Diagnosis of Alzheimer's Disease

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In 1906, Alois Alzheimer described a complex neuropsychiatric disorder in a 55-year-old woman that began as a paranoid delusion regarding her husband. There followed a rapid deterioration of memory and development of general paranoia and social dysfunction. Clinical examination was most marked by loss of the ability to encode information, with additional signs of aphasia, agnosia, and apraxia, but neurologic reflexes were otherwise normal. As symptoms progressed, Alzheimer also described bewilderment, psychosis, screaming, and fluctuation of symptoms. In the terminal state, after 4.5 years of illness, the patient was bedridden, contracted, and incontinent. At autopsy, he described her brain as showing atrophy, arteriosclerotic changes, neurofibrillary changes, plaques, and gliosis.[1]

The clinical and neuropathologic features of this case are now the hallmarks of a heterogeneous group of disorders that bears Alzheimer's name. Dementia of Alzheimer's type (DAT) refers to the clinical syndrome that manifests progressive decline[2,3] and meets certain pathologic criteria at autopsy[4-6]; however, the limitations of the current knowledge base still leave modern diagnosticians with several dilemmas, including early recognition, differential diagnosis, assessment of severity, and distinction of comorbid conditions. As knowledge about DAT continues to grow, clinicians will soon be determining which variety of DAT is present; what factors contributed to the development of this syndrome, including genetic predispositions[7]; and they will be able to make accurate prognostic statements about the patient's future course.

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INITIAL DETECTION OF DAT

In DAT, cognitive and social dysfunctions develop gradually, insidiously, and progressively over many months to a few years. Therefore, there is a clinical horizon that is associated with considerable uncertainty—the milder the case, the less certain the diagnosis. The converse is also true—the more severe the case, the more obvious the diagnosis. A common characteristic of DAT is the patients' general lack of awareness of the severity of their dysfunctions,[8] a condition known as anosagnosia. Consequently, a family member, a close friend, or a relative usually recognizes a problem and brings the patient to see the clinician for evaluation.

The patient may present to the clinician with any one of a variety of symptoms, although the most common difficulty is recent memory dysfunction. Occasionally, patients who present with depression or psychosis, as with Alzheimer's case, may actually be manifesting symptoms of DAT. Certain other neurologic-symptom complexes, particularly aphasia, apraxia, agnosia, and disturbance of executive function, frequently occur in DAT patients. In some cases, these symptoms are the presenting features of the disease; however, many of these problems can occur in nondemented elderly individuals with other neurologic diseases.

EARLY RECOGNITION OF DAT

An important challenge for clinical medicine is to recognize a patient's problems before a crisis brings them to the physician. Clinicians can recognize dementia with considerable accuracy in the office using short cognitive tests. The most

TABLE 1
Standard Laboratory Tests for Dementia Evaluation

- Medical history
- Family history
- Physical
- Neurologic
- Mental status/neuropsychological assessment
- Complete blood count
- Estimated sedimentation rate (check for inflammatory processes)
- Blood chemistry panel (including liver and kidney function tests)
- Serum electrolytes (including magnesium and zinc)
- Thyroid function tests
- Vitamin B_{12}/folic acid levels
- Serologic test for syphilis, HIV
- Routine urinalysis
- Chest radiograph
- Electrocardiogram
- Brain scan (CT at minimum; MRI and SPECT if available)

TABLE 2
DSM-IV Criteria for Dementia of Alzheimer Type

A. Development of multiple cognitive deficits including both:
   1. memory impairment
   2. one or more additional cognitive disturbances:
      a) aphasia
      b) apraxia
      c) agnosia
      d) disturbance in executive functioning

B. These cognitive deficits each cause significant functional impairment and represent a significant decline from a previous level of functioning.

C. Course is characterized by gradual onset and continuing decline.

D. The cognitive deficits are not due to:
   1. other central nervous system conditions
   2. systemic conditions
   3. substance-induced conditions

E. The deficits are not exclusively related to delirium.

F. Another Axis I (psychiatric) disorder does not account for the disturbance.

widely used test for screening for early dementia is the Mini-Mental State Examination (MMSE).[9] Many studies have examined the performance of elderly individuals on the MMSE and have generally supported the use of a score of 23 or below as a screen for impairment of cognitive function; however, this test is limited in its ability to distinguish normal individuals from those with mild dementia.[10,11] Further, cross-sectional studies have found MMSE scores to decrease with advanced age, and scores are also affected by education[12]; however, the incidence of DAT increases with age,[13] and DAT may be more prevalent in populations with less education or occupational attainment.[14] Therefore, early diagnosis of DAT must take into account the patient's age, education, and other potentially contributing or confounding conditions.[15]

Neuropsychological assessment can detect early DAT even before the patient's family or friends have recognized symptoms of early DAT or the disease process has significantly impaired daily functions.[16] Short test batteries currently under development can distinguish very mild Alzheimer cases[17,18] and diagnose DAT with up to 85% accuracy 4 years before it is possible to make a clinical diagnosis[19,20]; however, clinicians and health care agencies have not established a practical reason (eg, preventive interventions or pharmacotherapy) for urging widespread implementation of early recognition tools at this time.

CLINICAL DIAGNOSIS OF DEMENTIA

When the patient has presented to the office with a problem and a diagnosis of dementia is being entertained, the diagnostic regimen is well accepted (Table 1). The clinician should adjust the regimen for the individual patient, however.[21,22] The DSM-IV[2] provides an outline of criteria to ascertain the diagnosis of DAT (Table 2). The first criterion is disturbance of cognition, including disturbance of memory and another higher cognitive function. The disturbance must represent a deterioration from a higher level of functioning and cause interference with social function. In addition, the condition must not be occurring as part of a delirium or another psychiatric disturbance. These criteria are easily met by patients with moderate to severe dementia, but they are problematic in patients who have very mild DAT or have other medical or psychiatric problems.

Assessment of cognitive dysfunction by the clinician may be based on historical report, direct observation, or objective testing. The memory loss in DAT is most specifically a disorder of the ability to encode or learn new information.[10,17] As the disease advances, destruction of the fundamental neural substrate of memory is progressive and results in the eventual loss of previously formed memories. Structured neuropsychological examination can give an organized formulation of the cognitive deficits and track symptom progression.[16]

The associated social dysfunction can be effectively estimated through caregiver report using the Instrumental and Basic Activities of Daily Living (ADL) scales[23] or the Blessed Dementia Scale.[24,25] In patients with DAT,

TABLE 3
Reversible and Treatable Dementias

Depression
B_{12}/folate deficiency
Tumor (especially meningioma)
Subdural hematoma
Normal pressure hydrocephalus
Infections
Toxins
Endocrinopathy

scores on cognitive rating scales and ADL scales correspond highly with each other, suggesting that the underlying brain deficit is accurately reflected by both types of measurement.[23]

DIFFERENTIAL DIAGNOSIS OF DEMENTIA

While DAT accounts for at least half of the cases of dementia,[26,27] the diagnostic criteria for dementia are generic and apply to a syndrome that can be caused by a multitude of different conditions. The routine battery of examinations (Table 1) is a practical approach to investigating the possible causes of dementia other than Alzheimer's disease; however, this battery frequently does not clarify the diagnosis because various medical dementing conditions may coexist with other dementing processes. The principal justification for this battery of tests is the search for a reversible or treatable form of dementia (Table 3).[28] In the clinical setting, the need to discover a variety of potentially reversible causes of dementia is urgent because such conditions will become progressively more difficult to arrest or reverse.[22,27]

An important distinguishing clinical feature of DAT is the slow and insidious onset of the symptoms. For example, head trauma, surgery, or stroke may cause a rapid development of symptoms, yet the naturally slow development of some diseases may also induce an onset of symptoms with a time course indistinguishable from that of Alzheimer's disease. Further, even small strokes might induce a progressive loss of function that could not be distinguished from the DAT symptom constellation. Accordingly, no definite clinical features of DAT can confirm the diagnosis of Alzheimer's disease. The possibility or probability of Alzheimer's disease can be estimated based on the typicality of the presentation and the lack of other possible causes of dementia.[4] Using this clinical standard, diagnostic accuracy established at autopsy ranges from 60% for "possible" cases to 90% for "probable" cases.[29]

Review of the medical history should focus on illnesses that could have precipitated or led to the current condition. Of particular concern is the use of centrally active medications or toxins. The co-occurrence of different types of medical problems in the elderly individual, which could possibly account for the dementia, should be considered.[15,22,30] Although DAT accounts for more than half of the cases of dementia at autopsy, a host of other common conditions also frequently occur in dementia patients, including hypothyroidism, B_{12} deficiency, pulmonary disease, a history of falls, and surgery, any of which could also account for all or even part of the patient's cognitive dysfunction. Multi-infarct disease, alcoholism, diffuse Lewy-body disease, and Parkinson's disease are also commonly associated with dementia; the prevalence of these conditions seems to vary according to location (or at least to the institutions conducting the studies). Other important conditions to consider are normal pressure hydrocephalus, subdural hematoma, Huntington's disease, and hypoxic or hypoglycemic encephalopathy; however, existence of these conditions does not rule out the independent occurrence of Alzheimer's disease in a particular patient.

The issue that most complicates the diagnosis of Alzheimer's disease is the presence of vascular factors.[15] The criteria for vascular dementia provide no specific mechanism to exclude Alzheimer's pathology.[2] Arteriosclerotic pathology was even described in the first case reported by Alzheimer. Punctate white matter changes on MRI scans, suggestive of pathology in small penetrating arteries, are frequently seen in demented patients, even when the onset and progression have been reported as slow. These white matter changes are associated with increasing age, hypertension, heart disease, and diabetes,[31] but not an Alzheimer diagnosis.[32] The clinical significance of those white matter changes is not clear.

Other factors commonly complicate the diagnosis of Alzheimer's disease, such as the history of alcohol abuse. Dementia in the presence of incontinence, gait disturbance, and memory impairment, accompanied by a characteristic enlargement of the ventricles seen on brain scan, suggests normal pressure hydrocephalus, which should be excluded by cisternography.

USE OF BRAIN IMAGING IN DAT DIAGNOSIS

Brain imaging is a rapidly developing field of study in the diagnosis of Alzheimer's disease. There is little doubt that a brain scan is a justifiable procedure to rule out a tumor, stroke, or normal pressure hydrocephalus, and this can be accomplished with computed tomography (CT) without contrast. Further, atrophy in the medial temporal lobe can be assessed with this technique to give an accurate estimation of the atrophy associated with Alzheimer's disease.[33] The justification for a more extensive or expensive examination, such as magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), or positron emission tomography (PET), is a contested issue, however. MRI, particularly the coronal sections, shows atrophy of the hippocampus and temporal lobe (Figure 1), which can support the diagnosis of Alzheimer's disease and give an estimation of the severity of the disease process,[34] but quan-

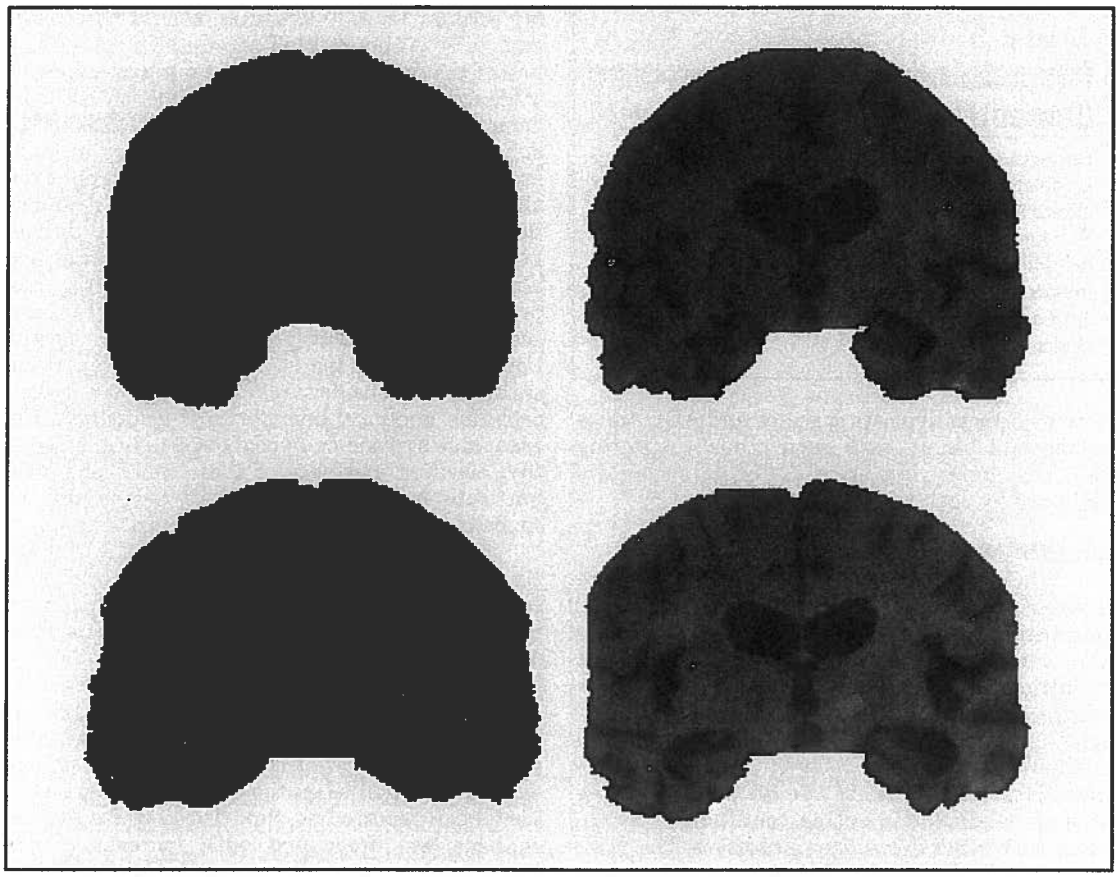

Figure 1. T1-weighted MRI scans of the brain in the coronal plane just posterior to the amygdala show the temporal lobe (inferior-lateral) including the hippocampus and temporal horns of the lateral ventricles (inferior-medial). Top left: 30-year-old male with high function. The hippocampus is large and the temporal horns are barely visible. Top right: 69-year-old male with mild memory impairment, MMSE=28, global score=3/50,[23] who was having some difficulties at work; possible Alzheimer diagnosis. Note the enlarged bodies of the lateral ventricles, but minimal enlargement of the left temporal horn (viewer's right) and sylvian fissure (top of temporal lobe). Lower left: 74-year-old female with probable Alzheimer's disease of mild severity, MMSE=18, global score=15/50. Note the enlarged temporal horns and sylvian fissures and some shrinkage of the hippocampus. Lower right shows a 70-year-old male with moderate dementia, MMSE=17, global score=19/50. The temporal horns are enlarged and the temporal lobe shriveled. Diagnosis of Alzheimer's disease was confirmed at autopsy 5 months later.

tification using this technique is not standardized. PET, measuring metabolic activity, and SPECT, measuring cerebral blood flow, both show characteristic decreases of activity in the temporal and parietal regions of the brain (Figure 2).[35-38] Combination of morphologic imaging and SPECT can further improve diagnostic power.[33,39] In the future, use of the more advanced imaging techniques and radioactive agents that can selectively tag neurotransmitter systems or neuropathology will be increased. The practical use of the range of imaging tools in clinical practice is not established, however.

ASSESSMENT OF DAT SEVERITY AND CLINICAL COURSE

An important component of dementia diagnosis is the assessment of severity. Numerous methods have been advanced to quantitate dementia severity. The Blessed Dementia Scale[24] was long considered the most reliable because it had been associated with the neuropathologic changes. Numerous measures of dementia severity have been developed and extensively studied, such as the Global Deterioration Scale,[40] the Clinical Dementia Rating scale,[41] the MMSE,[11] and systematic composites of other scales, which improve precision and reliability of the severity estimate.[23]

Quantification of dementia severity has been a controversial issue because of the lack of a fundamental physical standard against which to calibrate such scales; however, severity assessments can be translated to an absolute physical quantity: time course.[42,43] The time course can be used to estimate the duration of the illness and predict the future pattern of the patient's deterioration. Patients with DAT usually follow a typical downhill course that lasts about 8 years, on average, from the first symptoms until the most profound level of impairment, clearly a devastating decline relative to normal aging. The time course estimation provides the caregivers with a time line of expected changes and, thus, can help the family to prepare for the future.

PSYCHIATRIC CONCOMITANTS OF DAT

While searching for treatable dementias, the clinician must perform a complete mental

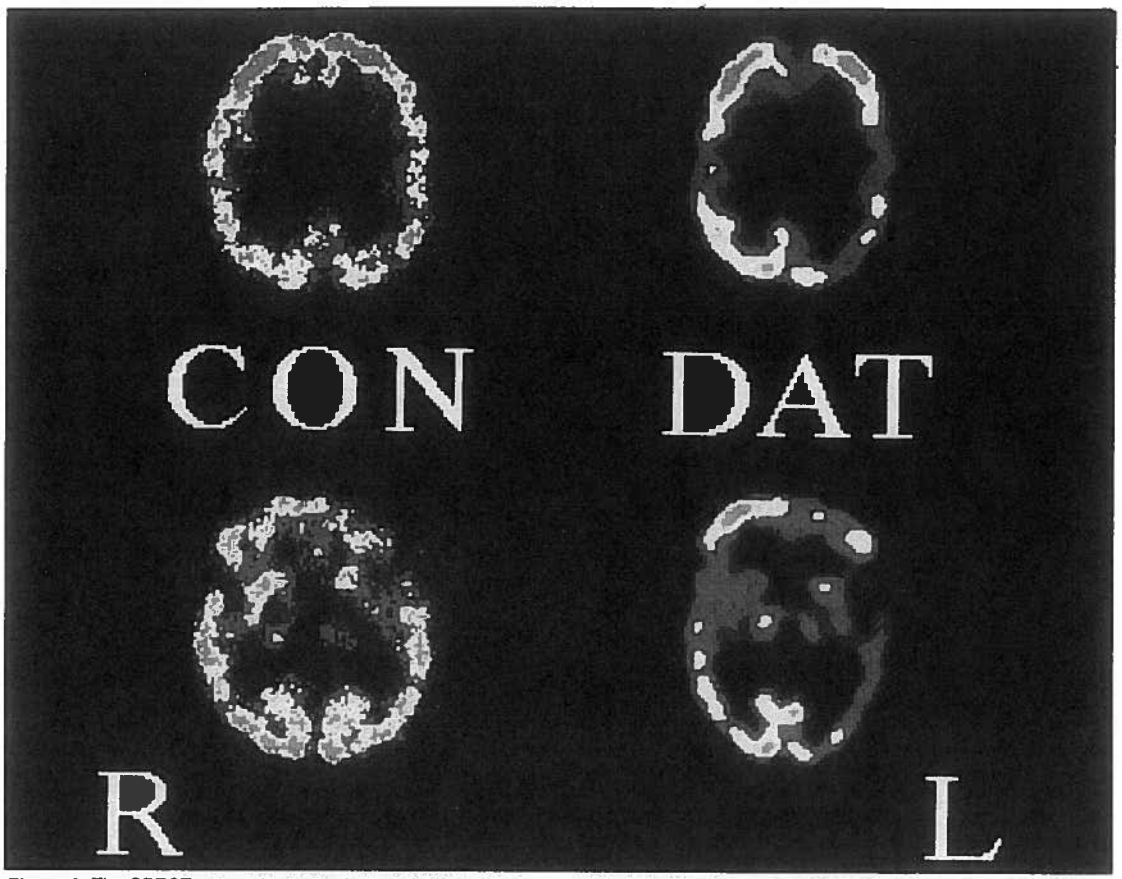

Figure 2. The SPECT scans shown are in the horizontal plane through the superior (upper) and inferior (lower) parts of the temporal lobe. The scans were done using ECD (Neurolite), injected 30 minutes before scanning. Scans were made on a three-headed Picker camera with 120 angles obtained in 20 minutes, with 2.2-mm thick sections, isotope resolution 6.2 mm at 10 cm, full-width, half-max. Filtered back-projected images show voxels 2.2 mm on a side. An elderly normal (CON) shows normal blood flow activity (red and yellow) in the frontal cortex (top), occipital cortex (bottom), temporal cortex (sides), and hippocampus (medial to the temporal cortex on the lower image). The patient with DAT (moderate) shows severe decrease of activity (blue) in the temporal cortex and hippocampus bilaterally. This pattern mirrors results obtained with PET scanning.

status examination, paying particular attention to depression, psychosis, agitation, and other behavior problems.[22] These symptoms are common in Alzheimer patients,[44] and can occur as the presenting symptom in one third of the patients.[45] Depression is important because it can be a cause of dementia, it occurs in approximately 25% of demented patients, and its treatment can improve the function of the demented patient.[46] Psychotic symptoms, particularly common in Alzheimer patients, are associated with more rapid dementia progression but are somewhat amenable to treatment with neuroleptic medication.[47] Agitation is more problematic in demented patients. This class of symptoms can be upsetting and disruptive to the caregiver and be a major precipitant of placement in a long-term care setting. In the long-term care setting, management of agitation is one of the most resource-consuming aspects of treatment.

GENETICS OF ALZHEIMER'S DISEASE

Knowledge about the relationship between Alzheimer's disease and genetic factors has grown recently.[7] A family history of dementia, particularly Alzheimer's type, increases the diagnostic likelihood of Alzheimer's disease in the patient. Several rare genetic factors are associated with Alzheimer's disease, for example, on chromosomes 14 and 21. Recently, the gene for apolipoprotein E—allele 4, which occurs with a frequency of about 15% in the population—has been associated with an earlier age of Alzheimer diagnosis. Homozygotes have a mean onset of dementia in the mid-60s, heterozygotes in the mid-70s, and noncarriers in the mid-80s[48]; however, the range of onset age is broad, and disease duration may be longer in allele 4 carriers.[49] Further, many patients who experience the onset of dementia before age 60 have two biologic parents that are alive and free of dementia symptoms.

NEUROPATHOLOGY OF ALZHEIMER'S DISEASE

In 1968, Blessed, Tomlinson, and Roth demonstrated, in a large group of patients, an association between symptoms in both the cognitive and social domains and the presence of Alzheimer's disease histopathologically.[24] According to their findings and those of many

epidemiologic and histopathologic studies, the pathologic changes associated with Alzheimer's disease appear in many individuals by the age of 60 years.[50] These neuropathologic changes are frequently seen in the aging brain, but the concentrations of these changes must reach a certain threshold to be associated with the diagnosis of Alzheimer's disease.[3,5,6]

The most careful application of clinical diagnostic criteria still results in uncertainty. The issues of diagnostic uncertainty lead to the question of the final diagnosis. Autopsy is the only means available for establishing the variety of dementia. Diagnostic clarification by autopsy is important for the patient's family members and the advancement of research into the cause and treatment of Alzheimer's disease and the other dementias that remain poorly understood. For research purposes, diagnostic certainty must be improved to support epidemiologic, etiologic, and prevention studies.

FUTURE CONSIDERATIONS FOR DAT DIAGNOSIS

In the future, research must focus on prevention and early intervention. Accordingly, the diagnosis of Alzheimer's disease must be moved back several years into the preclinical phase of this disease. Several recent studies have suggested that Alzheimer's disease can be predicted up to 4 years before a clinical diagnosis can be made.[19,20] Efficient recognition of preclinical Alzheimer's disease might be achieved by computer tests of cognition or more focused psychological tests until specific biologic markers are developed.

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