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Predicting Rate of Cognitive Decline in Probable Alzheimer's Disease

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Recent attempts to identify predictors of rate of decline in Alzheimer's disease (AD) have been extremely variable in choice of outcome variables, predictor variables tested, timing of assessments, and statistical approaches. In this study, a ran-

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dom effects regression model was applied to seek predictors of decline on the Mini-Mental State Exam in 132 patients with probable AD reassessed every 6 months for up to 7.5 years. Potential predictor variables at baseline were of three types: patient characteristics, clinical variables, and cognitive performances. The final multivariate analysis indicated that the following characteristics predicted more rapid cognitive decline: more education, history of dementia in a first degree relative, non-right handedness, better performances on Boston Naming Test, Gollin Incomplete Figures Test, and Benton Visual Retention Test-Delay, and worse performances on Responsive Naming Test, WAIS-R Block Design, and Benton Visual Retention Test-Copy.

For a variety of scientific and social planning reasons, it would be desirable to be able to predict the rate at which the functioning of individual patients with Alzheimer's disease (AD) will deteriorate. Several recent investigations have found that the presence of hallucinations, delusions, behavioral disturbance, and extrapyramidal motor signs predict rapid illness progression (e.g., Mortimer, Ebbitt, Jun, & Finch, 1992; Stern et al., 1994; Chui, Lyness, Sobel, & Schneider, 1994). However, investigations of other predictor variables have yielded inconsistent or conflicting results. For example, rapid illness progression has been reported both for cases with onset at a young age (e.g., Seltzer & Sherwin, 1983; Jacobs et al., 1994) and onset at an older age (Huff, Growdon, Corkin, & Rosen, 1987; Bracco et al., 1994). Still other studies have found no association between age of onset and rate of decline (e.g., Katzman et al., 1993; Mayeux, Stern, & Spanton, 1985). Neuropsychological deficits and other indices of brain dysfunction have also received much attention as potential predictors of illness progression in AD.

Linguistic deficits have often been reported to predict rate of illness progression in AD. For example, Kaszniak et al. (1978) found abnormalities on a sentence production test to be the most robust predictor of death within 12 months. A discriminant analysis by Berg et al. (1984) found that poor performances on an aphasia battery and the Digit Symbol subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) predicted more advanced dementia at 12 month follow-up. More rapid cognitive decline has been predicted by impaired naming in several studies (e.g., Boller, Becker, Holland, Forbes, Hood, & McGonigle-Gibson, 1991; Huff et al., 1987; Knesevich, LaBarge, & Edwards, 1986). However, Becker, Huff, Nebes, Holland, and Boller (1988) found that performance on lexical/semantic cognitive tasks (i.e., word generation, confrontation naming, and paired-associate learning) did not predict rate of cognitive decline. Becker et al. (1988) went on to suggest that impaired syntactic abilities result in deficits in sentence comprehension and written expression, and such deficits are associated with early symptom onset and rapid cognitive decline. Using a multiple regression model, Mortimer et al. (1992) found performance on a verbal test factor (composed of word generation, confrontation naming, verbal recall and recognition, WAIS-R Similarities subtest, and the Token Test) to account for the greatest amount of variance in cognitive decline. The results of Mortimer

et al. (1992) do not, however, indicate whether any specific aspect of verbal dysfunction is predictive of rapid cognitive decline. At least one study has shown that the development of either aphasia or apraxia at any point of the disease appears to predict rapid subsequent cognitive decline (Yesavage, Brooks, Taylor, & Tinklenberg, 1993).

Nonlinguistic cognitive measures have been studied more rarely as potential predictor variables; accordingly, they have been reported to have prognostic value less frequently. However, Drachman, O'Donnell, Lew, and Swearer (1990) found that poor performance on Picture Completion and Digit Symbol subtests of the WAIS-R predicted total dependence in activities of daily living (ADLs), incontinence, and institutionalization. In addition, Mortimer, Ebbitt, and Jun (1991) reported that low scores on a visuospatial factor predicted rapid cognitive and functional decline. However, the same group's later effort (Mortimer et al., 1992) found a nonverbal cognitive factor (i.e., Wepman Visual Discrimination Test, Spatial Orientation Memory Test, Copy-a-Cube, Draw-a-Clock, and WAIS-R Digit Span) to predict functional decline, but not cognitive decline. In summary, of neuropsychological features studied, various aspects of language disturbance appear to be most consistently reported as predictors of rapid cognitive decline, although this finding has not been universal (e.g., Becker et al., 1988).

Other indices of brain dysfunction and illness severity have also been examined in efforts to predict rapidity of cognitive deterioration in AD. The presence of myoclonus and extrapyramidal symptoms (resting tremor, rigidity, bradykinesia) seems to predict a more malignant disease course (Chui et al., 1994; Mayeux, Stern, & Spanton, 1985; Mortimer et al., 1992; Stern et al., 1994). The presence of delusions and/or hallucinations (Chui et al., 1994; Stern, Mayeux, Sano, Hauser, & Bush, 1987), behavioral agitation (Bliwise, Yesavage, & Tinklenberg, 1992; Mortimer et al., 1992), and sleep disturbance (Mortimer et al., 1992) has also been found to predict more rapid progression. However, studies of noncognitive symptoms as predictors of rate of cognitive decline have also had inconsistent results. For example, Mortimer et al. (1992) found extrapyramidal symptoms, hallucinations, and paranoid and delusional ideas to predict rapid functional, but not cognitive, decline in AD patients. In contrast, Drachman et al. (1990) found that extrapyramidal symptoms did not predict time to reach functional endpoints.

Methodological differences across studies may account for much of the inconsistency in the literature. First, the length of time over which patients are studied has often been short and the spacing of assessments unstandardized. Second, illness progression has been operationalized using a number of methods, only some of which consider the varying number of data-collection observations. Change in patient status at follow-up (Berg et al., 1984; Kaszniak et al., 1978) or dividing the difference between first and last test scores by a unit of time (Katzman, 1993; Huff et al., 1987) are typical indices of illness progression. There has been a trend in the recent literature to summa-

rize change in test performance over time with the slope of a regression line through each subjects' serial cognitive test scores (e.g., Ortof & Crystal, 1989; Mortimer et al., 1992; Yesavage, Brooks, Taylor, & Tinklenberg, 1993). Third, different statistical methods have been applied to study the association between potential predictor variables and the operational measure of decline such as comparison of means (Kazniak et al., 1978; Mayeux, Stern, & Spanton, 1985), survival analysis (Chui, Lyness, Sobel, & Schneider, 1994), discriminant function analysis (Berg et al., 1984), and multiple regression analysis (Mortimer et al., 1992). Even among the studies employing multiple regression analysis, the technique has been used differently. For example, Mortimer et al. (1992) weighted each subject's estimate of the rate of decline in a regression model by a measure of the precision (standard error) of the estimate. This may make comparison of their results with the results from nonweighted regression analyses difficult. Fourth, although potential predictor variables may share names across studies, this does not mean that they have been measured in the same way. For example, extrapyramidal symptom ratings have come from scores on a standardized neurological examination (e.g., Stern et al., 1987), have been coded as absent or present (i.e., Mortimer et al., 1992), have meant the presence of a single sign (i.e., cogwheel rigidity; Chui et al., 1994), and have been disregarded entirely if neuroleptic medications were thought to be responsible (e.g., Chui et al., 1994; Stern et al., 1994). Prior research has varied in the variables considered; some studies may have failed to find important relationships by focusing on only one or two predictor variables, while other studies considered the interrelatedness of many variables. Finally, clinical study samples are likely to vary in their stage of illness and may include up to 20% non-AD dementia cases (Galasko et al., 1994; Morris, McKeel, Fulling, & Torack, 1988). The conflicting literature is not surprising given these great variations in methodology.

The current study sought to overcome some of the limitations of the prior research in the area of predicting rate of cognitive decline in AD. The prognostic value of a number of potential predictor variables using a random effects regression model in a cohort of 132 patients with probable or definite AD examined every 6 months is reported here. The random effects regression model is ideally suited for this purpose because it allows patients to begin at different levels of dementia and uses all of the data which reduces error associated with summarizing longitudinal data points. Thus, the present study reports the findings from an improved statistical method considering a wide variety of predictor variables in AD patients evaluated at regular intervals for up to 7.5 years with few non-AD cases.

METHODS

Subjects

Between November 1984 and March 1987, the Johns Hopkins Alzheimer's Disease Research Center (ADRC) enrolled for longitudinal study 210 patients who met NINCDS-

ADRDA criteria for probable or possible AD (McKhann et al., 1984). A complete medical history, neuropsychological evaluation, neurological and psychiatric examinations, and appropriate laboratory studies were all part of the initial evaluation prior to entry into the ADRC. Exclusion criteria were current or past history of major mental illness, current alcohol or drug abuse, or central nervous system disorder (e.g., stroke, epilepsy, severe traumatic brain injury, Parkinson's disease). Extrapyramidal signs insufficient to diagnose Parkinson's disease or marked behavioral disturbance did not exclude entry into the study. Procedures were fully explained to the subjects and their guardians and informed consent was obtained before enrollment. At each semiannual visit to the ADRC, interim histories were taken and neurological examination and neuropsychological testing repeated. This information was used to monitor each patient's disease course and to determine whether clinical diagnoses should be reconsidered.

Data from 132 ADRC participants were used in the present analysis of predictors of cognitive decline. These 132 subjects were selected from the cohort by virtue of meeting two criteria: (1) they met clinical criteria for probable AD at entry and at every subsequent semiannual evaluation, and (2) they obtained a score of 10 or higher on the Mini-Mental State Exam (MMSE) at entry into the ADRC. The sample consisted of 84 women and 48 men; 114 Caucasians and 18 African-Americans. Mean age at entry was 70.09 years ($SD = 8.25$), and average age at symptom onset was 66.39 years ($SD = 8.42$). The sample had a mean of 12.66 years of education ($SD = 3.71$). Average MMSE score at entry was 16.73 ($SD = 3.97$). These 132 patients were evaluated an average of 6.57 times ($SD = 3.47$) at 6-month intervals (range, 1 to 16 visits). Thus, the present data reflect an average of 2.5 years (and as many as 7.5 years) of disease progression.

Procedures

MMSE scores at entry and each return visit were used as the outcome measure. MMSE scores for each subject were considered valid until one of the following occurred: (1) a score of zero was reached; (2) the patient had two missing data points.

Potential predictors of decline were of three main types:

(1) Patient Characteristics: sex (male/female), race (white/black), education (years), age at study entry, estimated age at illness onset, estimated illness duration at entry (years), handedness (right handed/not right handed), history of dementia in a first-degree relative (yes/no).

(2) Clinical Variables at study entry: MMSE score, Rating Scale for Extrapyramidal Symptoms score (DiMascio, Bernardo, Greenblatt, & Marder, 1976), the presence of delusions (yes/no), presence of hallucinations (yes/no), Hamilton Depression Scale score (Hamilton, 1967), and the Psychogeriatric Dependency Rating Scale scores (Orientation, Behavior Disturbance, and Physical Capacity subscales; Wilkinson & Graham-White, 1981).

(3) Cognitive Performance at study entry: Block Design subtest of the WAIS-R, Spatial Delayed Recognition Span Test, Benton Visual Retention Test (BVRT; Copy and 10-sec delay), Responsive Naming Test, Boston Naming Test, Category Fluency, Token Test, and Gollin Incomplete Figures Test. This cognitive test battery and the cohort's longitudinal performance on it are described in detail in Rebok, Brandt, and Folstein (1991).

Statistical Analysis

Analysis of longitudinal data requires some special considerations. Longitudinal data are considered correlated because each individual in the study contributes multiple data points (Diggle, Liang, & Zeger, 1994). A random effects regression model predicting the trajectory of MMSE score over time was used to take into account this correlation (Laird & Ware, 1982). This regression model included a random intercept term for each individual (i.e., baseline MMSE score), covariates measured at baseline (predictor variables), follow-up visit number,

and interaction term between the visit number and the covariates. A significant interaction term indicates that a covariate significantly predicted the decline of MMSE scores over time.

First, a series of analyses was performed to examine the effects of a single covariate on MMSE score over follow-up visits. This was based on a random effects model that included the covariate at baseline, visit number, and an interaction term between the visit number and the covariate. Next, all covariates were considered simultaneously to identify a subset of variables that together predicted rates of decline. This was based on a multiple regression analysis with random effects. The multiple regression included all covariates that had strong associations ($p < .10$) with either MMSE at visit 1 or MMSE decline over visits, as revealed by the univariate analyses. Finally, a series of regression models was fit to the data by removing nonsignificant covariates one at a time. The random effects model was fit using the Statistical Analysis System (SAS, Proc Mixed). Because of the great number of analyses performed, only results with $p < .01$ were considered significant.

RESULTS

Univariate Analyses

Several patient variables at entry were significantly associated with change in MMSE score over the follow-up period. Tables 1a–1c show the results of the univariate analyses grouped by predictor type (Patient Characteristics, Clinical Measures, and Cognitive Performance). Each table lists the rate of decline associated with different values of the covariates (predictor variables). For dichotomous variables, the two possible values are listed. For

TABLE 1

Results of Univariate Analyses for Different Classes of Potential Predictors of Rate of Cognitive Decline in Probable AD: (1a) Patient Characteristics, (1b) Clinical Measures, and (1c) Neuropsychological Performance

a. Patient characteristics

Patient Characteristic[a]	Value	MMSE change/visit	*p* value
Sex	Male	−1.49	
	Female	−1.42	.41
Race	White	−1.46	
	Black	−1.37	.34
Education	10 years	−1.36	
	16 years	−1.64	<.001
Age at entry	65	−1.56	
	75	−1.33	<.001
Age of onset	60	−1.61	
	70	−1.37	<.001
Illness duration at entry	2 years	−1.36	
	5 years	−1.56	.006
Handedness	Right	−1.43	
	Not Right	−2.25	.003
Family history of dementia	No	−1.36	
	Yes	−1.58	.005

TABLE 1—*Continued*

b. Clinical measures

Clinical Measure[b]	Value	MMSE change/visit	*p* value
MMSE at entry	10	−1.33	
	20	−1.46	.25
Delusions	No	−1.42	
	Yes	−1.56	.15
Hallucinations	No	−1.44	
	Yes	−1.89	.02
Extrapyramidal signs	0	−1.43	
	3	−1.62	.30
PGDRS-Orientation	0	−1.38	
	5	−1.63	.21
PGDRS-Behavioral Disturbance	1	−1.34	
	6	−1.62	<.001
PGDRS-Physical Capacity	1	−1.37	
	7	−1.63	.01
Hamilton Depression Scale	2	−1.52	
	8	−1.33	.01

c. Neuropsychological performance

Cognitive Measure	Value	MMSE change/visit	*p* value
30 Item Boston Naming Test	7	−1.27	
	22	−1.54	<.001
Category Fluency (total correct)	10	−1.42	
	25	−1.45	.77
Spatial Delayed Recognition Span	2	−1.68	
	6	−1.38	<.001
Gollin Incomplete Figures Test	3.7	−1.38	
	2.4	−1.54	.002
WAIS-R Block Design	0	−1.56	
	12	−1.39	.006
Benton Visual Retention Test-Copy	0	−1.49	
	9	−1.41	.37
Benton Visual Retention Test-Recall	0	−1.31	
	1	−1.50	<.001
Responsive Naming Test	6	−1.42	
	12	−1.46	.58
Token Test	123	−1.57	
	149	−1.39	.004

Note. MMSE change/visit reflects change on Mini-Mental State Exam per 6-month visit for the two alternatives of dichotomous variables and for selected values of continuous variables (25th and 75th percentiles). *p* values reflect the significance of the association between the variable and MMSE score over time.

[a] Sex, race, handedness, and family history of dementia were dichotomous variables; all others were continuous variables.

[b] Hallucinations and delusions were coded as present or absent; all others were continuous variables.

TABLE 2
Multivariate Predictors of Rate of Decline on MMSE

Variable	Definition	β	SE
Handedness	Left/Ambidextrous = 1 Right = 0	−0.773	0.215
Family Hx of Dementia	Yes = 1 No = 0	−0.221	0.073
Education	Years of Education	−0.037	0.008
Boston Naming Test	Total Correct	−0.075	0.009
Gollin Incomplete Figures	Average of 3 Trials	0.179	0.051
WAIS-R Block Design	Raw Score	0.017	0.005
BVRT-Copy	Total Correct	0.070	0.013
BVRT-Recall	Total Correct	−0.344	0.060
Responsive Naming Test	Total Correct	0.174	0.021

Note. The variables listed had interaction terms over time that were significant at $p < .01$. β reflects the change in rate of decline on MMSE per 6 months per unit change of each variable holding all other variables constant. The rate of decline when all variables are equal to zero (the ''intercept'') was −2.213 (SE = 0.258) points per 6-month period.

continuous variables, the integer value closest to the lower and upper quartiles for the study sample is listed.

Table 1a shows that more years of education, younger age at entry, earlier age of onset, longer illness duration, non-right-handedness, and history of dementia in a first-degree relative independently predicted more rapid decline on the MMSE. Table 1b shows that greater behavioral disturbance at entry to the study predicted more rapid decline on the MMSE. Table 1c shows that better performance on Boston Naming Test, Gollin Incomplete Figures Test (lower score indicates better performance), and BVRT 10-sec delay and worse performance on Spatial Delayed Recognition Span Test, Block Design, and Token Test predicted more rapid subsequent decline on the MMSE.

Multivariate Analyses

Results of the backward stepwise multivariate analysis are listed in Table 2. The intercept value of −2.212 indicates that, overall, patients' MMSE scores declined 2.212 points per 6-month interval (before considering the effects of any predictor variables). The variables listed in Table 2 are those which were found to significantly alter rate of decline on the MMSE ($p < .01$) when all independent variables were considered simultaneously. Variables with a negative coefficient add to the rate of decline, while those with a positive coefficient contribute to a slower rate of decline. Thus, more rapid decline would be predicted in patients who have the following characteristics: non-right-handedness, family history of dementia, more education, better performance on the Boston Naming Test, Gollin Incomplete Figures Test (lower score indicates

TABLE 3

Illustration of the Relative Influence of Sample Values (x) of Significant Predictor Variables on the Predicted Rate of Decline per 6 Months on the MMSE (βx), Defined as the Product of the Regression Coefficient (β) and the Covariate Sample Value (x)

		Sample Values A		Sample Values B	
Covariate	β	x (Value)	βx (Decline)	x (Value)	βx (Decline)
Intercept			−2.212		−2.212
Handedness	−0.773	0	0.0	1	−0.773
Family Hx of Dementia	−0.221	0	0.0	1	−0.221
Education	−0.037	10	−0.370	16	−0.592
Boston Naming Test	−0.075	22	−1.650	7	−0.525
Gollin Incomplete Figures	0.179	2.4	0.429	3.7	0.662
WAIS-R Block Design	0.017	12	0.204	0	0.0
BVRT-Copy	0.070	9	0.63	0	0.0
BVRT-Recall	−0.344	1	−0.344	0	0.0
Responsive Naming Test	0.174	12	2.088	6	1.044
Predicted Estimate of Rate of Decline			−1.225		−2.621

Note. Sample Values A are at the 75th percentile for all neuropsychological variables, the 25th percentile for education, and the more desirable of the two possible values for dichotomous variables. Sample Values B, are at the 25th percentile for all neuropsychological variables, 75th percentile for education, and the less desirable of the dichotomous values.

better performance), and BVRT-Delay, and poor performances on WAIS-R Block Design, BVRT-Copy, and Responsive Naming Test.

At the time of this analysis, APO-E genotype was available for 29 of the 132 subjects. The final multivariate model was tested on these 29 subjects with APO-E genotype included (presence or absence of allele 4). The presence of allele 4 did not significantly predict rate of decline and most of the other variables remained significant despite the reduced statistical power.

Table 3 illustrates the relative influence of selected values for the significant predictor variables on the predicted rate of cognitive decline. Sample values (at the 25th and 75th percentiles, or the two possible values for dichotomous variables) were entered into the regression equation derived from the multivariate analysis. Overall, the Sample Values A (75th percentile or the more desirable of the two possible values for dichotomous variables) predict decline of 1.225 points per 6 months on the MMSE (95% CI = 1.091 to 1.359). In contrast, Sample Values B (25th percentile or the less desirable of the two values of dichotomous variables) predict decline of 2.617 points per 6 months on the MMSE (95% CI = 2.166 to 3.068). The values listed under βx are the product of the regression coefficient β and the covariate value x and illustrate the relative influence of each variable on rate of decline when representative values in appropriate units are entered into the regression equation. The values in those columns indicate that performance on

the Boston Naming and Responsive Naming Tests appears to most strongly influence subsequent rate of decline on the MMSE.

The accuracy of this model in predicting rate of decline was assessed by comparing the predicted rate of decline, calculated as illustrated in Table 3, with the observed rate of decline. The observed rate of decline was summarized by the slope of a regression line through each subject's MMSE scores. On average, the rate of cognitive decline predicted by the regression model underestimated the observed rate of decline by 11.54%, or 0.31 points per 6 months.

DISCUSSION

Many of the findings of this study are consistent with trends in the existing literature, while others are not. Several patient characteristics were found to predict more rapid cognitive decline in univariate analyses. Earlier age at symptom onset (e.g., Jacobs et al., 1994) and longer duration of illness (e.g., Berg et al., 1984) have been associated with more rapid cognitive decline in prior studies. The association between non-right-handedness and a severe course of illness has been reported less often (e.g., Seltzer & Sherwin, 1983), but the inverse has never been reported. A family history of dementia has been linked indirectly to rapid illness progression (Heston, Mastri, Anderson, & White, 1981; Luchins et al., 1992) and reported for patients with symptom onset after 65 years of age (Burns, Jacoby, & Levy, 1991). Many studies using standardized measures of rate of decline have either not included family history of dementia as a potential predictor variable or not found an association with illness progression. However, sample sizes in some of those studies have been small (e.g., 54 patients in Ortof & Crystal, 1989; 42 patients in Drachman et al., 1990) and insufficient statistical power may account for the negative findings. Our preliminary findings that APO-E genotype does not predict rate of decline nor account for the influence of family history of dementia on rate of decline may also be due to low statistical power. This issue is currently being pursued in a full-scale study among this population.

The observation that greater education predicts more rapid decline has been reported previously in an abstract by Mortimer et al. (1991). A similar trend ($p = .06$) was reported in Katzman et al. (1988), although the strength of the relationship was very low. In the present study, education was a significant predictor of decline in both the univariate and multivariate analyses. At first, this finding may seem to contradict the recent reports that education exerts a protective effect against dementia and AD (Katzman, 1993; Stern et al., 1994). However, there is good reason to believe that the detection of dementia in highly educated people is delayed until the disease is more advanced (Friedland, 1993; Stern, Alexander, Prohovnik, & Mayeux, 1992). As evidence, Stern et al. (1992b) found lower temporoparietal cerebral blood flow in patients with more education when dementia severity was controlled.

Thus, unambiguous dementia in a person with high education may indicate a relatively advanced stage of neuropathology. Therefore, our finding that higher education predicted more rapid cognitive decline is consistent with the notion that signs of advanced disease predict rapid subsequent decline (e.g., Drachman et al., 1990). Measures of cognitive performance may underestimate ''how far'' the disease has progressed in patients with high premorbid cognitive ability.

Of the clinical variables studied, the most significant predictor of decline was greater behavioral disturbance. This has also been reported by several other investigators (Mortimer et al., 1992; Stern et al., 1994; Chui et al., 1994). Higher scores on the Behavior subscale of the PGDRS (e.g., the presence of wandering, aggression, delusions, and/or hallucinations) may be an index of disease severity that is less sensitive to level of premorbid function. There was a strong trend ($p = .02$) for hallucinations alone at study entry to predict more rapid decline over time, as others have reported (Mortimer et al., 1992; Stern et al., 1994; Chui et al., 1994). We found little relationship between delusions or extrapyramidal signs and rate of cognitive decline. These findings should be interpreted with caution because previous investigations have used more rigorous methods for measuring these two variables. A unique finding in our study was the trend for less severe depression at baseline to predict more rapid cognitive decline ($p = .01$). This may be an artifact of our subsequent treatment of depression; patients with more depressive symptoms at entry would more likely be treated with antidepressant medications and may show a slight improvement, or apparent plateau, in cognitive function.

It is important to note that no clinical measure and only three patient characteristics (education, handedness, and family history of dementia) emerged as significant in the multivariate analysis. Thus, those variables that dropped out must share variance with one or more of the variables that were retained in the multivariate model. For example, when age of onset was forced into the multivariate model in place of family history of dementia, it was significant but with a smaller effect size than family history of dementia. Thus, the variance in rate of decline that was accounted for by age of onset may have been better explained by family history of dementia. It is possible that other combinations of variables may have similar interrelationships. Failure to understand or control for such interrelationships may account for some of the inconsistent findings among published studies.

Several tests of language processing were found to predict a severe disease course. Rapid cognitive decline was associated with poor performance on the Token Test, but better performance on Boston Naming Test in univariate analyses. In the multivariate analysis, better performance on the Boston Naming Test, and poor performance on the Responsive Naming Test emerged to predict a faster rate of cognitive decline. This is opposite of the previous finding that poor performance on the Boston Naming Test predicts

rapid illness progression in AD (e.g., Knesevich et al., 1986). However, these findings are in some ways consistent with the hypothesis that lexical/semantic impairment involved in word production (i.e., Boston Naming Test, Controlled Oral Word Association) is unrelated to age of onset or progression of symptoms, while syntactic impairment (i.e., Responsive Naming, Token Test) may be associated with earlier onset and more rapid cognitive decline (Becker et al., 1988). Such a relationship may also be indicated by the results from an earlier cross-sectional analysis of data from some of the present patients. Brandt et al. (1989) reported that Boston Naming Test score was negatively correlated with disease duration among patients with early onset but not among those with late onset.

Performance on non-verbal tests also predicted rate of decline. In the univariate analyses, rapid cognitive decline was associated with poor performance on Spatial Delayed Recognition Span and Block Design, but better performance on the recall condition of the Benton Visual Retention Test and the Gollin Incomplete Figures Test. Spatial Delayed Recognition Span did not emerge in the multivariate analysis, although poor performance on Block Design, BVRT-Copy, and better performance on BVRT-Recall and the Gollin Test did. This set of results is consistent with the previous finding that rapid cognitive decline is predicted by the presence of apraxia (Yesavage et al., 1993). The Gollin Test involves naming pictures that have been perceptually degraded. Therefore, it is, in a sense, a confrontation naming test with greater involvement of visuospatial abilities; hence, this finding can be seen as consistent with that on the Boston Naming Test.

The statistical model employed in this study offers several advantages over other methods. Many prior experiments have calculated rates of change per month over unstandardized intervals and/or for short or variable follow-up intervals. Some studies (i.e., Mortimer et al., 1992; Jacobs et al., 1994) have dealt with this limitation by weighting subjects by an estimate of the accuracy of the calculated rate of decline (i.e., inverse of the standard error of measure). In the present study, reevaluations were performed every 6 months for up to 7.5 years. The random effects regression model assessed the interaction of the covariate (i.e., predictor variable) on the outcome measure (i.e., MMSE score) over time. Thus, this model eliminates the need to calculate an estimate of rate of decline, and subjects with more serial measurements contribute more observations to the model. This method has been used previously by Bliwise et al. (1992) in their study reporting more rapid cognitive decline among patients with afternoon, evening, or nocturnal exacerbation of disruptive behavior. The use of both univariate and multivariate analyses suggested some complex relationships that are often not considered in the literature and may contribute to the conflicting results reviewed in the Introduction.

Recent evidence suggesting that rate of decline varies at different points in the course of illness (e.g., Morris et al., 1988; Stern et al., 1994) may prompt some to question the use of a linear model. However, the present study found that baseline MMSE score did not predict rate of subsequent

decline. Katzman et al. (1988) found that only the most severely demented (excluded from this study sample) showed a slower rate of subsequent decline and attributed the finding to a floor effect. Furthermore, the non-linear trend appears to be small and linear models seem to provide the best fit to longitudinal cognitive data in AD (Stern et al., 1992a). However, there is sure to be some variability in rate of cognitive decline that is not captured by any type of statistical model. That is, unforeseeable events during the course of illness may serve to alter what would have been a steady, gradual cognitive decline. Thus, even the best statistical model cannot predict when a patient might experience medication-induced delirium or a serious medical illness. Concurrent events during the course of illness may be just as important as initial patient characteristics and have been largely ignored in the literature to date.

Finally, data contamination by non-AD cases is always possible when relying on the clinical diagnosis of AD. For example, 73% of the possible and probable AD patients used by Mortimer et al. (1992) who came to autopsy had AD confirmed neuropathologically (11 of 15 cases). In the cohort from which the present subjects were drawn, 93% of the patients who met criteria for possible or probable AD throughout the course of their illness had AD confirmed at autopsy (Rasmusson et al., in press). We would expect a similar or higher rate of case confirmation among the subjects in this study because they met criteria for probable AD on all reassessments.

In conclusion, the present study used an improved statistical approach to search for predictors of rate of decline in a large group of well-studied probable AD patients. Several predictors were uncovered, and many appeared to be interrelated. Left-handedness, family history of dementia, and more years of education were characteristics predictive of more rapid cognitive decline in AD. In terms of cognitive characteristics, poor visuospatial construction and naming to description, but good naming to confrontation, predicted more rapid cognitive decline. Future research into the determinants of disease course may continue to improve our understanding of the natural history of AD, our ability to evaluate treatment effects, and our ability to give accurate prognoses to caregivers.

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