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Predictors of Survival in Clinically Diagnosed Alzheimer's Disease and Multi-Infarct Dementia

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• **Duration of survival from time of first evaluation was studied in 61 patients with clinically diagnosed Alzheimer's disease (senile dementia of the Alzheimer type [SDAT]) and 34 patients with clinically diagnosed multi-infarct dementia (MID). Duration of survival did not differ significantly between MID and SDAT. However, since MID patients were younger at onset, MID patients had a lower life quotient than SDAT patients. Race, sex, and age at onset were not predictive of survival in SDAT. History of hypertension, elevated systolic blood pressure, lower scores on tests of Block Designs, and Logico-Grammatical Comprehension predicted shorter survival in SDAT. Age at onset and race were not predictive of survival in MID. Male sex, lower educational attainment, as well as low scores on tests of Logico-Grammatical Comprehension, Digit Span, Naming, Verbal Fluency, and receptive vocabulary, predicted shorter survival in MID.**

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A number of factors have been associated with duration of survival in senile dementia of the Alzheimer type (SDAT) and multi-infarct dementia (MID). Younger age at onset[1-3] and male sex have been associated with shorter duration of survival in SDAT.[1] The effect of race on survival in either MID or SDAT has not been carefully examined. Neither educational attainment nor duration of dementia has been associated with shorter survival rates.[1,2,4] Language disorder including anomia has been associated with shorter survival in some studies of SDAT,[5] but not in others.[6] Diesfeldt et al[4] found apathy, age at admission to nursing home, physical disability, and dependency predictive of mortality in a nursing home population with SDAT.

The effects of medical risk factors (eg, hypertension, heart disease, diabetes mellitus) on survival in MID and SDAT have not been carefully studied. Several studies have suggested that mean duration of survival after diagnosis is shorter in MID than in SDAT.[7]

Cognitive measures (such as the Haycox behavioral score, the Mini-Mental State score, and the Clinical Dementia Rating Scale score) have been shown to have some predictive value for disease course and survival in SDAT.[1,3,8]

In this study, we examined the predictive power of several medical risk factors and several neuropsychological measures for survival in SDAT and MID. In addition, we compared duration of survival in MID and SDAT.

PATIENTS AND METHODS

All patients were evaluated by the Center for Alzheimer's Disease at Michael Reese Hospital and Medical Center, Chicago, Ill, between January 1, 1981, and January 1, 1988. Sixty-one patients with clinically diagnosed Alzheimer's disease and 34 patients with clinically diagnosed MID were studied. Diagnostic criteria for a clinical diagnosis of probable Alzheimer's disease were consistent with those of McKhann et al.[9] All patients with clinically diagnosed Alzheimer's disease had a history of a gradually progressive dementia that was of insidious onset. Other causes of dementia were specifically excluded by history, physical examination, and laboratory tests. Computed tomographic scans of patients with Alzheimer's disease were free of focal abnormality. All patients with clinically diagnosed Alzheimer's disease had Hachinski Ischemic Scores less than 4. Patients with clinically diagnosed MID met the *Diagnostic and Statistical Manual of Mental Disorders*, ed 3,[10] diagnostic criteria, including evidence of dementia on psychological testing, a stepwise deteriorating course, clinical or roentgenographic evidence of at least one cerebral infarction, and focal neurological signs or symptoms. All patients clinically diagnosed as having MID patients had Hachinski Ischemic Scores greater than 7. Autopsy confirmation of the diagnosis was made in 6 patients.

The duration of symptoms was defined as the interval from first symptoms as estimated by the patient's family or caregiver to time of initial evaluation. The period of observation was defined as the interval between time of initial evaluation and time of last patient contact. Grip strength was determined by hand dynamometer. Educational attainment was expressed as years of schooling. Age at onset was defined as patient age when symptoms were first reported. Survival status was ascertained by either direct patient contact or telephone contact at 6-month intervals.

Psychological testing included the Block Designs, Vocabulary (odd items only), and Digit Span (sum of digits forward and backward) subtests from the Wechsler Adult Intelligence Test[11] and the Information, Orientation, and Logical Memory subtests from the Wechsler Memory Scale.[12] Additional tests included Verbal Fluency (animals named in 60 seconds), the Wiig-Semel Logico-Grammatical Comprehension Test,[13] a confrontation naming test,[14] and the Quick Test of receptive vocabulary.[15] In addition, all patients were rated on the Global Deterioration Scale[16] and the Hachinski Ischemic Score.[17]

Group means were compared with unpaired t tests. Survival estimates were made by the product-limit method.[18] Predictors for survival were evaluated by a proportional hazards regression analysis using survival analysis with covariates.[18] Life quotients were calculated by dividing

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estimated survival duration (product-limit method) by expected survival based on United States life tables for individuals of comparable age, sex, and race.[19]

RESULTS

The patients with SDAT were 45% black, 55% white, 59% female, and 4% left-handed. The patients with MID were 76% black, 24% white, 50% female, and 3% left-handed. Heart disease (either hypertensive or ischemic) was present in 17% of the patients with SDAT and in 30% of the patients with MID. Hypertension was present in 21% of the patients with SDAT and 78% of the patients with MID. Diabetes mellitus was found in 6% of the patients with SDAT and 30% of the patients with MID.

Mean survival (product-limit method) did not differ significantly between patients with MID and patients with SDAT (Table 1). The patients with SDAT were older, had lower systolic and diastolic blood pressures, and had greater grip strength than the patients with MID (Table 2). There were no significant intergroup differences with regard to duration of symptoms prior to evaluation, period of observation, Global Deterioration Scale rating, or educational attainment. The SDAT patients outperformed the MID patients on Total Digits, Quick Test (receptive vocabulary), and Wechsler Adult Intelligence Test Vocabulary (defining vocabulary). The MID patients performed better on the Verbal Memory subtest of the Wechsler Memory Scale.

The proportional hazards model was used to evaluate predictors of survival (survival analysis with Cox covariates). Univariate analyses showed that age at onset, race, sex, educational attainment, history of diabetes mellitus, Hachinski Ischemic Score, Global Deterioration Scale, grip strength, and history of heart disease were not predictive of survival in SDAT. Systolic blood pressure and history of hypertension were negatively correlated with survival in SDAT. Among the psychological tests, Block Designs and Logico-Grammatical Comprehension correlated with survival, with better scores predicting longer survival in SDAT (Table 3).

Univariate analyses showed that survival in MID did not correlate with age at onset, race, hypertension, diabetes mellitus, heart disease, or blood pressure. Longer survival in MID was positively correlated with higher educational attainment and female. Higher scores on a variety of cognitive measures, including Total Digits, Naming, Quick Test (receptive vocabulary), Verbal Fluency, Logico-Grammatical Comprehension, and the Global Deterioration Scale, predicted longer survival in MID.

Multivariate models of survival (Cox proportional linear hazards model) in Alzheimer's disease and MID were developed by stepwise entry of predictors that were individually predictive of survival (Table 3). Retained predictors in the Alzheimer's disease model included systolic blood pressure and Block Designs. Retained predictors in the MID model included education, Quick Test, sex, and Logico-Grammatical Comprehension (Table 4).

Table 1.—Mean Duration of Survival (Product-Limit Method) for Dementia Subjects by Diagnosis, Race, and Sex

	Alzheimer Disease				Multi-Infarct Dementia			
	N	Mean, y	SE	LQ*	N	Mean, y	SE	LQ*
Race								
White	33	4.8	0.5	0.82	9	3.8	0.8	0.52
Black	28	3.6	0.5	0.72	25	4.7	0.6	0.63
Sex								
Male	25	3.8	0.5	0.88	17	3.0†	0.6	0.55
Female	36	4.5	0.4	0.71	17	5.6†	0.7	0.63
All	61	4.3	0.5	0.78	34	4.5	0.4	0.57

*Life quotient (LQ) defined as mean survival from product-limit estimate divided by predicted life expectancy from US Life Tables[19] for persons of comparable age, sex, and race.
†Groups differ, two-tailed t test, $df = 1$, $P < .05$.

Table 2.—Intergroup Comparisons*

	Alzheimer's Disease (N = 61)		Multi-Infarct Dementia (N = 34)	
	Mean	SD	Mean	SD
Age at onset†	71.0	6.1	65.1	8.7
Duration of symptoms, y	5.4	3.0	5.0	4.8
Period of observation, y	2.8	1.5	2.7	1.9
Education, y	11.3	3.9	10.9	3.0
Systolic BP, mm Hg†	130.5	19.6	142.8	22.8
Diastolic BP, mm Hg†	78.9	8.0	86.3	10.4
Grip right, kg†	15.9	9.7	10.5	8.9
Grip left, kg†	15.3	9.3	9.1	7.6
GDS	5.2	0.6	5.0	0.7
Block Designs (WAIS)	7.8	10.1	6.3	7.8
Total Digits (WAIS)†	8.8	2.7	7.5	2.4
Orientation (WMS)	3.0	1.5	3.1	1.5
Information (WMS)	2.7	2.0	3.3	2.0
Naming	12.0	4.2	12.1	4.9
Verbal Fluency	7.2	3.9	6.5	3.6
Quick Test†	28.1	12.3	21.4	13.1
Vocabulary (WAIS)†	16.0	9.5	11.7	8.3
Logico-Grammatical	11.2	5.0	9.7	4.2
Verbal Memory (WMS)†	2.3	2.0	3.3	2.6

*BP indicates blood pressure; GDS, Global Deterioration Scale; WAIS, Wechsler Adult Intelligence Test; and WMS, Wechsler Memory Scale.
†Groups differ, two-tailed t test, $df = 1$, $P < .05$.

COMMENT

Survival from time of diagnosis did not differ significantly between patients with MID (4.5 years) and patients with SDAT (4.3 years). Martin et al[20] found survival somewhat shorter in 41 patients with MID compared with 134 patients with SDAT, but the difference was not statistically significant. Barclay et al[2] found a mean survival in MID (2.6 years) that was significantly shorter than mean survival in SDAT (3.4 years). Similarly, Molsa et al[7] found a mean survival of 5.7 years in SDAT and 5.2 years in MID. Our estimates of survival are based on the period of observation (time from first evaluation until death). Survival from time of first symptoms is considerably longer, since the mean duration of symptoms prior to diagnosis was 5.4 years for the patients with SDAT and 5.0 years for the patients with MID. This implies a mean duration of illness of 9.7 years for the Alzheimer patients and 9.5 years for the patients with MID. However, establishing the exact

Table 3.—Significant Univariate Predictors of Survival in Alzheimer's Disease and Multi-Infarct Dementia

	Beta Coefficient*	χ^2	Mean Survival†		Relative Hazard‡
			Top Half	Lower Half	
Alzheimer's disease					
Systolic blood pressure	.0212	6.8	2.9	5.1	2.3
Hypertension (by history)	.9966	3.9	2.9	4.6	2.7
Block Designs	−.0782	10.0	5.6	3.7	0.2
Logico-Grammatical	−.1005	5.1	4.8	3.7	0.3
Multi-infarct dementia					
Education	−.3423	5.3	4.7	3.7	0.1
Female sex	−1.337	4.6	5.6	3.0	0.3
Logico-Grammatical	−.1526	4.6	4.7	4.0	0.3
Total Digits	−.2787	4.5	5.1	3.4	0.3
Naming	−.1053	4.2	4.8	3.4	0.3
Verbal Fluency	−.187	4.3	4.8	3.7	0.3
Quick Test	−.0766	6.3	5.4	3.0	0.1
GDS	.8618	3.8	3.3	4.9	3.3

*Negative beta coefficients indicate favorable and positive beta coefficients adverse predictors of survival. All beta coefficients are significant at $P < .05$. Hypertension dummy coded as 0, absent; 1, present; sex coded as 1, male; and 2, female.

†Mean survival is in years. Mean survivals are given for patients above mean score (upper half) and below mean score (lower half). For mean scores see Table 2.

‡Relative hazard is ratio between risk of dying for patients 1 SD above mean divided by risk of dying for patients 1 SD below mean. For means and SDs see Table 2. Relative hazards of greater than 1 for systolic blood pressure, hypertension, and Global Deterioration Scale (GDS) are associated with shortened survival. Relative hazards of less than 1 for Block Designs, Logico-Grammatical Comprehension, education, female sex, Total Digits, Naming, Verbal Fluency, and Quick Test are associated with longer survivals.

Table 4.—Multivariate Predictive Model of Survival in Alzheimer's Disease and Multi-Infarct Dementia*

	Beta Coefficient	Improvement, χ^2	*P* Value	*df*
Alzheimer's disease				
Systolic blood pressure	0.0157	9.4	.002	1
Block Designs	−.0668	3.9	.047	2
Multi-infarct dementia				
Education	−.3216	6.7	.010	1
Quick Test	−.1105	6.1	.013	2
Female sex†	−2.0528	5.3	.021	3
Logico-Grammatical	−.2398	5.4	.020	4

*Significant univariate predictors from Table 3 were entered stepwise into a multivariate Cox proportional hazards model. Positive beta coefficients are associated with adverse predictors, negative beta coefficients are associated with favorable predictors. Global χ^2 for the Alzheimer model is 14.1 ($df = 2$; $P < .001$). Global χ^2 for the multi-infarct dementia model is 19.0 ($df = 4$; $P < .001$).

†Sex was dummy coded (1, male; 2, female). Female sex was associated with longer survival.

onset of symptoms is difficult, especially in SDAT. Furthermore, comparisons between survival in MID and SDAT are hazardous, given the variability in severity of both diseases. Multi-infarct dementia is a particularly heterogeneous entity that includes dementia due to superficial cortical infarcts, borderzone infarcts, lacunar infarcts, large deep infarcts, and white matter disease.[21] Case selection biases also make comparisons difficult. Disease treatment, especially in MID, may influence disease course.[22] With improving medical care for both SDAT and MID, improvements in survival may occur in the future. Thus, differences in survival between MID and SDAT must be interpreted cautiously. A demonstration of convincing differences in survival between MID and SDAT would require a prospective population-based study that took into account significant confounding factors such as access to and quality of medical care.

We assessed the predictive value for survival of various demographic factors in Alzheimer's disease. Like Diesfeldt et al,[4] we did not find sex to be predictive of survival in SDAT (Table 1). We did not confirm the suggestion of Barclay et al[1] that male sex predicts shorter survival in SDAT. Race was not a significant predictor of survival in SDAT. Likewise, age at onset was not a significant predictor of survival in SDAT. Recently, Huff et al[23] have shown that age does not seem to influence rate of progression of SDAT. However, since younger patients have significantly longer life expectancies than older patients, the effect on life quotient (actual years surviving/expected years of survival) is greater for younger patients than older patients. Diesfeldt et al[4] have estimated that patients with Alzheimer's disease under age 71 years have a life quotient of 0.67, whereas patients over age 80 years have a life quotient of 0.93. As a group, our SDAT patients had a life quotient of 0.78 (Table 1) consistent with their mean age of 71.0 years. The life quotient was substantially lower for the patients with MID (0.57), reflecting not the shorter duration of their illness, but rather the younger age of onset of the patients with MID. Multi-infarct dementia has a much greater impact on life expectancy than SDAT because it has an onset in a younger patient population.

Certain medical risk factors influenced survival in SDAT. A history of hypertension and first recorded systolic blood pressure were negatively correlated with survival among the patients with SDAT. Thus, even in a group of patients with SDAT, hypertension still has an adverse effect on survival. Control of medical risk factors may prevent death due to intercurrent causes and extend survival in Alzheimer's disease as suggested by Chandra et al.[24]

Consistent with prior studies,[1,3,4] degree of cognitive impairment appears to have modest predictive value for survival in SDAT. We sampled several areas of cognition, including language, visuoconstructive ability, memory, orientation, and attention. Measures of memory, attention, and orientation were not predictive of survival in SDAT. The visuoconstructive measure (Block Designs) and one language measure (Logico-Grammatical Comprehension) were significantly correlated with survival, with better scores predicting longer survival (Table 3). The mean survival of patients with SDAT scoring above the mean on the Block Designs and Logico-Grammatical Comprehension tests was 5.6 years and 4.8 years, respectively, compared with a mean of 3.7 years for patients scoring below the mean (Table 3). Furthermore, the relative hazard for death (derived from the Cox proportional hazards model) was 4.1 times higher for patients scoring 1 SD below the mean on the Block Designs test as compared with patients scoring 1 SD above the mean. The similar relative hazard for death for patients scoring 1 SD below the mean compared with patients scoring 1 SD above the mean on

the Logico-Grammatical Comprehension test was 3.1 times. Taken together, these findings suggest that poor performance on these two tests is associated with significantly shorter survival in SDAT.

Unlike other investigators, we were unable to show that either degree of anomia[8] or memory loss[25] was predictive of survival in SDAT. Knesevich et al[8] reported that anomia on initial evaluation was associated with a more rapidly progressive course in SDAT. However, anomia as measured by a naming test was not a significant predictor of survival in patients with Alzheimer's disease. The only language measure predictive of survival in SDAT was the Logico-Grammatical Comprehension test. This is a test of the comprehension of syntax. The predictive value of this test is consistent with the suggestion of Becker et al[26] that syntactic measures of language may prove more predictive of outcome in SDAT than semantic measures such as vocabulary and naming. Stepwise entry of the significant univariate predictors of survival in Alzheimer's disease into a Cox linear proportional hazards model retained history of hypertension and Block Designs as the two best predictors of survival in Alzheimer's disease (Table 4).

Two demographic variables (higher educational level and female sex) were associated with longer survival in MID. Men with MID had shorter mean survivals than women (3.0 years vs 5.6 years). Some of this sex difference may reflect the fact that the women were evaluated for dementia sooner after onset of their symptoms than the men (3.8 years for women and 4.7 years for men). However, this does not exclude the possibility that there are sex-related differences in the severity of the underlying vascular disease.[27] Better educated patients with MID lived significantly longer. The Cox proportional hazards model suggests that patients with MID with 8 years of education have a relative hazard that is 7.8 times higher than patients with 14 years of education (Table 3). The origin of this effect is uncertain. One possible explanation is that either adherence to medical regimens or access to sophisticated medical care is associated with higher educational attainment. This suggests that control of risk factors could influence survival in MID.[22] Careful studies are needed to determine whether aggressive management of risk factors (eg, heart disease, diabetes mellitus, hypertension) can improve survival in MID. However, it should be noted that none of the usual medical risk factors for stroke (diabetes mellitus, hypertension, heart disease) were found to be predictive of survival in the patients with MID. This may reflect the fact that the patients with MID represent a highly selected group that is already at high risk for vascular disease, hence minimizing the predictive value of the presence of individual medical risk factors. Nonetheless, this observation is not inconsistent with the hypothesis that control of medical risk factors could extend life expectancy in MID.

Cognitive tests were better predictors of survival in MID than in SDAT. Five of the psychological tests were predictive of survival in MID (Logico-Grammatical Comprehension, Total Digits, Naming, Verbal Fluency, and Quick Test), whereas only two of the cognitive tests were predictive of survival in SDAT. One explanation for this finding would be that survival in MID may be related to the severity of vascular disease, and that the degree of a dementia may serve as a marker for the severity of the underlying vascular disease. Contrariwise, survival in SDAT may depend more on rate of progression of the dementia as opposed to absolute degree of dementia. The absolute level of cognitive deterioration as measured at first examination is probably not a good marker for the rate of disease progression in SDAT. It should be emphasized that predicting survival in either SDAT or MID based on a single evaluation is a difficult enterprise. Predictors based on the rate of change of dementia rather than on the absolute degree of dementia may prove more accurate.

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