather than memory and is a hallmark of aging. It is often accompanied by the "tip of the tongue" phenomenon, in which the word or name comes back some time later. Two other cognitive changes associated with aging are slowing of cognitive processing and increased dif-

iculty with multitasking, or susceptibility to interference. Careful questioning can reveal that the patient is able to complete a complex task, given enough time and the absence of distraction. This may not be the case for someone with early dementia.

Symptoms of other areas of cognitive decline are shown in **Table 6-1**. Language problems may include difficulty with names of people or objects, shorter sentences, circumlocution (ie, empty speech when describing things or answering a question), paraphasic errors, or mispronunciation of words. Speech problems such as dysarthria may be associated with decreased or slower language output. Patients with executive problems may have difficulty initiating activities, making plans, performing complicated tasks at work or in hobbies, or following multistep processes such as using a cell phone, computer, or remote control. Questioning about executive abilities therefore often overlaps with functional abilities. Patients with visuospatial problems may report unusual symptoms such as difficulty using their hands for fine coordinated activities (eg, typing on a keyboard, using a screwdriver, or knitting) or misjudging where objects are in space. They may have vague difficulty in reading or distinguishing objects or people's faces, and often receive an ophthalmologic evaluation before the problem is attributed to the brain rather than the eyes.

History of Functional Ability

An assessment of functional abilities is best obtained from a knowledgeable informant. For clinical assessment, it is helpful to divide activities of daily living (ADL) into two categories. Basic ADL include activities that are essential to self-maintenance: grooming, bathing, dressing, eating, and continence. In most patients with AD, independence

KEY POINT

- Symptoms that point to a major memory problem include asking questions repeatedly; forgetting details of conversations, appointments, and plans; not paying bills on time; and not recalling the details of TV shows or movies. These types of problems need to be distinguished from complaints that are usually blamed on memory but reflect age-associated cognitive changes.

TABLE 6-1 Clinical Presentations of Alzheimer Disease and Other Degenerative Dementias

Clinical Presentations	Symptoms	Clinical Findings	MRI/Imaging Findings
Typical amnesic Alzheimer disease (AD)	Forgets conversations, appointments, and plans	Impaired learning and memory Normal neurologic examination	Atrophy, especially in the hippocampus and temporal lobe, and ventricular enlargement
Posterior cortical atrophy	Difficulty recognizing faces or objects, locating or manipulating objects that are in view, reading, and judging distances	Simultagnosia, Balint syndrome Difficulty reading or drawing intersecting or visually complex figures	Occipital lobe atrophy
AD with aphasia—logopenic	Difficulty with word-finding and pauses during speech	Impaired single-word retrieval in spontaneous speech Impaired repetition of phrases or longer sentences	Left posterior perisylvian or parietal atrophy, or hypometabolism
Lewy body dementia	Variable alertness and attention Visual hallucinations REM sleep behavior disorder	Cognitive impairment, often with relative sparing of memory Impaired visuospatial tests Parkinsonism	Less atrophy than in AD Occipital hypometabolism on fluorodeoxyglucose (FDG) positron emission tomography (PET)
Behavioral-variant frontotemporal dementia	Disinhibition: change in personal decorum, inappropriate interpersonal behavior, and rash/impulsive behavior Apathy or inertia Loss of empathy Repetitive, ritualistic behavior Hyperorality and diet changes	Executive impairment, relatively preserved memory, and visuospatial skills Normal neurologic examination; some patients may have ALS or mild parkinsonism	Frontal or anterior temporal lobe atrophy (CT or MRI) or hypometabolism (FDG PET)
Primary progressive aphasia—semantic variant	Difficulty thinking of words (eg, names of objects) Fluent language output	Impaired confrontation naming Impaired single-word comprehension Loss of object knowledge Surface dyslexia (misreading of irregularly pronounced words)	Anterior temporal lobe atrophy or hypometabolism on FDG PET
Primary progressive aphasia—nonfluent	Slow, halting speech	Agrammatism Halting speech, sometimes speech sound distortions or errors Spared word knowledge/comprehension	Left posterior frontoinsula atrophy or hypometabolism

Continued on next page

TABLE 6-1 *Continued*

Clinical Presentations	Symptoms	Clinical Findings	MRI/Imaging Findings
Corticobasal syndrome	Variable: eg, difficulty with movement, clumsiness, stiffness of affected limb; visual or language symptoms	Rigidity, apraxia, cortical sensory loss, alien limb, limb dystonia, reflex focal myoclonus—often starts in one limb	Asymmetrical cortical atrophy, often parietal
Progressive supranuclear palsy	Slow speech, dysarthria, and dysphagia Slow gait, falls Apathy	Impaired eye movements, especially vertical gaze Postural instability Akinesia, rigidity, retrocollis Slowed cognition, dysexecutive syndrome	Atrophy of midbrain, “hummingbird sign”

in basic ADL is preserved until late in the course; early problems with basic ADL may be due to physical problems such as a gait disorder or urological problem. Identifying impairments in more complex tasks, referred to as instrumental activities of daily living (IADL), is a critical part of the history. Structured questionnaires such as the AD8 (which combines cognition and function)² or functional activities questionnaire³ can be useful tools. Alternatively, tailoring functional inquiries to the patient’s activities and lifestyle can also provide useful information. The clinician should always inquire about activities that could pose significant safety risks in the setting of dementia; for example, even though the potential loss of driving privileges is a highly sensitive issue, the clinician must ask whether the patient has had problems such as getting lost while driving, having accidents (even minor ones), or being unable to locate the car in a large parking lot. The clinician must be aware of local legal reporting requirements for dementia—in many states, a report does not automatically lead to a suspension of driving privileges but may result in the Department of Motor

Vehicles performing a driving evaluation through a written or observed driving test. Handling medications accurately, managing small sums of money, balancing a checkbook or credit card statement, paying bills, and completing income tax returns are other examples of IADL that could pose substantial risks.

Other IADL matters worth probing include trouble using gadgets such as a remote control, cell phone, or computer; difficulty with pastimes or hobbies, particularly when they are cognitively complex; and declining abilities to prepare food or perform household maintenance activities. Patients with dementia may have problems remembering appointments and plans even when they use a calendar, diary, or electronic device as a reminder. When there are changes in functional abilities, a physical health factor (eg, severe arthritis, impaired mobility, or poor vision or hearing) may need to be taken into account.

Assessing Changes in Behavior

Behavioral symptoms are common in patients with dementia, may provide diagnostic clues, and should be

KEY POINT

- The clinician should always inquire about activities that could pose significant safety risks in the setting of dementia.

KEY POINT

■ Behavioral symptoms are common in patients with dementia, may provide diagnostic clues, and should be considered when formulating a treatment plan.

considered when formulating a treatment plan. Patients with behavioral-variant frontotemporal dementia (bvFTD) characteristically have early symptoms reflecting a deterioration of personality, social conduct, and interpersonal relations; loss of interest; withdrawal; and difficulty with planning.⁴ Although apathy, inertia, and poor planning may also occur in AD, the manifestation of these distinctive symptoms of social and personality changes in a patient with preserved memory abilities points to bvFTD. Symptoms such as depression, delusions, and hallucinations (particularly visual) can provide clues to specific types of dementia. In addition, these behavioral changes are often distressing to family members and make care more difficult. Although the treatment of behavioral problems can be challenging, it is important to inquire about and treat them whenever possible.

Changes in sleep are important behavioral symptoms that also provide clues to specific types of dementia. For example, REM sleep behavior disorder occurs in Parkinson disease and Lewy body dementia and can be assessed by asking whether patients appear to act out their dreams during sleep.⁵ Insomnia or sleep apnea may affect memory consolidation and daytime cognitive abilities. Excessive daytime sleepiness usually occurs in moderate to severe dementia, although it can be a prominent and early feature of Lewy body dementia.

Points to Emphasize in the Rest of the History

Other components of the medical history color the background of evolving cognitive problems. A patient's handedness and educational and work history are relevant to the interpretation of cognitive testing and may influence the health literacy of the patient and family.

Social history should focus on marital status, the existence of a social support network of family and friends, and exposure to alcohol and drugs. Physical activity, including walking or other forms of exercise, should be documented. Medical history should highlight risk factors that could contribute to dementia. Vascular risk factors such as heart disease, diabetes, hypertension, transient ischemic attack, and stroke should be recorded in detail. Traumatic brain injury, particularly with loss of consciousness, and coexisting neurologic problems such as seizures, Parkinson disease, multiple sclerosis, or other disorders that could affect cognition should be noted. Problems with vision and hearing can contribute, and a history of major psychiatric disorders may be relevant.

Medications may also be relevant to the assessment and management of dementia. Drugs with strong anticholinergic actions⁶ or sedating side effects can play a role in worsening cognitive impairment, although it is unusual for them to be the sole cause. If cardiovascular risk factors are present, the adequacy of their medical treatment should be assessed.

Hints of a family history of dementia should be systematically reviewed. It is often helpful to record a detailed pedigree, particularly for patients with cognitive or behavioral symptoms before the age of 65. The family history should inquire broadly about different symptoms or phenotypes among relatives; for example, some inherited disorders may produce a picture of progressive dementia in one relative and ALS or a combination of cognitive and motor dysfunction in another.

THE NEUROCOGNITIVE (OR MENTAL STATE) EXAMINATION

The neurocognitive examination is of prime importance in the diagnosis of

dementia. During a clinical office visit, cognitive testing needs to strike a balance between comprehensiveness and practicality. The goals are to document performance of memory and other key cognitive domains, to define areas of strength and weakness that may support a diagnosis, and to help stage the severity of dementia. There are two main approaches: overall cognitive tests and detailed batteries that cover specific cognitive domains.

Overall Cognitive Tests

Overall cognitive tests provide a brief, structured approach and are widely used for screening in general neurologic and medical practices.⁷ The Mini-Mental State Examination (MMSE) is one of the best known of these tests. It probes memory (through the task of learning and recalling three words), orientation (predominantly through a memory test), working memory (through the task of serial 7 subtraction or spelling *world* backward), language (through tasks of naming, repetition, reading, writing, and following a three-step command), and visuospatial abilities (through the task of copying interlocking pentagons). Advantages of the MMSE are its ease of use, familiarity to physicians and families of patients with AD, and moderate sensitivity for the diagnosis of dementia. It is also helpful in staging and tracking progression over time. However, there are many problems with the MMSE, including insensitivity for mild dementia, test-retest variability of a patient's scores, and a lack of readily available translations and alternative versions (some patients rehearse the date and words typically used to test recall in the MMSE while en route to the clinic). In addition, the MMSE is not available for use free of charge; a fee of \$1.20 for each administration is supposed to be paid to Psychology As-

essment Resources, Inc, which holds a publishing copyright to the MMSE. There may also be problems in applying the MMSE to criteria for the diagnosis of AD or other forms of dementia. Although a cutoff score of 24 or below may support the diagnosis, it is difficult to use the MMSE to formally document impairment of memory and an additional area of cognition. Recall of three words is an insensitive and inaccurate test of memory, although combining it with orientation may improve the assessment. Moreover, language is superficially assessed, and visuospatial abilities and executive function are minimally, if at all, assessed by the MMSE.

Slightly longer overall tests such as the Montreal Cognitive Assessment (MoCA) (www.mocatest.org)⁸ and the Saint Louis University Mental Status (SLUMS) examination⁹ offer greater sensitivity than the MMSE, as well as the ability to sample cognitive domains more widely. The MoCA and SLUMS examination both take about 7 to 10 minutes to administer and yield scores that range from 0 to 30. The MoCA is available in three alternative versions in English, and translations of the original version are available in many languages. Diagnostic cutoffs for AD and for mild cognitive impairment have been suggested based on several studies. The MoCA screens attention and components of executive function and probes language and memory in more detail than the MMSE. However, one needs to be cautious about using a cutoff score as a diagnostic test. The five-item word list on the MoCA is a more difficult learning and recall task than the three-word test on the MMSE. The MoCA uses only two encoding trials (compared to formal psychometric word list tasks, which typically use four to five trials of longer word lists), and some subjects with no dementia may show a falsely positive apparent memory

KEY POINT

- The goals of cognitive testing are to document performance of memory and other key cognitive domains, to define areas of strength and weakness that may support a diagnosis, and to help stage the severity of dementia.

deficit if they do not attend adequately to the learning trials. Repetition of complex sentences on the MoCA can be nonspecifically affected by problems such as decreased hearing. The MoCA adjusts for people with fewer than 12 years of formal education by recommending adding one point to the total score, but cutoffs and test performance among less well-educated individuals have not been widely studied. A test like the MoCA can form the foundation of a detailed cognitive evaluation in clinic (**Case 6-1**). Besides considering the total score for the MoCA, the domains that are affected should be examined. Additional cognitive testing may be carried out to help

to confirm impairment in suspected domains. If uncertainty remains, formal neuropsychological testing will provide a clearer picture of cognitive strengths and weaknesses.

Evaluating Cognitive Domains

Some dementia specialists with appropriate expertise may perform and bill for detailed cognitive evaluations. Although many formal psychometric tests with norms for age and education are available,¹⁰ it is often beyond the resources or time availability of a general neurologist to perform such testing. Computerized batteries have been used in research settings, but few have been validated in clinical practice.

Case 6-1

A 77-year-old retired college professor was brought to the clinic by his wife. He denied any problems, although she stated that he sometimes asked questions repeatedly, forgot details of conversation, had trouble remembering computer passwords, and struggled to recall details or the plots of novels. He could write emails and letters, drive, and manage a credit card without difficulty. His wife thought that he sometimes forgot to take his medications. His problems had been present for about 12 months. Medical history was notable for hypertension and increased cholesterol; family history was negative for cognitive or neurologic problems. Medications included antihypertensives, a statin, and aspirin. He sometimes slept poorly, and his general health was notable for slowing of gait. He showed less interest in attending social functions but did not have symptoms of depression. A primary care physician noted that he scored 29/30 on the Mini-Mental State Examination.

On mental state examination, he scored 26/30 on the Montreal Cognitive Assessment, losing three points for recall and one for executive function. Results of the remainder of the neurologic examination and of laboratory blood tests were normal. Brain MRI showed cortical atrophy consistent with age and a few hyperintensities in the periventricular white matter. Neuropsychological testing revealed impairment of learning and memory on both a list-learning test and a task of copying and recalling a complex figure. He had impairment on category fluency, the Trail-Making Test Part B, and the Stroop Color-Word Association Test. The diagnosis of Alzheimer disease was made and discussed in detail with the patient and his family at a follow-up visit.

Comment. This case illustrates the importance of detailed history taking from a knowledgeable informant, the exclusion of other contributory factors in the evaluation, the insensitivity of screening cognitive tests in patients with high levels of education, and the value of neuropsychological testing.

Suggestions for testing a variety of cognitive domains in a clinical setting are outlined below. An important consideration in interpreting tests is that relatively few of them probe a single cognitive domain exclusively. For example, drawing a clock and setting the time depends on judgment and planning (executive function) as well as visuospatial abilities. Patients with impairment in a key domain such as language may show impairment across tests with verbal instructions and responses, and patients with markedly impaired attention may show difficulty with learning and memory due to failure to encode material.

The term “memory impairment” is often used loosely in relation to AD. The major feature of memory impairment in AD is episodic memory, which depends on the structural integrity of the hippocampus and allows us to encode and remember where or when something happened. Semantic memory (the knowledge of what objects, words, or ideas are) may be impaired later in the course of AD and is a defining feature of a form of progressive aphasia called semantic dementia. Procedural memory (the memory of skilled or sequential motor tasks) is preserved in AD. Among the most widely used tests of memory is list-learning, in which 10 to 16 words are read to the patient, who is asked to repeat as many as he or she can remember. A series of trials is given and an index of immediate recall or learning across these trials is calculated. After a typically 15-minute or longer delay filled with distractor tests, the patient is asked to recall as many of the words as possible. Impaired recall, in particular rapid forgetting (defined as recalling less than 50% of the words that were learned), is suggestive of a major memory disorder such as AD. Another psychometric approach to memory testing is story recall, in which brief

narratives are read to the patient, who is asked to repeat as many details as possible and then to recall as much of the story as possible after a delay. The logical memory test (part of the Wechsler Adult Intelligence Scale) involves recall of two stories, each of which consists of 25 embedded factoids. Nonverbal memory and learning can be tested through copying a complex drawing (eg, the Rey-Osterreith figure) and drawing it after a delay. Without recourse to the time or structured testing environment needed for these procedures, testing memory and learning can be difficult for a clinician. Some suggestions for additional office-based tests of memory include having the patient learn and recall a five-item name and address, asking the patient to describe what she or he ate for each meal the day before, and asking about an outing or event the patient attended in the past month or two, if there is an informant who can verify the details. Asking the patient to describe details of major recent news events can also be informative, provided that they have heard about these events (eg, through reading a newspaper or watching TV); recent bad-weather events, earthquakes, accidents, sports events, or news involving celebrities or politicians are examples.

Attention includes the important capacity of working memory: the ability to maintain a short piece of information, such as a telephone number, in memory storage for a short interval. It is important to test in its own right, early in a cognitive examination, because inability to attend can markedly affect other cognitive domains. Digit span is a typical approach. Most people can remember at least six digits forward and four backward (the MoCA is more lenient, using four digits forward and three backward).

Language testing begins by listening to the patient’s spontaneous output. Naming objects or their parts, including

KEY POINT

- The term “memory impairment” is often used loosely in relation to Alzheimer disease. The major feature of memory impairment in Alzheimer disease is episodic memory, which depends on the structural integrity of the hippocampus and allows us to encode and remember where or when something happened.

KEY POINT

■ Focal findings consistent with stroke, or a gait disorder not explained by other factors, may support a cerebrovascular contribution to dementia.

some lower-frequency words, can be a good screen for anomia, a common finding in many types of aphasia. Asking the patient to repeat or read consonant sounds (eg, P-T-K) and single words of increasing length can screen for dysarthria. Fluency tests, such as naming as many words as possible in 1 minute belonging to a specific category or with a specific first letter, probe language as well as executive function. Assessment procedures and criteria for diagnosing subtypes of primary progressive aphasia were recently proposed.¹¹

There are many aspects of executive function, and testing for it often places demands on other cognitive abilities as well. Clock drawing, for example, depends on judgment, planning, and visuospatial abilities. Explaining similarities between word pairs is a better test of reasoning than explaining proverbs, because the meanings of proverbs are typically learned at school rather than solved on the spot. Attention tasks such as reciting the months backward (or, more difficult, letters of the alphabet backward) also depend on executive function. Calculation tasks, such as serial 7 subtraction or making change, depend on attention, right parietal abilities, and frontal lobe function.

As visuospatial tests, clock drawing and copying complex intersecting figures can extend a screening examination. If the examiner suspects posterior cortical atrophy, then asking the patient to describe a visually rich and complex drawing or photograph can help to screen for simultagnosia.

THE REMAINDER OF THE NEUROLOGIC EXAMINATION

Beyond mental status testing, the remainder of the neurologic examination can yield important clues about etiology, particularly for less common disorders. The clinician should be prepared to apply extra diligence in testing visual

fields, examining eye movements, assessing praxis, or looking for signs of motor neuron disease when evaluating a patient who does not have a typical AD presentation.

In a patient with AD, normal neurologic examination results are expected. During the neurologic examination of an elderly patient, the examiner will often identify findings associated with normal aging, such as decreased large-fiber sensation in the toes, decreased or absent ankle reflexes, a mildly stooped posture, and marked difficulty with tandem gait. Frontal release signs or primitive reflexes (such as the glabellar tap, snout, suck, palmar-mental reflex, and grasp reflex) are of dubious diagnostic value because they occur in many normal elderly people as well as in patients with AD or frontotemporal dementia. Procedures to elicit them (eg, the number of glabellar taps that continue to produce a blink beyond what is thought of as normal) are not agreed upon, and many specialists in neurodegenerative or cognitive disorders do not assign any special significance to these signs.

The neurologic examination is sometimes revealing. Focal findings consistent with stroke, or a gait disorder not explained by other factors, may support a cerebrovascular contribution to dementia. The gait in vascular dementia due to multiple lacunes is often described as *marche à petits pas*, referring to a slow gait with short steps and an upright posture. Normal pressure hydrocephalus classically results in a magnetic gait, in which the patient's feet appear stuck to the ground; however, nonspecific gait slowing with poor balance may be a more common picture. Signs of parkinsonism may point to Lewy body dementia. These can be subtle; a common pattern is slowing of movement, slightly increased tone, parkinsonian gait and postural instability

(demonstrated on a backward pull), and the absence of rest tremor. Parkinsonian findings are less specific in patients with moderate to severe dementia.

In posterior cortical atrophy, elements of Balint syndrome may be present, namely difficulty perceiving the entire visual field, fixating the eyes, and moving a hand to a precise location or specific object by using vision.¹² These features can be identified by careful testing of visual fields, having the patient reach into space to a defined location and move his or her eyes to selected areas of gaze. Asking the patient to describe a photograph or painting of a complex scene and looking for elements of Gerstmann syndrome or apraxia can help with the clinical characterization (Case 6-2).

Progressive supranuclear palsy may have several clinical variants.¹³ It is easiest to diagnose when the characteristic eye-movement abnormalities appear, including slow saccades and impaired vertical then horizontal gaze, which are correctable with the doll's head maneuver. In some patients, these findings may appear late. Other features are dysarthria, increased tone (especially axial rigidity), and slowing of gait with retropulsion. Corticobasal syndrome may be difficult to diagnose, especially early in the course.¹⁴ The typical motor features such as akinesia, rigidity, dystonia, focal myoclonus, ideomotor apraxia, and alien-limb phenomenon, affecting one limb or one side of the body predominantly, are not always present. Presentations with dysarthria, aphasia (usually

Case 6-2

A 61-year-old journalist had difficulty typing on a keyboard and trouble reading for 18 months. He had a car accident 6 months ago in which he had difficulty judging how close a traffic barrier was when he changed lanes. He saw an ophthalmologist and received new glasses, but problems persisted. He reduced his workload and stopped driving on freeways because of his symptoms. There were no visual hallucinations. He had no significant medical history.

On the Montreal Cognitive Assessment he lost two points for recall, one for copying a cube, and one for poor layout of numbers on a clock, with a final score of 26/30. Visual fields were grossly intact. He had difficulty describing details of a painting, with some slowing and a need to direct his gaze carefully. When reading, he sometimes omitted words at the ends of lines. The remainder of his neurologic examination was otherwise unremarkable. Neuropsychological testing revealed impairment on visuospatial tasks, borderline performance on recall of a word list, and slowing on the Trail-Making Test Part B.

A brain MRI showed slight atrophy of the left parieto-occipital area. CSF biomarkers showed a decreased level of amyloid- β 42, increased total tau, and borderline phosphorylated tau. An amyloid imaging positron emission tomography (PET) scan was positive, with widespread binding of tracer throughout the brain. A diagnosis of posterior cortical atrophy due to Alzheimer disease was made; the patient was started on a cholinesterase inhibitor and reported mild improvement of reading ability.

Comment. This patient has typical symptoms and findings of posterior cortical atrophy. Biomarkers enable the underlying diagnosis of Alzheimer disease to be made with greater confidence.

KEY POINT

■ In cases in which a decision about dementia could substantially alter the patient's life (eg, a patient who is still working) or in which there are legal questions (eg, competency to manage assets), detailed neuropsychological evaluation can strengthen the clinical diagnosis and provide sensitive indices of the degree of impairment.

nonfluent), or executive dysfunction may make the specific diagnosis difficult. Underlying pathology is variable, with corticobasal degeneration and AD the most common.

Suspicion for prion disorders should arise when patients have subacute or rapidly progressing dementia.¹⁵ Confusion or a deliriumlike picture may dominate, or focal cognitive deficits may be present. Myoclonus, while often present, tends to occur later in the course. Other presentations include ataxia and extrapyramidal signs.

NEUROPSYCHOLOGICAL TESTING

Although not mandatory to diagnose dementia, neuropsychological testing is valuable in a number of situations. When dealing with an unusual presentation of dementia, a comprehensive neuropsychological evaluation can define areas of impairment and preserved abilities. In cases in which a decision about dementia could substantially alter the patient's life (eg, a patient who is still working) or in which there are legal questions (eg, competency to manage assets), detailed neuropsychological evaluation can strengthen the clinical diagnosis and provide sensitive indices of the degree of impairment relative to normal performance. For details of neuropsychological testing and interpretation in dementia, see reference 10 in the list below.

LABORATORY WORKUP AND IMAGING

The American Academy of Neurology (AAN) guidelines for laboratory evaluation in suspected AD recommend routinely measuring B12 and thyroid-stimulating hormone levels.¹⁶ Other tests that provide information about factors that contribute to or worsen cognitive function include complete blood count (anemia) and creatinine (renal failure). Tests such as rapid

plasma reagin, HIV testing, or workup for unusual CNS inflammatory disorders are not part of a standard evaluation but should be used when clinical suspicion arises. Lumbar puncture is not recommended as a routine test but may be helpful to rule out meningitis or encephalitis, confirm suggested neurosyphilis, or measure CSF pressure in suspected normal-pressure hydrocephalus. An EEG does not have a place in the routine evaluation of dementia.

A structural brain imaging study—either MRI or head CT—is recommended in the AAN guidelines for AD. MRI has higher resolution and is strongly preferred. In addition to atrophy, stroke (including lacunes), and white matter changes, MRI can also detect microhemorrhages, which may indicate amyloid angiopathy, and problems such as subdural hematoma. The ability to obtain volumetric readout on MRI is not widely available.

It is extremely helpful to review neuroimaging tests and not merely to read a report. Findings such as hippocampal atrophy, focal atrophy affecting the cortex, and an appreciation of the extent and location of subcortical white matter changes are three areas where careful examination of the images can clarify the diagnosis.

The Workup for Rapidly Progressive Dementia

Brain imaging and CSF evaluation should be obtained in patients with rapidly progressive dementia. MRI may show evidence of unusual problems such as encephalitis, vasculitis, carcinomatous meningitis, primary or metastatic brain cancer, or other brain mass lesions. Diffusion-weighted MRI is the most sensitive way to detect findings consistent with prion disease.¹⁷ Findings such as a cortical ribbon appearance or altered appearance of basal ganglia structures should be carefully examined.

The CSF biomarkers of tau, P-tau, and 14-3-3 protein are often increased in prion disorders, but they have substantially lower sensitivity than abnormalities on diffusion-weighted MRI. Autoantibodies against a variety of brain proteins have been reported in patients with rapidly progressive or unusual dementia syndromes. These were reviewed comprehensively in **CONTINUUM** 2010;16:31–56.

BIOMARKERS

Biomarkers for AD are beginning to transition from research to practice, and the evidence for their use is covered by Drs Sperling and Johnson (**CONTINUUM**, this issue). New research criteria for AD proposed by the National Institute on Aging and Alzheimer's Association workgroup¹ and similar efforts by an international working group have divided biomarkers into categories according to the type of brain processes they measure. For example, MRI volumetric analysis or fluorodeoxyglucose positron emission tomography (PET) scans can measure regional atrophy or hypometabolism, and thus the topography of neurodegenerative changes in AD. Finding an increased level of CSF tau or P-tau proteins provides an index of neurodegeneration. Amyloid imaging using PET (which recently came a step closer to clinical use when the US Food and Drug Administration approved the ligand florbetapir) or CSF amyloid- β ₄₂ levels provide a readout reflecting amyloid deposition in the brain.

Guidelines for the clinical use of biomarkers in the diagnosis of dementia have not yet emerged. The new research criteria proposed for AD¹ provide some suggestions and caveats. In particular, efforts to standardize biomarker measurement and interpretation are still in progress, and these tests do not always provide a quantitative

readout or a definite positive or negative interpretation regarding suspected AD. Insurance coverage for biomarker tests is under negotiation. One of the few currently approved procedures, namely fluorodeoxyglucose PET brain scan to distinguish between AD and frontotemporal dementia, may need to be reappraised once amyloid PET imaging, which may address this question with greater accuracy,¹⁸ is available.

As mentioned above, a brain imaging test, typically MRI, is recommended as part of the dementia workup to rule out a structural (surgical) cause of dementia and estimate the extent of vascular changes. Volumetric measurements of the whole brain, hippocampus, and ventricles can help support the diagnosis of AD. At present these are available primarily through research, although computerized (automated) volumetric programs have been developed. Careful examination of a brain MRI can reveal whether there is focal atrophy affecting brain areas implicated in specific diagnoses.

REFERENCES

1. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's Disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7(3):263–269.
2. Galvin JE, Roe CM, Xiong C, Morris JC. Validity and reliability of the AD8 informant interview in dementia. *Neurology* 2006; 67(11):1942–1948.
3. Brown PJ, Devanand DP, Liu X, et al. Functional impairment in elderly patients with mild cognitive impairment and mild Alzheimer disease. *Arch Gen Psychiatry* 2011;68(6):617–626.
4. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* 2011;134(pt 9):2456–2477.
5. Ferman TJ, Boeve BF, Smith GE, et al. Inclusion of RBD improves the diagnostic classification of dementia with Lewy bodies. *Neurology* 2011;77(9):875–882.

6. Holsinger T, Deveau J, Boustani M, Williams JW Jr. Does this patient have dementia? *JAMA* 2007;297(21):2391–2404.
7. Appels BA, Scherder E. The diagnostic accuracy of dementia-screening instruments with an administration time of 10 to 45 minutes for use in secondary care: a systematic review. *Am J Alzheimers Dis Other Demen* 2010;25(4):301–316.
8. Markwick A, Zamboni G, de Jager CA. Profiles of cognitive subtest impairment on the Montreal Cognitive Assessment (MoCA) in a research cohort with normal Mini-Mental State Examination (MMSE) scores. *J Clin Exp Neuropsychol* 2012;34(7):750–757.
9. Tariq SH, Tumosa N, Chibnall JT, et al. Comparison of the Saint Louis University mental status examination and the mini-mental state examination for detecting dementia and mild neurocognitive disorder—a pilot study. *Am J Geriatr Psychiatry* 2006;14(11):900–910.
10. Salmon DP, Bondi MW. Neuropsychological assessment of dementia. *Annu Rev Psychol* 2009;60:257–282.
11. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. *Neurology* 2011;76(11):1006–1014.
12. Crutch SJ, Lehmann M, Schott JM, et al. Posterior cortical atrophy. *Lancet Neurol* 2012;11(2):170–178.
13. Schofield EC, Hodges JR, Macdonald V, et al. Cortical atrophy differentiates Richardson's syndrome from the parkinsonian form of progressive supranuclear palsy. *Mov Disord* 2011;26(2):256–263.
14. Lee SE, Rabinovici GD, Mayo MC, et al. Clinicopathological correlations in corticobasal degeneration. *Ann Neurol* 2011;70(2):327–340.
15. Geschwind MD, Shu H, Haman A, et al. Rapidly progressive dementia. *Ann Neurol* 2008;64(1):97–108.
16. Knopman DS, DeKosky ST, Cummings JL, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2001;56(9):1143–1153.
17. Vitali P, Maccagnano E, Caverzasi E, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology* 2011;76(20):1711–1719.
18. Rabinovici GD, Rosen HJ, Alkalay A, et al. Amyloid vs FDG-PET in the differential diagnosis of AD and FTL. *Neurology* 2011;77(23):2034–2042.