ONE MINUTE CONSULT

BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: What tests are necessary to diagnose Alzheimer disease?

RICHARD J. LEDERMAN, MD, PhD
Department of Neurology, Cleveland Clinic

A: THE MOST COMMONLY USED CRITERIA are those of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, published in 1984.[1] According to these criteria, a diagnosis of "probable" Alzheimer disease requires:

- Dementia, established by clinical examination and documented by the Mini-Mental State Examination[2] (MMSE) or a similar test, and confirmed by neuropsychological tests (under ordinary clinical circumstances the findings on the MMSE may be sufficient[3]—these criteria were devised for research purposes)
- Deficits in two more areas of cognition
- Progressive worsening of memory and other cognitive functions
- No disturbance of consciousness
- Onset between ages 40 and 90, most often after age 65
- No systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition.

Using these criteria, the accuracy of the clinical diagnosis in the best of hands, as determined by subsequent pathological confirmation, approaches 90%.[4]

The definitive diagnosis of Alzheimer disease depends on finding typical senile (amyloid) plaques and neurofibrillary tangles on microscopic examination of brain tissue. Rarely is this done by performing a biopsy in a living patient; the tissue is usually obtained at autopsy.

COGNITIVE SCREENING REQUIRED

The first step is to determine that the patient indeed has dementia and not an alternative form of apparent cognitive impairment such as delirium or the "pseudodementia" of depression.

Dementia, as defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition,[5] is a sustained decline in cognitive function, including impairment of memory and at least one other cognitive domain such as language function, praxis, perception, or executive function, of sufficient degree to affect a person's occupational or social functioning.

Therefore, the clinical diagnosis requires a thorough history from the patient, generally supplemented by information from family, friends, or colleagues in the work place. In addition, a complete general and neurologic examination is required, including some form of cognitive screening, most often the **MMSE** (TABLE 1).[2] Many other screening tests have been devised, but the MMSE remains the most frequently used and in many ways the most helpful, even though the score on the MMSE can vary with level of education and background, especially in those for whom English is a second language.[6]

I have found the **Clinical Dementia Rating** of great help as well, particularly for follow-up, since it incorporates information from the family or others (TABLE 2).[7]

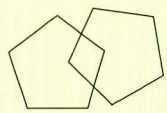
Comprehensive neuropsychologic testing is often but not always necessary to extend or confirm the findings on cognitive screening, particularly in patients with:

- Apparently mild cognitive impairment
- A previous intellectual level that was unusually high
- Atypical findings (eg, relative deficiencies in language but preserved memory, parkinsonian features, focal signs, early age at onset, or unusual temporal course)
- Possible depression as a cause of dementia.

For most patients with dementia, a clinical diagnosis is adequate

TABLE 1

Mini-Mental State Examination

QUESTIONS		MAXIMUM SCORE	PATIENT'S SCORE
Orientation			
1. Ask the patient what is the:	Year?	1	( )
	Season?	1	( )
	Date?	1	( )
	Day?	1	( )
	Month?	1	( )
2. Where are we?	State?	1	( )
	County?	1	( )
	Town or city?	1	( )
	Hospital?	1	( )
	Floor?	1	( )
Registration			
3. Ask the patient to listen while you name three objects, taking 1 second to say each. Then ask the patient to repeat all three after you have said them.		3	( )
Attention and calculation			
4. Ask the patient to count backward from 100 by sevens. Give one point for each correct answer. Stop after five answers. Alternate: spell "world" backwards.		5	( )
Recall			
5. Ask the patient to recall the three objects named in question 3. Give one point for each correct answer.		3	( )
Language			
6. Point to a pencil and a watch. Have the patient name them as you point.		2	( )
7. Have the patient repeat the following: "no ifs, ands, or buts."		1	( )
8. Have the patient follow a three-stage command: "Take a paper in your right hand. Fold the paper in half. Put the paper on the floor."		3	( )
9. Have the patient read and obey the following: "Close your eyes." (Write it in large letters.)		1	( )
10. Have the patient write a sentence of his or her choice. (The sentence should contain a subject and a verb and should make sense. Ignore spelling errors when scoring.)		1	( )
11. Have the patient copy the design shown here. (Give one point if all sides and angles are preserved and if the intersecting sides form a quadrangle.)		1	( )
	Total	30*	

*A score of 23 or less indicates dementia

SOURCE: FROM FOLSTEIN ET AL, REFERENCE 2

LABORATORY STUDIES: REQUIRED VS OPTIONAL

A relatively few laboratory studies are recommended in the evaluation of dementia[3,8]:

- A complete blood count
- A limited (at least) chemical survey
- A thyroid function screen
- A vitamin B_{12} level (serum folate is often obtained in conjunction with the B_{12} level, but it is of unclear usefulness)
- A serologic test for syphilis.

An abnormality of any or all of these does not preclude a diagnosis of Alzheimer disease but does indicate a need for further investigation and probable treatment.

OTHER STUDIES

In this country, most experts would also recommend some form of brain imaging; **a computed tomographic scan** of the head, without contrast, is usually sufficient. If cerebrovascular disease or vascular risk factors are present, **magnetic resonance imaging** of the brain is often preferred. Where access to neuroimaging is more limited, these studies are often considered optional.

A number of other studies are sometimes desirable, if not necessary, including HIV screening, urinalysis, chest x-ray, cerebrospinal fluid examination, electroencephalography, and special imaging procedures such as single-photon emission computed tomography or positron emission tomography. Some of these can be critical in certain cases, eg, a cerebrospinal fluid examination for 14-3-3 protein and an electroencephalogram in cases of suspected Creutzfeldt-Jakob disease, but in general these are carried out in conjunction with neurologic consultation.

CONTROVERSIAL RISK FACTORS AND BIOMARKERS

Apolipoprotein E genetic screening has been suggested to increase the accuracy of the clinical diagnosis of Alzheimer disease.[9] The presence of one or two epsilon-4 alleles (as opposed to epsilon-2 or epsilon-3 alleles) does increase the likelihood of Alzheimer disease,

TABLE 2

Clinical Dementia Rating

AREA	SCORE*	DESCRIPTION
Memory	0	No memory loss or slight inconstant forgetfulness
	0.5	Mild consistent forgetfulness; partial recollection of events; "benign" forgetfulness
	1	Moderate memory loss, more marked for recent events; defect interferes with everyday activities
	2	Severe memory loss; only highly learned material retained; new material rapidly lost
	3	Severe memory loss; only fragments remain
Orientation	0	Fully oriented
	0.5	Fully oriented
	1	Some difficulty with time relationships; oriented for place and person at examination but may have geographic disorientation
	2	Usually disoriented in time, often to place
	3	Oriented to person only
Judgment and problem-solving	0	Solves everyday problems well; judgment good in relation to past performance
	0.5	Only doubtful impairment in solving problems, similarities, differences
	1	Moderate difficulty in handling complex problems; social judgment usually maintained
	2	Severely impaired in handling problems, similarities, differences; social judgment usually impaired
	3	Unable to make judgments or solve problems
Community affairs	0.5	Independent function at usual level in job, shopping, business, and financial affairs, volunteer and social groups
	0.5	Only doubtful or mild impairment, if any, in these activities
	1	Unable to function independently at these activities, though may still be engaged in some; may still appear normal to casual inspection
	2	No pretense of independent function outside home
	3	No pretense of independent function outside home
Home and hobbies	0	Life at home, hobbies, intellectual interests well maintained
	0.5	Life at home, hobbies, intellectual interests well maintained or only slightly impaired
	1	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned
	2	Only simple chores preserved; very restricted interests, poorly sustained
	3	No significant function in home outside of own room
Personal care	0	Fully capable of self care
	0.5	Fully capable of self care
	1	Needs occasional prompting
	2	Requires assistance in dressing, hygiene, keeping of personal effects
	3	Requires much help with personal care; often incontinent

*Scores are assigned using information from family or caregiver and patient.
To determine the overall Clinical Dementia Rating, Memory is the primary area, and the others are secondary.
If at least three secondary areas are given the same score as Memory, the overall Clinical Dementia Rating is the same as for Memory.
If three or more secondary areas are given a score greater or less than the Memory score, then the Clinical Dementia Rating is the score of the majority of secondary areas, unless three secondary areas are scored on one side of Memory and two secondary categories are scored on the other side of Memory, in which case the score equals that of Memory.
Overall Clinical Dementia Rating: 0 healthy, 0.5 questionable dementia, 1 mild dementia, 2 moderate dementia, 3 severe dementia.

FROM HUGHES CP, BERGH L, DANZIGER WL, ET AL. A NEW CLINICAL SCALE FOR THE STAGING OF DEMENTIA. BR J PSYCHIATRY 1982; 140:566–572.

but the importance of this finding remains controversial.

The usefulness of **spinal fluid markers** for Alzheimer disease, including A-beta-42 and tau protein, is also uncertain.[10] A-beta-42 is the major peptide component of the amyloid precursor protein found in the neuritic plaque: tau, a microtubular-associated protein, is the

major component of neurofibrillary tangles. The combination of elevated tau and low A-beta-42 in cerebrospinal fluid is highly suggestive of Alzheimer disease and has relatively high specificity and sensitivity. I have used this only occasionally, usually when being pressed for a more certain diagnosis.

FOR NOW, CLINICAL DIAGNOSIS IS ADEQUATE

As specific therapy becomes available for different forms of dementia, the urgency of making a firm diagnosis of Alzheimer disease vs other causes will increase. At present, the guidelines outlined above are satisfactory for a large majority of patients with a clinical syndrome of dementia.

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ADDRESS: *Richard J. Lederman, MD, PhD, Department of Neurology, S91, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, e-mail ledermr@ccf.org.*