Clinical diagnosis of Alzheimer’s disease: Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer’s Disease

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Alzheimer’s disease is a brain disorder characterized by a progressive dementia that occurs in middle or late life. The pathologic characteristics are degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles. Alterations in transmitter-specific markers include forebrain cholinergic systems, and, in some cases, noradrenergic and somatostatinergic systems that innervate the telencephalon.

A Work Group on the Diagnosis of Alzheimer’s Disease was established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA). The group intended to establish and to describe clinical criteria for the diagnosis of Alzheimer’s disease of particular importance for research protocols and to describe approaches that would be useful for assessing the natural history of the disease. The need to refine clinical diagnostic criteria has been emphasized because 20% or more of cases with the clinical diagnosis of Alzheimer’s disease are found at autopsy to have other conditions and not Alzheimer’s disease. Moreover, therapeutic trials can be meaningfully compared only if uniform criteria are used for diagnosis and response to treatment.

The need for this report was suggested by the National Advisory Council of the NINCDS. The report has been reviewed by workshop participants, representatives of the National Advisory Neurological and Communicative Disorders and Stroke Council, representatives of the ADRDA, and designated reviewers representing professional societies concerned with the diagnosis of Alzheimer’s disease. (For list of professional societies and designated reviewers, see page 943.)

The report was developed by subgroups that addressed medical history, clinical examination, neuropsychological testing, and laboratory assessments; the report was then discussed in plenary session. Based on a consensus of the participants, criteria were developed to serve as a clinical basis for diagnosis. These criteria should be useful also for comparative studies of patients in different kinds of investigations, including case control studies, therapeutic trials, evaluation of new diagnostic laboratory tests, and clinicopathologic correlations.

The criteria are not yet fully operational because of insufficient knowledge about the disease. The criteria are compatible with definitions in the current Diagnostic and Statistical Manual of Mental Disorders (DSM III) and in the International Classification of Diseases. These criteria must be regarded as tentative and subject to change. Additional longitudinal studies, confirmed by autopsy, are necessary to establish the validity of these criteria in com-

*For Work Group Participants and Affiliations, see page 943.

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Table 1. Criteria for clinical diagnosis of Alzheimer’s disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer’s disease include:

- dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or 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; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer’s disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (anosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques,
  - normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
  - evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer’s disease, after exclusion of causes of dementia other than Alzheimer’s disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss; other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer’s disease uncertain or unlikely include:

- sudden, apoplectic onset;
- focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer’s disease:

- may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer’s disease are:

- the clinical criteria for probable Alzheimer’s disease and histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer’s disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- familial occurrence;
- onset before age of 65;
- presence of trisomy 21; and
- coexistence of other relevant conditions such as Parkinson’s disease.

Criteria for dementia syndrome. Dementia is the decline of memory and other cognitive functions in comparison with the patient’s previous level of function as determined by a history of decline in performance and by abnormalities noted from clinical examination and neuropsychological tests. A diagnosis of dementia cannot be made when consciousness is impaired by delirium, drowsiness, stupor, or coma or when other clinical abnormalities prevent adequate evaluation of mental status. Dementia is a diagnosis based on behavior and cannot be determined by computerized tomography, electroencephalography, or other laboratory instruments, although specific causes of dementia may be identified by these means.

Criteria for Alzheimer’s disease. Alzheimer’s disease is a progressive, dementing disorder, usually of middle or late life. The clinical criteria for the diagnosis of PROBABLE, POSSIBLE, and DEFINITE Alzheimer’s disease are outlined in table 1. A clinical diagnosis of probable Alzheimer’s disease can be made with confidence if there is a typical insidious onset of dementia with progression and if there are no other systemic or brain diseases that could account for the progressive memory and other cognitive deficits. Among the disorders that must be excluded are manic-depressive disorder, Parkinson’s
disease, multi-infarct dementia, and drug intoxication; less commonly encountered disorders that may cause dementia include thyroid disease, pernicious anemia, lupus brain disease and other chronic infections of the nervous system, subdural hematoma, occult hydrocephalus, Huntington's disease, Creutzfeldt-Jakob disease, and brain tumors.

A diagnosis of definite Alzheimer's disease requires histopathologic confirmation. A clinical diagnosis of possible Alzheimer's disease may be made in the presence of other significant diseases, particularly if, on clinical judgment, Alzheimer's disease is considered the more likely cause of the progressive dementia. The clinical diagnosis of possible rather than probable Alzheimer's disease may be used if the presentation or course is somewhat aberrant. The information needed to apply these criteria is obtained by standard methods of examination: the medical history; neurologic, psychiatric, and clinical examinations; neuropsychological tests; and laboratory studies.

Medical history. A medical history should be taken from the patient and from an informant who is well acquainted with the affected individual. This approach is essential to establish a history of progressive deterioration and for identifying tasks that the patient can no longer perform adequately. A diary maintained by an observer may be very helpful in documenting changes in various functions. The history discloses abnormalities including impaired memory and other cognitive functions, impaired activities of daily living, alterations in mood, often delusions and illusions, and sometimes hallucinations. Common complaints of patients or families include forgetfulness about appointments or errands; inability to find the way to an accustomed destination; inability to use money and instruments of daily living such as a telephone; deterioration in work or homemaking performance; difficulty adapting to changes in the workplace; difficulties in dressing, reading, and writing; and inability to recognize previously familiar individuals.

Clinical examination. The clinical examination provides data to fulfill inclusionary and exclusionary criteria for the diagnosis of Alzheimer's disease and to document symptoms such as delusions or depression that identify subgroups of patients important both for research studies and for patient care. Mental status testing, an essential component of the clinical examination, includes specific assessment of orientation, registration, attention, calculation, recent recall, naming, repeating, understanding, reading, writing, and ability to draw or copy. Because cognitive impairment may occur in depressive syndromes, it is important to inquire about affective state and depressive symptoms, such as disturbed sleep and weight loss, before diagnosing Alzheimer's disease. Inquiry specifically about the presence of delusions and hallucinations is needed to identify subgroups. Both symptoms may be experienced in a variety of neuropsychiatric disorders, which may or may not have known organic substrates.

Quantitative aids to the clinical examination include the Mini-Mental State Examination for cognitive screening; the Blessed Dementia Scale for clinical symptoms and social function; the Hamilton Depression Scale for severity of depression; the Present State Examination for anxiety, depression, delusions, and hallucinations; and the Hachinski Scale for estimating the likelihood of multi-infarct dementia. A complete psychiatric evaluation is needed to exclude the various psychiatric disorders.

Complete examination of sensory and motor systems (including cranial nerves, tone, reflexes, coordination, gait, and proprioception) is needed to exclude other neurologic disorders. In early stages, patients are alert and free of other neurologic changes related to the dementia except for the occasional presence of snout reflex, jaw jerk, rigidity, or myoclonus, all of which may be encountered in nondemented elderly people. As the disease progresses, some patients become apathetic or show irritability, agitation, paranoid ideas, sleep disorders, or incontinence. In the very advanced stages, patients may become mute and lose all ability to communicate.

Neuropsychological testing. Neuropsychological tests may provide additional information for the diagnosis of dementia. Because there are no normative population standards for many of these tests, abnormal performance can be determined only by comparison with a normal control group matched for age, sex, and local education. A score falling in the lowest fifth percentile of an individual's normal control group may be designated as "abnormal." One or more abnormal scores will identify an individual for research purposes who is highly likely to be cognitively impaired. Progressive worsening can be established by comparison with the patient's previous performance on these tests. Although there is continued debate about the tests that best measure these functions, the Work Group did make some suggestions (table 2).

Similar series of tests can be used to assess less severely affected patients by increasing the complexity of the neuropsychological tests. Further modification in the test procedure may be needed to detect impairment in highly intelligent patients. Confirmation of the dementia syndrome by neuropsychological tests should be based on measurable abnormalities in two or more aspects of cognition.

In longitudinal assessment, many patients with Alzheimer's disease show progressive loss of recent memory followed by disorders of language, praxis, or visual perception. In some patients with Alzheimer's disease, however, the first symptoms are difficulty in finding words, impaired visual perception, or apraxia, with memory impairment and other symptoms and signs appearing later.

Although neuropsychological tests are presently used primarily to provide confirmatory evidence for
Table 2. Neuropsychological evaluation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-Mental State Examination</td>
<td>A brief, standardized assessment of cognitive function</td>
</tr>
<tr>
<td>Recognition Span Test, Brown-Peterson Distractor Test</td>
<td>Tests of verbal and nonverbal memory</td>
</tr>
<tr>
<td>Gollin Incomplete-Pictures Test</td>
<td>Measures visual perception</td>
</tr>
<tr>
<td>Gomberg Incomplete-Pictures Test</td>
<td>Similar to Gollin test</td>
</tr>
<tr>
<td>Visual Form Discrimination Test</td>
<td>Another test of visual perception</td>
</tr>
<tr>
<td>Visual Retention Test</td>
<td>Measures visual memory</td>
</tr>
<tr>
<td>Boston Diagnostic Aphasia Examination</td>
<td>Tests for difficulty in communication and language</td>
</tr>
<tr>
<td>Western Aphasia Test</td>
<td>Additional aphasia test</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>Evaluates word recognition</td>
</tr>
<tr>
<td>Token Test I</td>
<td>Measures language fluency</td>
</tr>
<tr>
<td>Adult Intelligence Scale</td>
<td>Another test of language fluency</td>
</tr>
<tr>
<td>Hooper Test</td>
<td>Tests for motor function</td>
</tr>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td>Measures problem-solving skills</td>
</tr>
<tr>
<td>Poisoned Food Problem Task</td>
<td>Similar to Wisconsin Card Sorting Test</td>
</tr>
<tr>
<td>Reporters Test</td>
<td>Tests for word fluency</td>
</tr>
<tr>
<td>Test for Written Expression</td>
<td>Measures ability to copy a written drawing</td>
</tr>
<tr>
<td>Free-recall test</td>
<td>Measures memory recall</td>
</tr>
<tr>
<td>Continuous-Performance Test</td>
<td>Measures speed of cognition</td>
</tr>
</tbody>
</table>

The major cognitive processes that are impaired in Alzheimer's disease, with examples of the kinds of tests used to assess these functions, include:

- Orientation to place and time, graded by a test such as the Mini-Mental State Examination.
- Memory evaluated by tests such as a free-recall test of concrete nouns, a 3-4 paired-associate learning test (verbal and nonverbal) by use of a recognition paradigm, the Recognition Span Test, and the Brown-Peterson Distractor Test (stopping the task when the patient fails or begins to produce the distractor instead of the stimulus trigrams).
- Language skills tested by examination of verbal fluency of the semantic or category type, with the examiner writing responses, and by other tests such as the Boston Naming Test (preferably one of the abbreviated forms), the Boston Diagnostic Aphasia Examination, the Western Aphasia Test, and the Token Test with Reporters Test.
- Praxis evaluated by tests such as those in which the patient copies a drawing (cube, daisy, clock, or house) or performs the block design subtest of the Wechsler Adult Intelligence Scale.
- Attention monitored by tests such as a reaction-time task or by the Continuous-Performance Test.
- Visual perception studied by use of a variety of tasks, such as the Gollin Incomplete-Pictures Test and the Hooper Test.
- Problem-solving skills determined by tests such as the Wisconsin Card Sorting Test or The Poisoned Food Problem Task of Arenberg and the Token Test.
- Social function, activities of daily living, and instrumental activity of daily living, assessed by methods similar to those described in the Philadelphia Geriatrics Center Forms.

The EEG of some patients with Alzheimer's disease shows increased slow-wave activity that may become more pronounced with progression of the disease. Evoked potentials (EP) are brain waves associated with sensory or other events that may be auditory, somatosensory, or visual. Endogenous or cognitive potentials, such as P300, are thought to reflect speed of cognition. The latency of P300 is altered with age, and there appears to be an increased latency of P300 potentials in 50 to 80% of patients with Alzheimer's disease compared with age-matched control subjects. These changes occur in different dementias and are not specific to Alzheimer's disease. The P300 wave, however, is normal in depressive syndromes and may therefore be useful in differentiating the dementia of Alzheimer's disease from the dementia of depressive syndromes, particularly when adequate normal data become available.

Computerized tomography. CT is useful in the diagnosis of Alzheimer's disease because it permits the exclusion of other disorders such as subdural hematoma, brain tumor, hydrocephalus, and dementia associated with vascular disease. The technique can delineate gyri and sulci and quantitate tissue densities, ventricular size, CSF volume, and brain mass. In Alzheimer's disease, the volume of the ventricular system and the width of the third ventricle are increased, gyri are narrowed, and sulci are widened; however, these general patterns may not be particularly useful as diagnostic criteria in individual cases. Furthermore, available data do not indicate how well a qualitative observation correlates with the magnitude of cognitive abnormality or with evidence of progression of disease. There is a pressing need for quantitative CT studies of Alzheimer's disease patients during the course of disease and for correlation of CT images with clinical signs, neuropsychological test results, and autopsy findings.

Regional cerebral blood flow. Measurement of regional cerebral blood flow (rCBF), including 133Xe xenon clearance, may help differentiate Alzheimer's disease and dementia associated with cerebrovascular disease. In multi-infarct dementia (MID), early changes include decreased autoregulation; in the later stages of MID, rCBF and oxygen consumption are decreased. In patients who have Alzheimer's disease, rCBF and cerebral metabolic rate are decreased; but A-V differences, carbon dioxide responses, and autoregulation are preserved.

Positron emission tomography. Positron emission tomography (PET) is a research technique that allows quantitative assessment of the rate of glucose utilization, oxygen consumption, and rCBF. With some isotopes, these characteristics can be assessed during neuropsychological testing; moreover, 18F-markers may permit the use of retest paradigms. Early reports suggest that rCBF determined by PET may be reduced in areas of encephalomalacia. In contrast, most patients with Alzheimer's disease show cerebral hypometabolism when compared with
age-matched controls. These changes correlate with disease severity and may be correlated with neuropsychological test performance. For example, speech impairment may be correlated with decreased activity in the left hemisphere, whereas impaired performance on spatial tasks may be more closely correlated with impaired activity in the right hemisphere. Different approaches may be necessary for delineating presynaptic and postsynaptic markers of transmitter systems, as recently achieved with PET images of the dopamine system. Since PET reveals a significant variation even among normal subjects, any changes may have to be severe to be detected. The value of PET studies in determining the stage of disease, in documenting progression, and in assessing the effects of treatment is unknown.

Magnetic resonance imaging. The proton nuclear magnetic resonance (NMR) image, or magnetic resonance imaging (MRI), reveals the demarcation of gray and white matter of the brain and has therefore proved useful in studies of demyelinating disorders. Although the method has not been applied systematically to the study of dementia, it has potential for differentiating between Alzheimer's disease, multi-infarct dementia, and low-pressure hydrocephalus. Information should soon be available about the usefulness of MRI in the diagnosis of Alzheimer's disease.

Examination of body fluids and nonneural tissues. In the diagnosis of Alzheimer's disease, studies of blood and CSF are helpful in excluding chronic infections, such as cryptococcal meningitis and syphilis, and other disorders. To date, definitive diagnostic information about Alzheimer's disease from blood or CSF has not been sought consistently, but CSF should be studied to demonstrate neurotransmitters, metabolites, and synthesizing and degradative enzymes. Other techniques, such as sophisticated radioimmunoassays with specific antibodies, may be useful for detecting markers of the disease, such as constituents associated with the development of neurofibrillary tangles and neuritic plaques. Specific abnormalities have not been detected in nonneural tissues.

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