ORIGINAL CONTRIBUTION

The Natural History of Alzheimer's Disease

Description of Study Cohort and Accuracy of Diagnosis

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Objective: We describe the sampling, initial evaluation, and final diagnostic classification of subjects enrolled in a natural history study of Alzheimer's disease (AD).

Design: Volunteer cohort study.

Setting: Multidisciplinary behavioral neurology research clinic.

Patients or Other Participants: Three-hundred nineteen individuals were enrolled in the Alzheimer Research Program between March 1983 and March 1988. Of these, 204 were originally classified with AD, 102 were normal elderly control subjects, and 13 were considered special cases.

Main Outcome Measures: Final consensus clinical diagnosis, final neuropathologic diagnosis, and death.

Results: Of the 204 patients enrolled in the study, re-review after as many as 5 years of follow-up resulted in a final clinical classification of 188 with probable AD. Seven patients were believed to have a significant vascular component to the dementia, three were found to have developed depression, and six were excluded on other clinical grounds. Neuropathologic examination of 50 brains indicated definite AD in 43. After removing these seven misdiagnosed patients, the final group of probable/definite AD totaled 181 individuals. Accuracy of the baseline clinical diagnosis relative to neuropathology was 86%, and when follow-up clinical data were considered, 91.4%. Detailed neuropsychological testing yielded high sensitivity (0.988) and specificity (0.983) to dementia. Analyses of survival time from study entry until death revealed that older patients were significantly more likely to die during follow-up, but neither sex, years of education, nor pattern of cognitive impairment were related to survival.

Conclusions: These data provide the descriptive basis for future studies of this cohort. They indicate that longitudinal follow-up of demented cases increases accuracy of diagnosis, and that detailed cognitive testing aids in early classification.

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THE STUDY of the natural history of an illness provides some of the most valuable information to clinicians and scientists about the nature of the disease.[1-12] The evaluation of factors that can predict or modify the course of an illness reveals much about the underlying pathophysiology. Further, the efficacy of treatments designed to modify the course of an illness can only be assessed by having as background a detailed understanding of the illness in the absence of specific intervention.

In 1983, the National Institute on Aging (Bethesda, Md) funded the Alzheimer Research Program (ARP) at the University of Pittsburgh (Pa); the purpose of this research program was to evaluate the full spectrum of behavioral neurologic factors that could relate to the differential diagnosis of the illness and the natural history of the disease. At that time, there was no clear consensus of clinical diagnosis of Alzheimer's disease (AD), and diagnostic accuracy was considered of critical importance in light of new directions in treatment. Funding for this program ended in 1988, but many research publications have

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SUBJECTS, MATERIALS, AND METHODS

SUBJECTS

Individuals enrolled in the ARP between March 1983 and March 1988 were recruited from a variety of sources. The Benedum Geriatric Center, a multispecialty outpatient geriatric facility at the University of Pittsburgh Medical Center, provided direct patient referral. Notices to the Allegheny County Medical Society (Pittsburgh, Pa), local neurologists, and local psychiatrists, and public service messages on radio and television all served to inform the medical and lay public of the availability of the research program. Interactions with local and national organizations dealing with AD served to keep the study before the public eye, and staff members gave many presentations to local support groups and educational sessions. The ARP was always clearly labeled as *research*, and no direct clinical care was promised or provided.

Following telephone contact with the ARP staff, screening information was gathered by having the primary caregiver complete a mail-in questionnaire of symptoms of dementia and medical history. At the time of the first visit to the study site, the nature of the research was explained to both the patient and the family, and both the patient and the caregiver must have given informed consent to participate. If, in the opinion of the examining clinician, the patient did not appear to understand the nature of the evaluations to be undertaken, they were excluded from the research. The criteria for entry into the study are listed in **Table 1**.

SUBJECT EVALUATION

Each participant in the study, patient and control subject alike, received an extensive neuropsychiatric evaluation including medical history and physical examination, neurologic history and examination,[13,16,19,20] semistructured psychiatric interview,[23] and neuropsychological assessment. Each individual was interviewed by a psychiatric nurse to assess their physical and cognitive limitations, as well as the caregiving burden to their primary caregiver. Each evaluation was completed in approximately three sessions, generally within a 2-week period. The goal of this evaluation was to provide a carefully screened and uniformly evaluated cohort of AD patients and control subjects for longitudinal study.

In addition to the examinations listed above, each patient and control subject completed various laboratory studies. These included a standard battery of hematologic studies, blood chemistry studies, liver and thyroid function tests, vitamin levels, and a rapid plasmin reagin test. Each patient and control subject was given an electroencephalogram,[24,25] a computed tomogram of the head,[26,27] and a roentgenogram of the chest.

At the conclusion of the these studies, each individual set of results was reviewed by the study team. The neuropsychologic data per se were not used as selection criteria; to qualify as a "patient," the individual had only to demonstrate a history of progressive cognitive and functional decline and an abnormal mental status examination (performed during the neurologic examination). The medical and psychiatric evaluations were designed to eliminate those cases with confounding conditions which, in and of themselves, could have accounted for a dementia. At the time of the study inception the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria[28] did not exist, and the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*[29] did not allow for the differing patterns of presentation that might be encountered in AD patients. Thus, relatively greater emphasis was placed on clinical history and presentation than on strict adherence to research diagnostic criteria. Indeed, one of the goals of the study was to develop and/or evaluate such criteria.

COHORT SELECTION

Of the 319 individuals enrolled in the study, 102 were originally classified as control subjects and 204 as AD patients. Thirteen individuals were classified "special" cases and will not be discussed further in this article. After the study was closed, the clinical record of each individual patient and control subject was reviewed, and standard information was abstracted onto a specially designed coding form. These data, as well as significant outcome information (eg, death, institutionalization) were then reviewed by two of us (J.T.B. and O.L.L.) to arrive at a consensus classification based on the best available information as of March 1, 1992.

The results of the final classification review are shown in **Table 2**. The term *vascular component* as it is used here does *not* refer to a multi-infarct state, but rather to patients whose Hachinski rating[30] rose, or in whom there was clear evidence of a vascular component to their dementia.

As of March 1, 1992, 75 of the patients had died. Of these, 50 had autopsies (66.7%), and 43 were classified with definite AD (86.0%).[28,31] Seven patients were found to have other conditions based on a neuropathologic study that excluded them from the cohort. Thus, we were left with a final group of 181 probable and definite patients with AD.[28]

Of the 102 control subjects, one developed a dementia syndrome 5 years after study entry and 2 years after the ARP closed. Although there was no evidence of cognitive decline during the study period, this individual was excluded from the control group, and the data will be presented elsewhere.

used this extensive database.[13-22] Significant outcome data, such as death and institutionalization, are now available on virtually all of the original cohort of patients.

There were two overall aims of the ARP. The first was to determine which clinical signs or symptoms, observable *early* in the course of the dementia syndrome, were best able to diagnose AD reliably. The second was to determine which specific signs or symptoms could be used to predict pro-

Table 1. Study Eligibility Criteria

Age >44 years
Education more than seventh grade
Able to read and write English fluently before dementia onset (patients only)
No history of major nervous system disorders such as cerebral trauma, stroke, meningitis, epilepsy, mental retardation, hypothyroidism, excessive use of drugs (including alcohol), malnutrition, and major psychiatric disorder (ie, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition)* except dementia
Not maintained on any neuroleptic or other medication affecting central nervous system functions except antidepressants
Must be able to cooperate with neuropsychologic testing, and initial Mini-Mental State Examination score ≥10
Must be able to give informed consent
Must have an informant (patients only)

gression of the disease. While these goals were of high priority in 1983, they are especially important now in light of the new directions in therapeutics for AD. Studies that attempt to modify the natural progression of AD must have an understanding of the nonpharmacologic factors that can affect progression and outcome.

As a first step in achieving the goals of the research program with the final cohort of patients, we present the sampling, initial evaluation, and final classification of the individuals enrolled in the ARP. Information about patterns of impairment, and about factors related to risk to die during follow-up are also considered.

RESULTS

The demographic characteristics of the final group of study volunteers are shown in **Table 3**. The patients selected for study were older (t [279]=7.41, $P<.001$), less well educated (t [279]=−6.07, $P<.001$), and more likely to be women (χ^2=3.23, df=1, P=.07, Φ=.11) than were the normal elderly control subjects. Their performance on the Mini-Mental State Examination [32] (t [279]=−21.6, $P<.001$) and the ADL portion of the Blessed Dementia Rating Scale[33] (t [279]=15.1, $P<.001$) at study entry were significantly impaired. There was no difference between the groups in terms of risk factors for vascular dementia as identified by Hachinski's Ischemic Scale[30] (t [279]=0.36, $P>.50$).

NEUROLOGIC FINDINGS

The neurologic signs and symptoms of the patients and control subjects are shown in **Table 4**. These data are not appreciably different from those reported previously by Huff et al,[17] but are presented herein for the first time for the entire subject group. Individual contingency tables were analyzed using the χ^2 statistic or Fisher's Exact Test where appropriate. To arrive at a table-wide alpha level of 0.05, the critical value of P was set at .002 for each comparison. The proportions that are significantly different between the patients and control subjects are noted in Table 4.

Table 2. Study Patient Sample Characteristics*

Original sample	204
Vascular component	7
Non-AD (clinical)	9
Non-AD (pathologic)	7
Final sample	181
Clinical outcomes (Non-AD)	
Depression	3
Chromosomal abnormality	1
Mass lesion developed on computed tomographic scan	1
Ethanol abuse	2
Parkinson's disease	1
Not demented	1
Neuropathology outcomes	
Total deaths	76
Autopsies	50
Definite AD	43
Progressive supranuclear palsy	1
Motor neuron disease with dementia	1
Creutzfeldt-Jakob disease	1
Striatonigral degeneration	1
No distinct histopathologic features	3

AD indicates Alzheimer's disease.

Table 3. Characteristics of Final Sample of AD* Patients and Control Subjects

	Control Subjects (N=101)		AD Patients (N=181)	
	Mean (SD)	Range	Mean (SD)	Range
Age, y	63.8 (8.3)	46.2-81.9	71.4 (8.3)	50.0-88.7
Education, y	14.3 (2.9)	8-20	12.1 (2.9)	8-20
Mini-Mental State Examination	29.1 (1.1)	26-30	18.4 (5.2)	8-30
Blessed Activities of Daily Living	0.19 (0.95)	0-8	6.97 (4.1)	0-16.5
Hachinski rating	1.57 (0.77)	0-5	1.62 (1.1)	0-6
Sex (M/F)	44/57		59/121	
Handedness (R/L/Ambi)	93/7/1		172/4/5	

AD indicates Alzheimer's disease.

PSYCHIATRIC FINDINGS

Psychiatric symptoms identified during the initial evaluation are shown in **Table 5**. As we have noted previously,[18,19] strict adherence to *the Diagnostic and Statistical Manual of Mental Disorders, Third Edition,* criteria was not possible for affective disorder, but *syndromal* de-

Table 4. Neurologic Signs and Symptoms Among AD* Patients and Control Subjects

	No. (%)	
	Normal Control Subjects	AD Patients
Impaired olfaction	2 (2)	29 (16)†
Abnormal extraocular movements	0 (0)	1 (0.5)
Other cranial nerve abnormalities	0 (0)	0 (0)
Decreased strength	0 (0)	2 (1)
Gegenhalten	3 (3)	12 (7)
Cogwheeling	0 (0)	10 (5)
Lead pipe rigidity	0 (0)	6 (3)
Myoclonus	0 (0)	0 (0)
Tremor	1 (1)	24 (13)
Deep tendon reflexes abnormal	2 (2)	10 (5)†
Plantar response	0 (0)	0 (0)
Glabellar response	0 (0)	27 (15)†
Grasp reflex	0 (0)	14 (8)
Rooting reflex	0 (0)	0 (0)
Snout reflex	4 (4)	75 (41)†
Palmomental reflex	7 (7)	56 (30)†
Stereoagnosis abnormal	0 (0)	13 (7)
Agraphesthesia	3 (3)	33 (18)†
Cerebellar functions abnormal	0 (0)	20 (11)†
Gait impaired	2 (2)	48 (26)†
Falling	0 (0)	4 (2)
Incontinence	0 (0)	6 (3)
Motor impersistence	0 (0)	13 (7)
Dressing apraxia	0 (0)	14 (8)
Buccolingual praxis impaired	3 (3)	89 (48)†
Limb praxis impaired	7 (7)	135 (74)†
Unawareness of memory deficit	1 (1)	80 (49)†

*AD indicates Alzheimer's disease.
†Significantly different, P<.002.

Table 5. Psychiatric Symptoms and Syndromes

	No. (%)	
	Normal Controls	AD Patients*
Mood-related signs		
Sadness	18 (18)	56 (31)
Irritability	0 (0)	37 (20)†
Depressed mood	11 (11)	34 (19)
Anxiety	26 (26)	27 (15)
Social withdrawal	1 (1)	91 (49)†
Self-neglect	0 (0)	47 (26)†
Behavioral disturbances		
Agitation	14 (14)	47 (26)
Somatization	0 (0)	1 (0.5)
Loss of interest	10 (10)	119 (65)†
Loss of motivation	6 (6)	116 (63)†
Bizarre behavior	0 (0)	17 (9)†
Neurovegetative signs		
Appetite changes		
Increase	7 (7)	18 (10)
Decrease	15 (15)	64 (35)†
Sleep changes		
Hypersomnia	2 (2)	28 (15)†
Hyposomnia	41 (41)	45 (24)
Lack of energy	29 (29)	129 (70)†
Ideation disturbance		
Suicide	1 (1)	14 (8)
Poor self-esteem	2 (2)	49 (27)†
Paranoid and delusional ideation		
Delusions	0 (0)	37 (20)†
Suspiciousness	0 (0)	66 (37)†
Hallucinations		
Visual	0 (0)	13 (7)
Auditory	0 (0)	4 (2)
Both	0 (0)	1 (1)
Activity disturbances		
Wandering	0 (0)	16 (9)†
Syndromal major depression	0 (0)	25 (14)†
Aggressiveness	0 (0)	37 (20)
Sundowning	0 (0)	16 (9)†
Anxieties and phobias		
General anxiety	0 (0)	40 (22)†
Situational anxiety	2 (2)	21 (11)
Panic attacks	0 (0)	6 (3)

*AD indicates Alzheimer's disease.
†Significantly different, P<.002.

pression could be identified. Further, because we were not a clinical site, we had no direct control over whether an individual received medication and, if so, how well it was monitored. As was the case for the neurologic signs and symptoms, we established a critical value of *P* at .002 to have a table-wide error rate of .05. The significant differences between patients and control subjects are noted in Table 5.

NEUROPSYCHOLOGIC TEST DATA

The performance of the patients and control subjects on the various neuropsychologic tests is shown in **Table 6**. In some cases, noted in Table 6, the particular test was not instituted at the beginning of the project, and, therefore, data are not available on every individual. In the case where data were missing on five or fewer patients on a particular measure, the mean patient score was substituted. In the case when five or fewer patients were unable to complete a measure due to the severity of their dementia, the lowest accuracy score (or highest error score) was substituted.

To determine the extent of the dementia syndrome in each of the patients, the data from all subjects were compiled into seven composite scores representing the domains of memory, language, visual perception, visual construction, attention, executive functions, and orientation. The procedure for computing these scores has been described previously,[13-15,18,19] and these derived vari-

Table 6. Performance on Neuropsychologic Tests—Baseline Only

		Normal Elderly		AD* Patients	
	Test Range	Mean (SD)	Range	Mean (SD)	Range
Memory and Learning					
Verbal[42] (trials to criterion)					
Easy pairs	9-33	9.36 (0.93)	9-15	16.34 (7.36)	9-33
Hard pairs	9-33	14.28 (5.35)	9-32	30.30 (4.91)	9-33
Delayed recall[42] (No. correct)					
Easy	0-3	2.77 (0.51)	1-3	1.02 (1.02)	0-3
Hard	0-3	2.00 (1.09)	0-3	0.14 (0.49)	0-3
Face-name†					
Trials to criterion	12-44	12.41 (1.08)	12-16	27.93 (9.51)	12-44
Delayed recall correct	0-4	3.83 (0.46)	2-4	1.25 (1.38)	0-4
Recognition memory[43]					
Words					
Misses	0-5	0.25 (0.57)	0-3	1.82 (1.6)	0-5
False alarms	0-15	0.44 (0.81)	0-2	3.16 (3.73)	0-15
Faces					
Misses	0-5	0.27 (0.53)	0-2	1.82 (1.67)	0-5
False alarms	0-15	0.44 (0.81)	0-4	3.97 (4.12)	0-15
Memory					
Short story[44]					
Immediate recall	0-18	7.43 (2.6)	1.5-14.5	1.65 (1.8)	0-15
Delayed recall	0-18	6.45 (2.8)	1-15	0.41 (1.1)	0-5.5
Modified Rey figure[45,46]					
Copy	0-24	23.5 (0.94)	20-24	16.9 (7.3)	0-24
Immediate recall	0-24	20.0 (3.3)	9.5-24	5.73 (5.0)	0-22
Delayed recall	0-24	19.6 (3.4)	10-24	3.95 (5.2)	0-24
Orientation					
Time[34]	0-113	0.13 (0.46)	0-3	37.3 (39.9)	0-113
Person/place[47]	0-12	11.9 (0.22)	8-12	6.14 (3.14)	0-12
President's test[47]					
Verbal					
Naming	0-6	5.93 (0.51)	1-6	3.67 (2.1)	0-6
Sequence	−1.00-1.00	0.98 (0.05)	0.72-1.0	0.46 (0.41)	−0.83-1.00
Photo					
Naming	0-6	5.95 (0.49)	1-6	2.85 (2.23)	0-6
Sequence	−1.00-1.00	0.98 (0.5)	0.72-1.0	0.49 (0.38)	−0.66-1.00
Attention and Concentration					
Digit spans[44]					
Forward	0-9	6.99 (1.2)	5-9	5.51 (1.1)	3-9
Backward	0-9	5.53 (1.5)	2-8	3.39 (1.3)	0-7
Letter cancellation[48]					
Time, seconds	0-240	66.5 (16.8)	40-124	122.8 (53.4)	34-240
Reaction time, seconds					
Complex[50]	0-2.40	0.42 (0.09)	0.27-0.70	0.87 (0.56)	0.33-2.40
Simple[49]	0-2.40	0.33 (0.10)	0.20-0.72	0.68 (0.57)	0.19-2.40
Visuospatial Functions					
Simple drawings[51]	0-18	16.3 (1.3)	13-18	11.86 (3.2)	0-18
Block design[34]	0-44	43.1 (2.1)	32-44	29.9 (15.1)	0-44
Form discrimination[34]	0-32	29.8 (2.2)	20-32	20.7 (8.8)	0-32
Facial recognition[34]	0-60	47.3 (4.7)	26-55	37.5 (12.1)	0-53
Problem Solving/Executive					
Similarities[52]	0-12	11.3 (1.1)	6-12	4.92 (3.6)	0-12
Trailmaking,[53] seconds					
Part A, seconds	0-240	39.1 (13.8)	17-97	121.3 (70.8)	27-240
Part B, seconds	0-240	90.6 (38.9)	34-240	223.7 (36.4)	83-240
Weigl Sorting†[54]	0-15	11.96 (1.9)	8-15	5.81 (3.5)	0-15
Raven's colored matrices†[55]	0-36	32.4 (5.1)	3-36	16.7 (7.7)	0-34

(continued)

Table 6. Performance on Neuropsychologic Tests—Baseline Only (cont)

	Test Range	Normal Elderly		AD* Patients	
		Mean (SD)	Range	Mean (SD)	Range
Language					
Reading[56]	0-40	39.5 (20.0)	32-40	30.32 (9.9)	0-40
Writing[56]	0-22	21.9 (0.37)	20-22	19.16 (4.0)	1-22
Repetition[56]	0-140	139.7 (1.0)	132-140	133.00 (14.3)	0-140
Naming[51,57]					
Visual confrontation	0-42	38.6 (2.8)	30-42	23.07 (9.3)	0-42
Boston responsive†	0-12	11.4 (1.0)	7-12	5.95 (3.0)	0-12
Number information†	0-24	22.0 (2.3)	15-24	13.4 (5.7)	1-24
Auditory comprehension[56]	0-60	59.8 (0.84)	54-60	57.8 (3.3)	36-60
Production					
Letter fluency[58]	n/a	14.2 (4.7)	5-26	7.60 (4.3)	0-22
Category fluency[59]	n/a	18.6 (4.3)	6-29	5.82 (4.2)	0-21
Semantic correction task[60]					
Correct	0-10	9.77 (0.50)	8-10	8.48 (1.8)	0-10
Plausible reconstruction	0-14	6.13 (0.90)	3-7	4.05 (1.9)	0-7
Token test (part VI)†[61]	0-13	11.53 (3.01)	11-13	7.40 (3.8)	0-13

*AD indicates Alzheimer's disease.
†N=150. n/a indicates not available.

ables have been found useful in identifying patient subgroups.[13,18,19] However, given the importance of these methods, they are described here for clarity. First, with the exception of the orientation domain, which will be discussed separately, scores on each of the individual neuropsychologic tests comprising each cognitive domain (**Table 7**) were transformed using the mean and SD of the control group for that particular test. The scores comprising a single domain were then averaged (using the appropriate sign) and these scores were considered the *observed* performance values for each domain. Each composite from the 101 normal control subjects was then analyzed using multiple regression procedures using age, education, and sex as independent variables. From these regression models we then computed, for both patients and control subjects, the *expected* composite score based on the individual's age, education, and sex. Finally, we computed the difference between the observed and expected scores. This difference score, which reflected each subject's deviation from the performance expected based on their age, education, and gender, had a mean of approximately zero in the control group (Table 7). The mean scores of the patients were negative, indicating performance poorer than that expected. Finally, the fifth percentile of these scores was determined in the normal control group, and the percentage of abnormal scores was calculated for the patients (Table 7).

For the orientation tests (temporal, and person and place),[34] the distribution of normal performance was so highly skewed that arbitrary cut-off scores were established as we had done previously.[13] Thus, if a patient made any errors in orientation to person and place (maximum score, 12), or more than three errors on the temporal orientation test (maximum errors, 113), they were classified as impaired in orientation.

We then counted the number of "impaired" cognitive domains based on these composite scores for each subject, and these results are shown in **Table 8**. The left-hand column, labeled 'five domains' replicates the original table of Huff et al[16] and includes memory, language, perception, construction, and attention. The middle columns, also used previously,[16] include those same five variables, as well as the orientation domain. Finally, the right-hand column shows the distribution of impairments of all seven cognitive domains evaluated. If the criterion of having impairment in two or more areas of function is applied as the standard to classify individuals as 'demented' in each of these schemes, as was suggested by McKhann and colleagues,[28] the resulting calculations yield sensitivities of 0.933 (five domains), 0.988 (six domains), and 0.994 (seven domains). The specificity of each scheme was 0.988, 0.983, and 0.967, respectively. That is, of the patients in the final AD group, 168 had impairments (93.3%) in two of five domains. In terms of the control subjects, 97 did not meet this same criterion for dementia (98.8%).

Of the three patients noted to have developed major depression within the first year of follow-up, and who were thus excluded from the final study sample, none had impairments in two or more areas of cognitive function at study entry. Of the seven patients who had a vascular component to their dementia, six had impairments (86%) in two or more areas when using the six cognitive domains shown in Table 8. Of the remaining

Table 7. Composite Scores of Neurologic Functions*

	Normal Elderly		AD Patients		
Domain	Mean (SD)	Range	Mean (SD)	Range	% Abnormal†
Memory	−0.01 (0.76)	−1.96-+1.69	−3.09 (0.88)	−4.45-+0.03	95.6
Language	0.00 (0.59)	−1.96-+1.23	−4.72 (3.4)	−13.8-+0.49	86.7
Constructional praxis	0.06 (0.74)	−3.79-+0.98	−5.26 (5.1)	−17.3-+1.02	78.3
Visual perception	−0.01 (0.73)	−2.22-+1.36	−2.91 (2.8)	−11.9-+1.00	60.0
Attention	0.01 (0.71)	−2.59-+1.27	−3.11 (3.7)	−15.5-+1.37	62.2
Executive	0.00 (1.4)	−3.87-+2.67	−7.83 (6.7)	−25.3-+1.16	82.8

*The tests used in calculating each composite score were memory—immediate story recall,[44] immediate figure recall[45,46]; language,—Boston naming,[51,57] word generation (category),[58,59] easy-paired associates[42]; constructional praxis—block designs,[34] simple designs[51]; visual perception—form and facial discrimination[34]; attention—simple reaction time,[49] letter cancellation time[48]; executive—complex reaction time,[50] and trailmaking (part B).[53] AD indicates Alzheimer's disease.

†Based on fifth percentile of normal group; see text for details.

13 patients classified as not having AD, either on clinical or neuropathologic grounds, nine had impairment (69%) in two or more areas of cognitive function. Thus, of all of the patients excluded from the final study, 15 (65.2%) of 23 met the criteria for 'dementia' based on neuropsychologic test performance. All had presented with consistent histories of progressive memory loss and other cognitive impairments.

In an effort to determine which of the cognitive domains contributed most to the pattern of impairment of AD, the six composite variables (ie, memory, language, attention, perception, construction, and executive functions) were entered into a stepwise logistic regression (SPSS/PC)[35] to predict group membership (ie, patient vs control subject). The forward stepwise procedure ended with an overall classification accuracy of 97.5%, missing only two of the patients, and misidentifying four of the control subjects (χ^2=325.5, df=3, P<.001). The three variables in the final equation were memory (r=−.22, P<.001), perception (r=−.12, P=.007), and language (r=−.13, P=.004). Construction, attention, and executive functions did not significantly add to the variance accounted for by the remaining three variables.

SURVIVAL ANALYSIS

Sixty-four of the patients in the final group died during the course of follow-up. An analysis of the factors that were related to time until death was conducted using Kaplan-Meier procedures.[35] For those patients who did not die, the date of their last contact was used as the censoring date, and time on study (ie, until death or censoring) was calculated for each patient.

Since none of the normal control subjects died during the follow-up period, our attention focused on the patients with AD. Among those patients 70 years of age or older, 41.9% died during follow-up, which is significantly greater than the 26.7% of the younger individuals (Mantel-Cox χ^2=8.683, P=.0032). Neither education (high school or less vs more than high school) (χ^2=0.816, P=.37) nor sex (χ^2=2.03, P=.15) were significantly associated with survival. Even after stratification for age, sex was not significantly associated with risk to die (χ^2=1.5, P=.30).

We followed these analyses with an investigation of the role of patterns of cognitive function in predicting time to death. Performance by each subject in each of the six cognitive domains was classified relative to the median for the entire patient group (ie, either above or below the median). Six separate analyses of survival, using the grouping variable for each cognitive domain stratified for age, were completed. In none of the analyses did the classification by cognitive function predict survival.

Since many of the studies that have reported increased mortality among patients with specific impairments[36] classified the patients based on *pattern* of impairment, we attempted this procedure. Subjects were classified as either "nonfocal," "language impaired," or "visuospatially impaired" based on the patterns of their performance on the cognitive tests.[13] However, because there were relatively few patients classified as visuospatially impaired, and only one of them had died, we focused our attention on those patients who were considered to have pronounced language (ie, lexical/semantic) impairments. Forty-two percent of these patients died during follow-up, compared with 35.0% of the nonfocal patients. However, regardless of whether the patients were stratified on age, the difference in survival between these two groups was not significant.

COMMENT

The purpose of this article was to fully describe the study evaluation and to characterize the volunteers sufficiently so that others can fully understand this longitudinal research program. The details, while not exhaustive, do provide a broad description of the cohort of patients under study. In addition to this important descriptive information, however, these data also make several points concerning the diagnosis and outcome of elderly patients who present with a progressive dementing

Table 8. Cross-Tabulation of Number of Deficits by Clinical Classification

No. of Deficits	Five Domains*		Six Domains†		Seven Domains‡	
	Normal Elderly	Alzheimer's Disease	Normal Elderly	Alzheimer's Disease	Normal Elderly	Alzheimer's Disease
0	81	1	72	0	71	0
1	16	11	24	2	22	1
2	2	23	3	13	5	10
3	...	21	...	22	1	16
4	...	51	...	21	...	13
5	...	73	...	53	...	22
6	...	...	...	68	...	50
7	...	...	...	...	...	67
Total	99	180	99	179	99	179

*Memory, construction, perception, attention, and language.
†Five domains and orientation.
‡Six domains and executive functions.

disorder. It is clear that highly accurate clinical diagnosis can be accomplished. Of the patients included in the final study sample and who underwent autopsy, 87.8% had definite AD. If we exclude from that calculation the two cases whose clinical course identified them as having a disorder other than AD within the first year of follow-up (ie, Creutzfeldt-Jakob disease, amyotrophic lateral sclerosis), the accuracy rises to 91.4%.

The clinical follow-up of patients who are initially classified as having AD greatly increases the accuracy of the diagnosis. Of the original 204 patients, 16 were reclassified on clinical grounds based on information gathered during the first year of follow-up. Although the patients with a vascular component to their condition met the criteria for possible AD,[28] and perhaps for probable AD, they were excluded here so that we had the most carefully defined group possible. In terms of clinical management, a diagnosis of AD should not end the careful monitoring of a patient's condition. While it is relatively unlikely that a rediagnosis will occur (approximately 8%), it is clearly the case that other conditions (eg, cerebrovascular disease) that were not evident at the initial evaluation can become significant over time.[27]

As was noted in our previous article[16] the criteria of impairments in two or more areas of cognitive function has a high sensitivity and specificity for diagnosis of dementia. Using the six cognitive domains suggested by Huff and colleagues,[16] high sensitivity is obtained without sacrificing specificity of diagnosis (see center columns of Table 8). Of the six patients who scored above 26 on the Mini-Mental State Examination, four (67%) were impaired in two or more domains, reinforcing the need for detailed neuropsychologic evaluation when summary measures (eg, Mini-Mental State Examination, Blessed Dementia Rating Scale) suggest "normal" cognitive function in the face of a clear history of progressive functional decline. The two cases with Mini-Mental State Examination scores of 30, and with impairments in only one area of cognitive function, nevertheless declined dramatically over the next years—further confirming the importance of clinical follow-up in patients evaluated for dementia.

The accuracy of the clinical diagnosis relative to the pathologic classification presented herein may appear at variance with a previous article from this center.[22] In that study approximately 80% accuracy was reported when two neurologists retrospectively reviewed clinical information available on 54 demented patients. The dementia among these patients was of various causes, and in only 12 cases were longitudinal data available. When attention focused on the AD diagnosis, accuracy was 85% to 95%, which is consistent with these findings.

The results of the survival analysis must be viewed as preliminary, although they do make a number of interesting points. First, while age was significantly associated with mortality, neither sex nor education modified an individual's risk to die during follow-up. In both cases, the failure to find an association may be due to the fact that we were examining only individuals with a known brain disease. Thus, while females in the general population survive longer than males,[37] in the presence of AD this effect is dramatically attenuated. Similarly, while lower education may be a marker for decreased cerebral reserve capacity placing individuals at greater risk for displaying impairment,[38,39] it does not appear related to physical survival in the presence of diagnosed disease.

The role of patterns of cognitive dysfunction in predicting mortality is difficult to determine. In this study, simply being relatively more impaired in one domain (eg, memory) was not associated with survival. Further, among those patients considered to have greater impairments in language function (relative to visuospatial function), the rate of death was not significantly greater than that of the nonfocal patients. As noted above, however, all of these findings from the survival analyses need to be viewed as

tentative. There are a variety of different ways to measure progression of a disease such as AD (eg, decline of cognitive functions below an arbitrary level; entry into full-time nursing care) and these effects may be moderated by a number of social factors (eg, marital status and living arrangements) as well as medical comorbidities. These questions await further, and more detailed, analyses.

The signs and symptoms of neurologic dysfunction and psychiatric distress are consistent with previously reported findings. As reported by Huff and colleagues[17] in an early article from this cohort, and in a more recent study by Galasko et al,[40] the neurologic findings are consistent with generalized damage to the central nervous system. Prominent among the signs and symptoms was the presence of primitive reflexes and both limb and buccolingual dyspraxia. The significance of these signs and symptoms in terms of rates of progression and patterns of decline will be the subject of other research studies.

Of the signs and symptoms of psychiatric distress, behavioral manifestations of the dementia syndrome were of particular note. Social withdrawal, loss of interest, decreasing motivation, and lack of energy were prominent. Moreover, decreasing appetite and hypersomnia were noted. Syndromal major depression was noted in 14% of the cohort, and although this has been associated with greater impairment in cognitive function,[41] it does not appear to affect the rate of decline over 1 year.[18] The presence of delusions (20%) and hallucinations (10%) is associated with more severe electroencephalographic abnormality at study entry, and with a faster rate of decline in the mental state.[19] The relationships between other psychiatric signs and symptoms, especially the symptoms of anxiety and/or suspiciousness, await further examination.

The purpose of the ARP was to gather information about the natural history of dementia to increase diagnostic and prognostic accuracy and reliability. As with any longitudinal cohort study, there are inherent study design problems related to the changing knowledge base as the study matures. Thus, what was a reasonable protocol in 1983, is certainly not state-of-the-art in 1993. Nevertheless, important, perhaps unique, data are available from studies of this kind. This article demonstrates that highly accurate diagnosis is possible in AD, especially if detailed cognitive testing is used, and clinical reevaluation is made to monitor progression. The preliminary survival studies suggests that multivariate models, involving both medical and social variables, may be needed to predict patterns of physical and cognitive decline.

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