"Doctor, I'm always misplacing my glasses, my pocketbook, my keys. Is this the beginning of Alzheimer's disease?" Physicians often hear similar questions from elderly patients (ie, those over age 65), because cognitive impairment, particularly decline in recent-memory function, is common in the elderly. This outcome frequently reflects benign changes of an aging nervous system, commonly referred to as "senior moments." However, when changes in cognitive function interfere with daily life, dementia is suspected. The challenge facing the examining physician is distinguishing among the cognitive and behavioral changes expected with normal aging versus those of brain disease (eg, Alzheimer's disease) and treatable conditions (eg, depression).

Evaluation of mental status is especially important in detection of early-stage Alzheimer's disease, because memory symptoms may be ambiguous and not clearly elicited during a clinical interview. Despite recent medical advances, diagnosis of Alzheimer's disease and other neurologic disorders of aging continues to rely on sound clinical methods. Therefore, the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society organized a consensus conference to establish a basic clinical approach to early diagnosis and management of dementia (1). The guidelines established by members of this group can assist physicians in evaluation of elderly patients with memory complaints (2).

**Normal aging versus early Alzheimer's disease**

When the elderly are asked to compare their current memory with that of their younger years, almost all report memory loss. On formal assessment, a much smaller group (10% to 20%) of elderly people have objective evidence of memory problems that suggests brain disease. Results of testing or complaints of memory loss that lead to medical attention are important predictors of progression to Alzheimer's disease (3).

Nonetheless, establishing a diagnosis in patients with recent-memory complaints is challenging because of overlap between symptoms that are benign and those that characterize early Alzheimer's disease. As the article in this symposium by Steffens and Morgenlander (page 72) indicates, interviewing a close friend or family member may provide valuable details. In addition, appropriate laboratory testing may rule out treatable medical causes.

Detailed neuropsychological evaluation also can be informative. Results of a clinical study (4) of patients with isolated memory loss (documented with use of formal neuropsychological evaluation) suggest that about 50% of these patients have progression to identifiable disease over the course of 5 years. In most cases of memory complaints requiring referral to a physician,
cognitive changes of early Alzheimer's disease can be discerned with formal neuropsychological testing (table 1: not shown).

The brain in normal aging

Evaluation of cognitive function in a normally aging person typically reveals some decline in processing and retrieval of new information. This selective impairment leads to specific deficits on tests of word retrieval, memory recall, divided attention, and procedures involving rapid processing or working memory (eg, doing two tasks simultaneously). For example, patients may report that they cannot quickly remember the names of acquaintances or that they become forgetful when their attention is divided. They may feel that learning new information takes more effort than it once did. However, in normal brain aging, structural cueing maneuvers (eg, use of reminders, visual tips) can facilitate recall to normal levels.

As a general rule of thumb, normal aging is characterized by the following findings:

1. A testing profile consistent with the normal aging changes described and summarized in table 1
2. The absence of consistent deviations on testing of recent memory and other functions that suggest a diagnosis of Alzheimer's disease
3. The absence of significant changes in instrumental activities of daily living (eg, ability to work, manage the home, function independently)

The brain in early Alzheimer's disease

Early Alzheimer's disease is characterized by severe, progressive problems in moving newly learned information into long-term memory. Unlike the memory problems in healthy aging people, which may be intermittent or simply annoying, the memory disorder in Alzheimer's disease is relentless and disabling. Even in early disease, memory deficits do not improve substantively with structural cueing.

Cognitive changes other than memory impairment are also typical in Alzheimer's disease. Physicians can use patients' language and communication abilities and some nonverbal aspects to determine the likelihood of neurologic disease. Patients with early Alzheimer's disease have difficulty expressing themselves, often having to search for words or using imprecise terms or long descriptions when a single word would suffice (ie, circumlocution).

Even in early Alzheimer's disease, on formal language evaluation patients demonstrate difficulty naming items and generating words that fit into a category (eg, animals). Elderly patients without brain impairment who have at least a high school education can usually give at least 10 examples of animals in 60 seconds. Providing fewer than 10 may indicate acquired language impairment (ie, aphasia). However, test anxiety could also explain poor performance and should be considered.

Lexical fluency (eg, ability to generate words that start with a certain letter) and aural comprehension tend to be preserved until later in the illness.
Nonverbal deficits, not as readily evident on mental-status testing, also characterize Alzheimer's disease and are probably due to pathological changes occurring in the posterior temporoparietal cortices. Difficulties in constructional praxis and spatial abilities are typical. In early disease, impairments in spatial navigation and locomotion (eg, difficulty finding a location while driving) may be very subtle but may be detectable through careful history taking (5). Perceptual problems, although not common initially, are present later in the disease and can lead to the troubling misidentification of objects or people's faces.

On formal mental-status testing, the ability to copy uncomplicated geometric shapes may be preserved, but impairments can be elicited by requiring mental flexibility and spatial integration when performing the task. A simple way to assess spatial integration is to ask the patient to draw a clock face set at 8:20. Patients with early Alzheimer's disease often have difficulty in conceptualization and may hesitate or misplace the minute hand (6).

Diagnostic accuracy in early Alzheimer's disease may be further enhanced with use of apolipoprotein E genotyping (see article by Steffens and Morgenlander, page 72). The constellation of documented memory loss on neuropsychological testing, a history of cognitive decline, and the presence of an apolipoprotein E epsilon 4 allele on genotyping tends to support clinical suspicion of early Alzheimer's disease. The absence of an epsilon 4 allele does not exclude the diagnosis but does suggest that additional diagnostic evaluation may be warranted (7).

The cognitive effects of depression

Depression is common with aging (a prevalence of 7% to 10% among elderly in the community) and is one of the principal causes of memory impairment in elderly people. Nevertheless, it is often overlooked in clinical practice. Recognizing depression in older patients is important, because it is treatable and the associated memory disorder is potentially reversible.

Late-life depression, when it occurs in isolation, can cause cognitive impairments that are easily mistaken for degenerative dementia. However, it is also common for depression or depressive symptoms to occur along with primary progressive dementia, exacerbating the underlying degenerative condition and complicating diagnosis (8). In addition, depression can be an early manifestation of Alzheimer's disease (9). The most commonly accepted criteria for depression are those in the Diagnostic and Statistical Manual of Mental Disorders (table 2: not shown) (10).

Diagnosing depression in the elderly can be difficult because symptoms may not be spontaneously volunteered and they may be different from those found in younger adults. For example, in the depressed elderly, psychomotor retardation, passive refusal, apathy, and blunting of affect are common, whereas despondency and depressed affect are not necessarily present. Somatic concerns (eg, sleep disturbance, fatigue, decline in sexual function) are less useful because these problems are common among nondepressed elderly.

In differentiating depression from early dementia, the examining clinician cannot rely on memory performance or self-reported mood alone. Clinical evaluation should include thorough questioning of the patient for symptom onset, temporal sequencing of cognitive and depressive
symptoms, the course of the illness, and response to treatment. Patients with major depression are likely to have a relatively normal functioning state punctuated by an abrupt cognitive decline.

Elderly patients with dementia may not be able to accurately report their cognitive symptoms and mood state, whereas patients with depression are often acutely aware of them and may overestimate the extent of impairment. (However, this can also be true of patients with mild dementia.) To ensure a reliable history in situations where dementia is suspected, it may be necessary to query family members.

Reactive depression may occur in the early stages of Alzheimer's disease and can cloud interpretation. Effective antidepressive therapy may lead to some reversal in cognitive symptoms, clarifying the underlying diagnosis and enhancing the patient's general quality of life.

In patients with depression, cognitive impairments are prominent on tests requiring concentration, processing speed, spontaneous elaboration of information, and attention to detail. As a consequence, the abilities to learn new information and to remember recent events are often affected. When structure and organization are provided (eg, a recognition format as opposed to unstructured free recall), learning and memory deficits are less apparent. This finding is in contrast to that in early dementia, in which cueing is largely ineffective in aiding recall.

In general, patients with depression uncomplicated by underlying dementia typically have a neuropsychological profile characterized by the following:

- A tendency toward superficial processing of information
- Impairment on tests requiring mental effort (versus simple tests that are performed automatically)
- Inconsistencies across tests of the same functional domain, presumably because of attentional and effort fluctuations

**In-office mental-status testing**

Several standardized mental-status tests are available to quickly assess the cognitive domains affected by neurologic dysfunction. However, most of these tests are influenced by other variables (eg, age, race, education) and are culturally sensitive. For example, they may underestimate cognitive decline in people who have high premorbid intellectual abilities and may show false-positive results in people who have less than 9 years of formal education or who are over age 85. Correction for cultural bias may be needed in minority groups, particularly if English is not the primary language. Nevertheless, these limitations should not discourage use of cognitive screening tests in diverse groups of people.

**Mini-Mental State Examination (MMSE)**

One of the most commonly used cognitive screening tests is the MMSE (summarized in figure 1: not shown). It assesses orientation, language, attention, concentration, mental flexibility (ie, working memory), short-term memory, and constructional praxis. A score of 24 or more is considered normal. At this cutoff point, the test's reported sensitivity is 87% to 90% and
specificity is 80% to 82% (11). Clinical decision making may be facilitated by attention to the types of items missed on the MMSE rather than to the absolute score. Patients with Alzheimer's disease and early-stage dementia tend to fail memory items (eg, retention over time), and these items are not heavily influenced by age, education, or cultural variables.

Patients with dementia uncomplicated by depression or other medical conditions have, on average, a 2-point decline in their MMSE score on annual reexamination. The level of change is not constant but, rather, is a function of the initial score (12). The rate of change is small when cognitive impairment is slight (MMSE score >24), is more pronounced when impairment is moderate (about 4 points/year with MMSE of 15), and diminishes with more severe impairment (MMSE <10).

People with normal age-associated cognitive disorders tend to show relatively little decline over time on the MMSE or other cognitive-screening tools; in fact, performance may improve owing to learning (ie, test-retest effects).

**Primary Care Evaluation of Mental Disorders (PRIME-MD)**

Short, easy-to-administer tests have been developed to help busy primary care physicians screen for common mental disorders. An example of such a test is the PRIME-MD (13), which evaluates patients for the four mental disorders most commonly encountered in primary care (ie, mood disorder, anxiety, somatoform disorder, and alcohol abuse). Constructed in a yes/no format, the PRIME-MD test takes patients only about 8 to 10 minutes to complete. The physician then follows up on positive responses with further questions provided in a clinical-evaluation guide. However, in assessment of older patients, this test may be somewhat more cumbersome than is desirable.

**Geriatric Depression Scale (GDS)**

One option is to screen specifically for depression because of its particular relevance in diagnosis of memory loss in the elderly. Use of patient-completed forms is a practical approach. The GDS (table 3) was developed to address the specific geriatric issues that can complicate diagnosis (14). It is easily completed, even by patients with mild to moderate dementia, and because of its yes/no format, it can be read to patients with impaired vision. A score of more than 5 indicates probable depression. The physician should query further and may elect to begin treatment or, particularly if the clinical picture is complex, refer the patient for additional evaluation.

Table 3: Geriatric Depression Scale (short form)

1. Are you basically satisfied with your life?

2. Have you dropped many of your activities and interests?

3. Do you feel that your life is empty?

4. Do you often get bored?
5. Are you in good spirits most of the time?

6. Are you afraid that something bad is going to happen to you?

7. Do you feel happy most of the time?

8. Do you often feel helpless?

9. Do you prefer to stay at home rather than going out and doing new things?

10. Do you feel you have more problems with memory than most people?

11. Do you think it is wonderful to be alive now?

12. Do you feel pretty worthless the way you are now?

13. Do you feel full of energy?

14. Do you feel that your situation is helpless?

15. Do you think that most people are better off than you are?

*Each starred answer counts 1 point. Scores of more than 5 points indicate probable depression.

Neuropsychological evaluation can be particularly helpful in patients with suspected dementia when memory impairment is a primary concern and depression confounds the picture. In addition, it provides a baseline for objectively tracking changes over time.

Referral for neuropsychological evaluation

Neuropsychological testing is systematic and detailed evaluation of a broad range of cognitive processes affected by neural disease. It is more sensitive and more specific than simple mental-status examination in reliably detecting early-stage dementia and distinguishing it from the effects of normal aging and other conditions. Factors that may influence mental-status testing in the office can be dealt with effectively in most neuropsychological evaluation procedures.

A useful rule of thumb in deciding whether neuropsychological evaluation is indicated (figure 2: not shown) is to disregard patient age and focus on memory complaints that are difficult to objectively verify on office mental-status evaluation or are confounded by depression or some other factor. A variety of disorders in the elderly fall into this category, including early brain disease and other neurologic disorders (eg, Parkinson's disease, stroke), and ambiguous presentations of normal aging resulting from stress, bereavement, medical problems (eg, hypothyroidism), or psychiatric conditions (eg, depression, anxiety disorders).

In-depth neuropsychological evaluation is particularly important when memory complaints occur in patients with a family history of dementia. These patients may be sensitized to the changes of
Alzheimer’s disease and present to their physician with seemingly benign complaints. Sometimes, the complaints are due to anxiety (so-called anticipatory dementia). Thorough neuropsychological evaluation reassures the concerned patient and establishes a baseline for follow-up. In other instances, neuropsychological evaluation may confirm the presence of early neurologic disorder. In these cases, it is helpful in establishing the correct diagnosis and in developing a plan for additional laboratory investigation, specialist referral, management, and family involvement.

Neuropsychological evaluation is important for providing management input and therapeutic alternatives in early disease. The psychological impact of a diagnosis of dementia can be emotionally devastating, and in some instances, psychological intervention may be necessary. Neuropsychologists can provide guidance to the physician regarding the patient's emotional adjustment and can suggest psychological treatment approaches and impairment-compensation strategies that may be useful in a given patient.

The technique of neuropsychological evaluation

Typically, the neuropsychologist begins by meeting the patient and family members, noting the reasons for referral, and observing the patient's level of awareness and limitations to testing. He or she outlines the testing procedures and what might be expected and, often (with the patient's consent), interviews a family member for verification of symptoms and clinical history.

Testing follows a standard systematic, objective procedure but is designed to optimize rapport and ensure maximum performance by providing a friendly environment and streamlining the session to meet the patient's special needs. Tests used can vary between neuropsychological practices, but in general, the following functions are assessed: (1) attention and concentration, (2) orientation to time, person, place, and situation and general insight, (3) intellect, (4) learning and memory, (5) language, (6) visuo-spatial function, (7) complex abstraction, creativity, multitasking, and behavioral flexibility (so-called executive functions), (8) bilateral sensorimotor function, and (9) mood and personality (15).

In a patient under age 60 with mild memory complaints, evaluation may take most of a day to reliably determine the extent of possible deficits. However, in most cases, especially in older patients, evaluation takes about 3 or 4 hours, sometimes even less depending on the referral issues.

Results of the battery of tests are interpreted taking into account important demographic factors that may modify performance and using clinical inferences established on the basis of understanding of neurobehavioral syndromes and brain-behavior relationships. Usually, the neuropsychologist meets with patients and families at the end of the testing session to clarify what has transpired and explain when to expect testing results and how to contact the office. Results and recommendations are provided directly to the referring physician for incorporation into the medical record.

Summary and conclusion
Improved understanding of neurobehavior in normal aging, Alzheimer's disease, and late-life depression makes early detection of neurodegenerative conditions possible. Primary care physicians can screen patients' mental status and mood states with simple in-office tests. When screening results or the clinical picture is ambiguous or complex, neuropsychological evaluation is useful in making an early, reliable differentiation between dementia and normal aging.

Early identification of neurologic problems provides an opportunity to enhance quality of life and long-term care. Medical interventions, such as a trial of donepezil hydrochloride (Aricept) or other memory-enhancing medications as they become available, can be started when results are likely to be optimal. Common coexisting problems (eg, depression, falls) can be sought and managed. Additional important medical decisions (eg, elective surgeries) may be considered differently when dementia is diagnosed early.

References:


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