Diagnostic Criteria for Primary Neuronal Degeneration of the Alzheimer's Type

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The diagnosis of patients presenting with memory or attentional deficits characteristic of dementia is a growing problem. Dementia may be symptomatic of a range of reversible medical and psychiatric conditions which appear to be indistinguishable from primary neuronal degeneration of the Alzheimer's type. While Alzheimer's disease is a neuropathological diagnosis, the importance of establishing a presumptive diagnosis which can be employed for investigational as well as clinical use is underscored. This paper proposes a diagnostic schema which reflects the current understanding of this disorder. There must be evidence of gradual progressive mental deterioration in attention, learning, memory, cognitive style, motivation, and higher order thinking. A comprehensive medical and psychiatric evaluation is obligatory to eliminate reversible physical illness, psychiatric disorder, or cerebrovascular condition as underlying causes of cognitive dysfunction.

Present estimates are that 10 to 20 percent of the population aged over 65 years have significant cognitive impairment,[1] and as the relative and absolute size of the middle-aged and aged population increases, the cognitively impaired aged will represent a substantial segment of the population. The dementing illnesses are characterized by a progressive decline in intellectual functioning from a previously higher level, and when irreversible, typically culminate in a profound loss of adaptive capacity and self-care. In the United States, the term "dementia" is used in clinical practice to describe those states that result from diseases (both known and unknown) of the cerebral hemispheres. In fact, since dementia per se is a symptom cluster, it implies only a limited knowledge about the etiology of the observed cognitive change. Among the aged, the most common form of irreversible dementing illness, involving perhaps 50 to 70 percent of all older persons with dementia, is primary neuronal degeneration of the Alzheimer's type.[2] The etiology is unknown and the specificity of the disease is in dispute because the rate of degeneration is variable and different patterns emerge in different patients, suggesting alternative causality.[3-5] It is, however, reported to be the fourth major killer of persons aged 65 years or over.[6]

Multi-infarct or vascular dementias probably account for 15 to 25 percent of the dementias.[7] Other irreversible dementias include "mixed" dementias resulting from a combination of vascular injury and primary neuronal damage, parkinsonism, Creutzfeld-Jakob disease, Huntington's chorea, Pick's disease, multiple sclerosis, and other disorders. It is also important to emphasize that a significant number of patients presenting symptoms of dementia (15 to 35 percent) have a pseudodementia; ie, a condition where somatic and psychiatric conditions, many of which are reversible, are causing the cognitive dysfunction.[8-10] The aged, as well as younger age groups, may also

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Table 1. University of Washington Research Diagnostic Criteria for Primary Neuronal Degeneration of the Alzheimer's Type

Clinical Features for Inclusion

A deterioration of general cognitive functions from a previously higher performance level compromising the ability to adapt to the environment, including:

	Yes	No
A. Onset		
1. Gradual progression	___	___
2. Duration of at least 6 months	___	___

B. Impairment of at least *two* of the following abilities (on the basis of performance on the Mini-Mental Status, the Wechsler Adult Intelligence Scale).

	Absent	Mild	Moderate	Severe
1. Learning	___	___	___	___
2. Attention	___	___	___	___
3. Memory	___	___	___	___
4. Orientation	___	___	___	___

C. Impairment on at least one of the following cognitive skills (on the basis of performance on the WAIS and Mini-Mental Status).

	Absent	Mild	Moderate	Severe
1. Calculation	___	___	___	___
2. Abstraction and judgment	___	___	___	___
3. Comprehension	___	___	___	___

D. Problems in at least one of the following areas (on the basis of the psychosocial examination.

	Absent	Mild	Moderate	Severe
1. Ability to work	___	___	___	___
2. Ability to relate to family	___	___	___	___
3. Ability to relate to peers	___	___	___	___
4. Ability to function socially	___	___	___	___

E. Indication of cerebral dysfunction on at least one of the following:

	Yes	No
1. Cerebral atrophy on CT scan		
2. Abnormal EEG (see also exclusion criteria)	___	___

F. Ischemic Score ≤ 4 (modified from Hachinski, 1978)

Feature	Possible Score	Real Score
1. Abrupt onset	2	___
2. Stepwise deterioration	1	___
3. Fluctuating course	2	___
4. Nocturnal confusion	1	___
5. Emotional lability	1	___
6. History of hypertension	1	___
7. History of strokes	2	___
8. Evidence of associated atherosclerosis	1	___
9. Focal neurologic symptoms	2	___
10. Focal neurologic signs	2	___

suffer from a range of other central nervous system disorders caused by trauma, neoplasms, alcohol and drug effects, infection, and endocrine disorders as well as inborn errors of metabolism.

Diagnosis

Although the clinical diagnosis of primary neuronal degeneration of the Alzheimer's type is nec-

Table 1. University of Washington Research Diagnostic Criteria for Primary Neuronal Degeneration of the Alzheimer's Type (Continued)

Medical Exclusion Criteria	Yes	No
A. Focal neurologic signs (including EEG foci)	___	___
B. Medical history of:		
1. Myocardial infarction or chronic cardiovascular disease	___	___
2. Cardiovascular accident	___	___
3. Alcoholism or substance abuse	___	___
4. Chronic psychiatric illness	___	___
5. Syphilis	___	___
6. Brain damage sustained earlier from a known cause, eg, hypoxia	___	___
7. Chronic renal, hepatic, pulmonary, or endocrine disease	___	___
8. Parkinson's disease, Huntington's chorea, Pick's disease, or related neurologic disorders selectively affecting specific brain regions	___	___
9. Multi-infarct dementia	___	___
10. Hypertensive cardiovascular disease	___	___
C. Pseudodementias		
1. Primary manic disorder	___	___
2. Primary depressive disorder	___	___
3. Physical disorders, metabolic intoxicity, drug interaction	___	___

essarily presumptive (since a confirmatory diagnosis must be derived from neuroanatomical features observable only on postmortem examination), it is important to maximize the accuracy of the evaluation. Even a presumptive diagnosis of Alzheimer's disease may have profound consequences for patient care. The increasing interest in the disease also requires that there exist a generally acceptable set of criteria defining the clinical state.

Several investigators[11-13] have discussed the need for a comprehensive approach to the differential diagnosis of the cognitively impaired aged. Diagnostic criteria for primary neuronal degeneration of the Alzheimer's type must be stated with a precision at least reflecting the status of the current clinical data base. Table 1 presents the authors' proposed Research and Clinical Diagnostic Criteria for assessing clinical features of the disease. The criteria reflect the current state of the literature as well as the concensus of more than 20 psychiatrists, neurologists, and internists, all of whom are actively engaged in investigational studies of patients with dementia, and all of whom were unanimous in accepting the criteria as presented here.

The examination of the patient should include a careful medical history and physical examination, including a drug inventory and evaluation of the sensorium; a neurologic evaluation; a comprehensive cognitive assessment, including an examination for aphasia; a psychiatric interview, including a mental status examination and psychosocial assessment of the patient's environment; and laboratory tests, including clinical chemistries, hematology, urinalysis, serology, chest x-ray films, and a computerized tomography (CT) scan. On this basis, it is possible to make a presumptive diagnosis of dementing illness secondary to biochemical or structural changes in the brain. While this is a comprehensive and expensive evaluation, it must be understood that a diagnosis of dementia of the Alzheimer's type typically has profound consequences for the patient and family. Indeed, with the recent data on the possible genetic diathesis associated with Alzheimer's disease, precision in diagnosis and widely accepted criteria are particularly important. The examination also has the obvious potential of identifying reversible causes of cognitive dysfunction.

While the early onset of the Alzheimer's-type dementia is often gradual, the course is a progressive one. The rate of degeneration is variable, and is dependent upon neuronal failure and somatic

decompensation as well as the adequacy of the medical and social support systems.[3] It should be emphasized that the natural course of the disorder has not been well documented. Clinical observations and reports of family members suggest that minor changes in personality, social behavior, and intellectual functioning are seen in the early stages of the disease.

In the later stages of Alzheimer's disease, patients may show marked restlessness, aphasia, perseveration, and emotional lability. The disorder eventually culminates by compromising the patient's knowledge regarding self and interpersonal relationships. It is also important to emphasize that although the afflicted individual becomes more disoriented and activities of daily living and self-care become progressively more difficult, there are marked differences in the type and extent of cognitive deficits. Documentation of the type and extent of specific areas of dysfunction can be most valuable for the physician.

The prominent clinical manifestations of the disease include deficits in attention, learning, memory, motivation, and expressive and receptive language skills. Impairment in focal skills such as calculation, abstraction, and orientation are also reported. Social skills, such as the ability or desire to communicate, work, and relate to family members or peers, are also impaired. Although the pattern of specific cognitive changes remains to be empirically determined in patient groups selected using precise diagnostic criteria, the clinician has the tools to roughly assess a range of cognitive skills.

Cognition is not a solitary process. It refers to an array of skills and abilities which define the range of ability or inability to adapt to the environment.[14] While, ideally, psychological examinations are indicated for a definite diagnosis, the examining physician is not without skills in this area. Attention may be determined by the patient's ability to attend to the questions raised during the interview and follow a series of specific simple instructions. Remembering the physician's name, as well as objects identified five or ten minutes earlier in the interview can help identify memory problems. Learning can be evaluated by having the patient repeat several word pairs such as paper-orange, ear-shoe. Three to five such pairs with low association values can be employed. The patient is given the first word, eg, paper, and asked to respond with the paired associated word. Orientation can be evaluated in several objective ways, including asking the patient how long he thinks the interview lasted.

Orientation questions are not, however, particularly effective ways to evaluate cognitive status. Deficits in attention and higher cognitive processes are discernible long before poor performance is noticed in orientation. Many patients who appear poorly oriented in time, person, and place, are readily manageable in the home, while others with less of an orientation deficit may demand significant care because of profound problems in other abilities to adapt. Impaired attentional scanning abilities may have a significant impact on the rate of decline in a patient who simply cannot handle the information load of daily living. Strong emphasis has been placed on the role of memory in dementia,[15] and although it is undeniably an important cognitive process, empirical support for the types and extent of memory loss in dementia remains inadequate.[16]

Because computerized tomography (CT) provides safe and accurate visualization of cerebral structures, it has become a useful tool in the differential diagnosis of dementia for identifying potentially "reversible" disorders such as trauma, mass lesions, or hydrocephalus.[17] Similarly, an individual presenting with dementia whose CT scan reveals no abnormality would lead the physician to suspect other reversible causes such as hypothyroidism or pernicious anemia. The ability of computerized tomography to demonstrate cerebral atrophy provides an important resource for documenting Alzheimer's disease, as gross atrophy of the brain with widening of the cortical sulci and enlargement of the ventricles is a characteristic feature. However, it is particularly noteworthy that cortical and ventricular atrophy are also seen in CT scans of the normal elderly. The presence of atrophy in the brains of normal, as well as demented, elderly has prompted researchers to investigate the clinical significance of the observed morphologic changes. The observation of cortical and central atrophy on CT scan in an elderly patient cannot itself be used to make a diagnosis of a cognitive disorder. Perhaps with advancing CT technology, parameters might be defined which will distinguish individuals with primary neuronal degeneration of the Alzheimer's type from normal elderly. Currently, computerized tomography ap-

pears most useful in its capacity to document cerebral atrophy in patients who present with clinical signs of dementia and to rule out focal lesions.

Although the electroencephalogram (EEG) has been well studied with relation to age and health, there is a paucity of data on the incidence and relevance of EEG changes in patients with varying stages of primary neuronal degeneration of the Alzheimer's type. The diagnostic utility of alpha rhythm slowing, an increase of slow wave activity, and other types of abnormalities remains to be evaluated during the course of the disease. Continued investigation of EEG parameters may eventually be useful to distinguish between multi-infarct and Alzheimer's-type dementia.[18]

The course of multi-infarct dementia is often a stepwise deterioration in contrast to the gradual decline observed in Alzheimer's disease. Multi-infarct dementias appear to occur in three forms: large, middle, and small vessel disease.[14] Whereas large vessel strokes are easy to identify, multiple smaller vessel infarcts can lead to a condition of cognitive dysfunction that is sometimes difficult to distinguish from Alzheimer's disease. Focal neurologic signs and symptoms are often seen in addition to cognitive impairment and the individual may have a history of hypertension, blackouts, cardiovascular illness, or stroke. The diagnostic criteria include the authors' modification of the Hachinski checklist for the evaluation of multi-infarct dementia.[19]

Dementing illness is a significant clinical problem not only because of its devastating effect on the health and quality of life of the patient and family, but also because of its malignancy and prevalence, and its consequent social and economic impact upon society at large.[20] The limited understanding of the etiology, pathophysiological mechanisms, and course of the major forms of dementing illness are a barrier to the development of an armamentarium of diagnostic techniques and treatment strategies. Since the dementias are symptom clusters involving deterioration of several cognitive dimensions in the absence of delirium, and since there are several types of age associated dementias which may differ in their initial presentation and response to treatment as well as developmental course, research and clinical diagnostic criteria should be employed to document clinical features. The failure to discriminate between patient groups using precise criteria will lead to the risk of errors in research, as well as patient care.

References

1. Kay DWK: The epidemiology and identification of brain deficit in the elderly. In Eisdorfer C, Friedel RO (eds): Cognitive and Emotional Disturbance in the Elderly: Clinical Issues. Chicago, Year Book Medical, 1979, pp 11-26
2. Terry RD, Wisniewski HM: Ultrastructure of senile dementia and of experimental analogs. In Gaitz C (ed): Aging and the Brain. New York, Plenum Press, 1973, pp 89-116
3. Eisdorfer C, Cohen D: Dementing illness in mid and late life. In Ebaugh FG (ed): Geriatrics for the Primary Care Physician. Menlo Park, California, Addison-Wesley, in press
4. Cohen D, Eisdorfer C: Serum immunoglobulins and cognitive studies in the elderly: A population study. Br J Psychiatry 136:33, 1980
5. Eisdorfer C, Cohen D: Serum immunoglobulins and cognitive status in the elderly: An immunologic-behavioral relationship? Br J Psychiatry 136:40, 1980
6. Katzman R: The prevalence and malignancy of Alzheimer's disease. Arch Neurol 33:217, 1976
7. Hachinski VC, Lassen NA, Marshal J: Multi-infarct dementia. Lancet 2:207, 1974
8. Eisdorfer C, Cohen D, Veith R: Psychiatric Aspects of Aging. Kalamazoo, Mich, Scope, in press
9. Wells CE: Pseudodementia. Am J Psychiatry 136: 895, 1979
10. Libow LS: "Pseudosenility:" Acute and reversible organic brain syndromes. J Am Geriatr Soc 21:112, 1973
11. Eisdorfer C, Cohen D: Differential diagnosis of the cognitively impaired elderly. In Storandt M, Siegler I, Elias MF (eds): Clinical Psychology of Aging. New York, Plenum Press, 1978, pp 7-42
12. Katzman R, Karasu T: Differential diagnosis of dementia. In Fields WS (ed): Neurological and Sensory Disorders in the Elderly. New York, Stratton, 1975
13. Wells CE (ed): Dementia, ed 2. Philadelphia, FA Davis, 1977
14. Cohen D, Eisdorfer C: Cognitive theory and the assessment of change in the elderly. In Raskin A, Jarvik LF (eds): Psychiatric Symptoms and Cognitive Loss in the Elderly. New York, Hemisphere, 1979, pp 273-282
15. Diagnostic and Statistical Manual of Mental Disorders, ed 3. Washington, DC, American Psychiatric Association, 1978
16. Eisdorfer C, Cohen D: The assessment of organic impairment in the aged: In search of a new mental status examination. In Burdock E, Sudilovsky A, Gershon S (eds): Quantitative Techniques for the Evaluation of Psychiatric Patients. New York, Marcel Dekker, in press
17. Jacobs L, Kinkel WR, Painter F, et al: Computerized tomography in dementia with special reference to change in size of normal ventricles during aging and normal pressure hydrocephalus. In Katzman R, Terry RD, Bick KL (eds): Alzheimer's Disease: Senile Dementia and Related Disorders. New York, Raven Press, 1978, pp 241-260
18. Obrist WD: Electroencephalography in aging and dementia. In Katzman R, Terry RD, Bick KL (eds): Alzheimer's Disease: Senile Dementia and Related Disorders. New York, Raven Press, 1978, pp 227-232
19. Hachinski V: Cerebral blood flow: Differentiation of Alzheimer's disease from multi-infarct dementia. In Katzman R, Terry RD, Bick KL (eds): Alzheimer's Disease: Senile Dementia and Related Disorders. New York, Raven, 1978
20. Butler RN: National Institutes of Mental Health Study. In Katzman R, Terry RD, Bick KL (eds): Alzheimer's Disease: Senile Dementia and Related Disorders. New York, Raven, 1978, pp 53-58
21. Eisdorfer C, Cohen D, Preston C: Behavioral and psychological therapies for the older patient with cognitive impairment. In Cohen G, Miller N (eds): The Clinical Aspects of Alzheimer's Disease and Senile Dementia. New York, Raven Press, 1978