'How Far' vs 'How Fast' in Alzheimer's Disease

The Question Revisited

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Objective: To expand on a recent study of 42 patients with probable Alzheimer's Disease that found that the only significant predictors of certain clinical end points were the degree of severity features at entry ("how far").

Design: A case series study of a cohort of 81 patients with Alzheimer's disease that used survival analysis methods similar those of the previous study but included a new technique for calculating rate of progression ("how fast") as well as entry characteristics ("how far").

Setting: A university medical center and its affiliated Veterans Affairs Medical Center.

Patients: All patients with probable and definite Alzheimer's disease studied at the Aging Clinical Research Center at Stanford University, Palo Alto, Calif, in the years 1981 and 1992 who met the following criteria: a mild to moderate level of severity of the disease (Mini-Mental State Examination score of 15 or above) at entry into the study and a minimum of three test points spaced approximately 6 months apart (to allow estimation of rate of progression). A total of 81 such patients were identified. These patients had been followed up for a mean of 4.53 ± 2.3 years, with a range of 1.0 to 14.5 years.

Main Outcome Measure: The outcome measure was the average rate of decline on the Mini-Mental State Examination.

Results: The results of our study replicated a previous finding that the degree of severity is a strong predictor of time course, but in addition we found that the rate of progression also appears to be a strong predictor of clinical course.

Conclusion: There appears to be substantial heterogeneity in the rate of progression in patients with Alzheimer's disease, and, like initial degree of severity, rate of progression appears to be a strong predictor of clinical course.

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DRACHMAN ET al[1] presented a new perspective in their article, "The Prognosis in Alzheimer's Disease: 'How Far' Rather Than 'How Fast' Best Predicts the Course." They studied 42 patients with probable Alzheimer's disease (AD) during a period of 10 to 130 months (mean, 54 ± 25 months) and examined three types of potential prognostic features measured at entry to the study: degree of severity (eg, IQ scores); variable clinical features (eg, extrapyramidal signs [EPSs]); and individual distinguishing features (eg, gender, education, and age). The power of these factors to predict prognosis was assessed by means of the Kaplan-Meier life table method and the Cox proportional hazards model. Three clinical end points were used: total dependence in activities of daily living; incontinence; and institutionalization. They found that at entry the only significant predictors of these clinical end points were the degree of severity features. They concluded that the initial degree of severity ("how far") rather than historical rate of progression ("how fast") predicts the time to clinical end points.

However, their conclusions (as they pointed out) were based on the assumption

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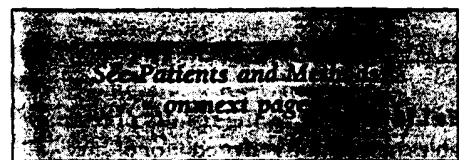
PATIENTS AND METHODS

PATIENTS

All patients with probable and definite AD studied at the Aging Clinical Research Center at Stanford University, Palo Alto, Calif, in the years 1981 and 1992 who met the following criteria were included in this study: a mild to moderate level of severity of the disease (Mini–Mental State Examination [MMSE] score, ≥15) at entry into the study and a minimum of three test points spaced approximately 6 months apart (to allow estimation of the rate of progression). A total of 81 such patients were identified. These patients had been followed up for a mean of 4.53 ± 2.3 years, with a range of 1.0 to 14.5 years.

The descriptive statistics for these patients are presented in **Table 1**. These descriptors include an assessment of clinical severity at entry (MMSE), assessments of clinical features at entry (aphasia, anxiety, EPSs, psychosis, depression, duration, age at onset), and individual distinguishing features (family history, gender, education). The sample seems generally comparable with that of Drachman et al with the exception of the gender distribution. The Drachman et al sample was approximately equally male and female; the present sample was predominantly (67%) female. However, Drachman et al detected no significant gender effect in prognosis, and hence this disparity would not be expected to change the results.

MEASURES

Throughout this study, the MMSE was used to characterize severity. The MMSE is a multi-item assessment that can be reliably and consistently used to make sensitive discriminations between the patients.[2] Eligibility required entry levels of at least 15 to ensure a mild to moderate level of disorder at entry. This is comparable with the severity at entry in the Drachman et al study, which reported a mean clinical severity score (on a four-point scale) of 2.4, where 2 indicated "mild impairment" and 3 "moderate impairment while still independent in basic self-care activities." The entry level of MMSE was used to characterize severity at entry for the subjects in this group. Finally, the clinical end point was defined as the first of any two consecutive MMSE scores of 0.

We have not included the time of institutionalization as a clinical end-point measure, for in this geographic area, institutionalization appears to be primarily dictated by the community and financial resources available to the family of the patients, rather than by the clinical disability of the patients. We have also not included time at which incontinence occurs as an end-point measure, because of the poor reliability of this measure and the inconsistency across families in what they characterize as "incontinence."

We believe it important to use a single, reliable, consistent, and sensitive measure of severity, such as the MMSE, throughout the study, both to ensure the quality of the dependent and independent variables (important in avoiding both type I and type II error) and to avoid problems in in-

that whatever interindividual differences there may be in the rate of progression are largely random variation, an assumption still viable because of the conflicting results in the research literature. Since the only measure of rate of progression in their study was retrospective, their data analysis approach could neither confirm nor disconfirm that crucial assumption. They suggested that any future claim of clinical significance for the rate of progression "would require clear evidence that the severity of AD has been adequately taken into account," and they pointed out, "Whether differences in the rate of progression represent random variations or specific differences in either the disease process or the host vulnerability remains uncertain at present."[1(p856)]

Thus, Drachman et al posed a challenge important both to clinical and research assessment of patients with AD. The following study attempted in independent analyses not only to replicate the Drachman et al study but also to repeat the same analysis on patients over time, in which both entry characteristics and subsequent rate of progression are considered.

RESULTS

Table 3 presents the results of testing each of the variables in isolation as a predictor of survival to the end point,

listed in order of the magnitude of the test statistic and hence of the P level. At entry, in order of statistical significance, the best single predictors were MMSE at entry, aphasia, anxiety, and EPSs at entry; subsequent rate of progression over time was superior to any predictor at entry.

The results of the multivariate analysis ignoring rate of progression, comparable with that done by Drachman et al, indicated that the variable with the greatest predictive power was indeed the "how far" measure (MMSE at entry). Presence of aphasia, EPSs, and anxiety at entry added significant predictive power.

However, the results of the second multivariate analysis in which the subsequent rate of progression was included indicated that the measure with the greatest predictive power was the rate of progression measure; thus, "how fast," not "how far," was the strongest predictor. Anxiety, aphasia, and EPSs continued to add significant predictive power. However, the rate of progression was a better prognostic factor than was MMSE at entry, and once rate of progression was taken into consideration, MMSE at entry did not add significant predictive power.

Thus, both "how far" and "how fast" appear important in prognosis, but "how fast" seems more important

terpreting inconsistent results that might result when different measures of severity are used that might not measure exactly the same characteristic.

Table 2 presents descriptive statistics from our entire database of observations (N=612), showing the clinical differences between patients seen with an MMSE score of 15 or greater (comparable with the eligible group in this study), those patients with an MMSE score of 0 (comparable with those at or past the end point), and those in the intermediate group. It can be seen that decreasing MMSE scores were systematically correlated with other clinical features and that an MMSE score of 0 is indicative of severe deterioration in terms of the Global Deterioration Scale (measures on a seven-point scale) and in terms of presence of symptoms. It should be particularly noted that when the MMSE score is at least 15, only 1% of patients are incontinent, whereas when the MMSE score is 0, 80% are incontinent. Thus, an MMSE score of 0 seems to be a reasonable clinical end point.

Other measures included in the analyses were reported duration of illness at entry; the presence or absence of specific signs and symptoms, including depression, anxiety, psychosis, EPSs, and aphasia; family history; reported age at onset; education; and gender. These were reported by means of the State of California Alzheimer's Disease Centers uniform methods listed in Table 1. Education was measured on a seven-point scale.

To develop a measure of rate of progression, the MMSE scores were converted to proportions by dividing each patient's score by the maximum MMSE score of 30. The average rates of decline were computed by regressing the converted MMSE score on the time (in years) since the patient entered the study; the resulting regression coefficient provides an estimate of the average rate of subsequent decline during the period studied. Because the unit of time was years and the MMSE scores were proportions, the average rate of decline may be expressed as the percentage of the total score by which a patient changed per year. Thus, for example, if a patient's average rate of decline were −0.13, this would mean that the patient declined an average of 13%, or 3.9 points, per year. This method is described in detail in other publications.[3]

ANALYSIS

We used the same plan of analysis as that described in the Drachman et al study. We used the Cox proportional hazards model[4] with the clinical end point of an MMSE score of 0, first using all the variables in Table 1 individually (ie, using each one alone and ignoring the rest). Then we used a stepwise procedure ($P<.05$, one tailed, to enter) to identify which of those variables, omitting only rate of progression ("how fast"), jointly predicted survival, and finally a second stepwise procedure to identify which of those variables, now including both "how far" and "how fast," jointly predicted survival.

Kaplan-Meier survival[5] curves were used to describe the effect sizes of the statistically significant predictors.

than "how far" in determining the prognosis when one restricts subjects to those with relatively early stages of the illness. It should be noted that early onset of aphasia was not included in the Drachman et al study. However, we have shown in independent samples that early onset of aphasia is an important predictor of course.[6] It should also be noted that, while anxiety and EPSs were included in the Drachman et al study, they were not found to be statistically significant. Since the present sample is almost twice as large as that in the Drachman et al study (81 vs 42), this finding may reflect the increased statistical power in this study. On the other hand, it may also be due to different methods of assessing the presence of symptoms.

The survival curve for the entire group is presented in **Figure 1**. Its shape suggests strongly that this is a situation with increasing, not constant, hazard. Overall, the median survival was 6.5 years, with the 25th percentile at 5.0 years and the 75th percentile at 8.5 years.

Figure 2 shows the four survival curves created by dichotomizing the severity at entry and the rate of progression, each at their medians. Those patients with an MMSE score greater than 20 at entry and a slow rate of progression have a median survival time of approximately 9.5 years, whereas those who at entry had an MMSE

Table 1. Patient Characteristics (N=81)	
Characteristic	**Median, SD or %**
Rate of progression	−0.102 ± 0.076
MMSE at entry*	21 ± 3.9
Duration, y	4.1 ± 2.3
Age at onset, y	62 ± 12.3
Education (7-point scale; 5=college degree)	2
Early-onset aphasia, %	
Early-onset anxiety, %	30
No early-onset aphasia, %	
Early onset of both aphasia and anxiety, %	33
Early onset of aphasia without anxiety, %	30
Early-onset extrapyramidal signs, %	
Early-onset psychosis, %	19
Early-onset depression, %	22
Family history, %	35
Gender, % M	33

*MMSE indicates Mini–Mental State Examination.

score less than 21 and a fast rate of progression had a median survival time of approximately 4.5 years. Those in the intermediate groups had a median survival time of approximately 6 years.

Table 2. Comparison of All Observations Taken in All Patients Seen at End Point, Intermediate, and Entry Levels of MMSE (N=612)*

	MMSE		
	0	1-14	15-30
Duration, y	8.1±2.9	6.5±3.8	5.5±4.5
Global deterioration scale	6.5±0.4	5.5±0.6	4.0±0.7
MMSE	0.0±0.0	8.2±4.2	20.7±3.9
Psychosis, %	50	36	12
Agitation, %	63	41	11
Depression, %	11	12	18
EPS, %	7		
Aphasia, %	100	95	54
Anxiety, %	34	63	38
Incontinence %	80	25	1

*MMSE indicates Mini–Mental State Examination; EPS, extrapyramidal signs.

Table 3. Predictors of Decline*

	Marginal†	Analysis 1,‡	Analysis 2,‡
	χ^2	Cumulative χ^2	Cumulative χ^2
Rate of MMSE decline	30.7§	Excluded	30.7 (1)§
MMSE at entry	17.5§	17.5 (1)§	
Aphasia	13.4§	22.9 (2)§	35.7 (3)§
Anxiety	4.3‖	27.0 (4)§	32.9 (2)§
EPS	3.4	26.1 (3)§	37.1 (4)§
Duration of illness	1.1		
Psychosis	0.7		
Family history	0.4		
Depression	0.4		
Gender	0.3		
Age at onset	0.2		
Education	0.0		

*MMSE indicates Mini–Mental State Examination; EPS, extrapyramidal signs.

†Test statistic χ^2, df=1, for the hypothesis that each factor (excluding the other) predicts survival.

‡Sequential tests in the stepwise forward procedure. Each tests the hypothesis that the factor adds predictive value to those previously entered. Order of entry is indicated in parentheses.

§$P<.001$.

‖$P<.05$.

Figure 1. Survival function estimates for the entire sample (N=81).

Figure 2. Survival function by severity at entry and rate of progression. A indicates entry Mini–Mental State Examination score less than 21 and fast progression (n=14); B, entry Mini–Mental State Examination score less than 21 and slow progression (n=17); C, entry Mini–Mental State Examination score greater than 20 and fast progression (n=17); and D, entry Mini–Mental State Examination score greater than 20 and slow progression (n=33).

COMMENT

Drachman et al[1] raised important questions about the methods of research in AD. We confirmed their conclusion that "how far" is a significant prognostic indicator. Since an assessment of rate of progression is never available at entry to a research study or to a clinic, a measure of "how far" combined with certain signs and symptoms is the only available prognostic index at entry, and clearly an important one. Thus, we agree with Drachman et al that on initial examination of patients with AD at en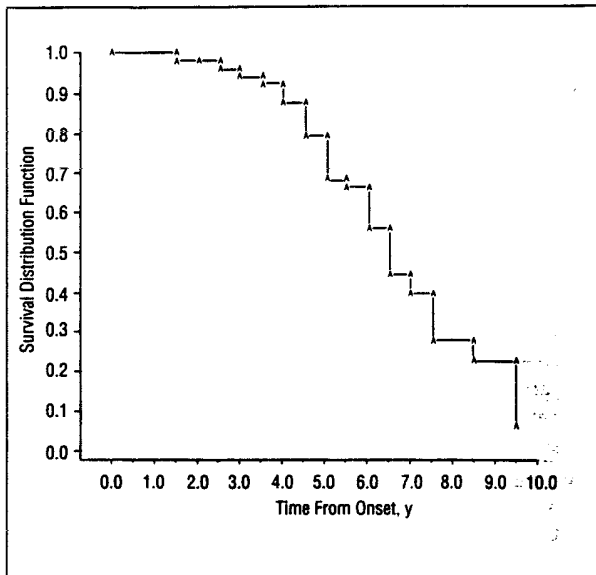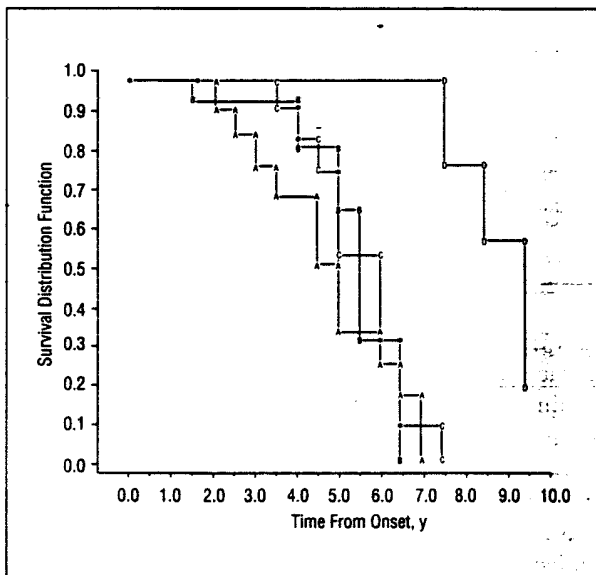try, no clinical or personal feature predicts the future progression as well as measures that reflect the severity of the disease at that time.

However, our results indicate that, given both types of information, that on "how far" and that on "how fast," prognosis appears to be better predicted by the rate of progression ("how fast") than by the clinical status at entry ("how far"). Therefore in such research applications as efforts to delineate subtypes of disorder, or to evaluate the efficacy or effectiveness of treatments, it appears important to include assessment of "how fast" as well as

of "how far." The shape of the overall survival curve in Figure 1 indicates that the hazard of reaching the end point is not a constant, but appears, in fact, to be a rapidly increasing phenomenon. In turn, this suggests that the rate of progression may well not be a constant across the entire illness. Our results, confirmed by others,[7] indicate that for any indicator of functional status measured on a sensitive scale, initially the rate of progression is near zero. This is followed by a period of relatively more rapid progression, culminating in a "bottoming out" phenomenon, where once again the rate of progression is zero. Analytic approaches that assume constant rates of progression across the time course of the illness (or indeed across different domains of clinical response) may provide misleading results.

The importance of these issues is underlined by several recent studies.[8-10] Using Kaplan-Meier and Cox techniques similar to those of the current study, Mayeux et al[9] found that "the presence of extrapyramidal signs or myoclonus early on predicts rapid progression of disease and early death."[9(p9)] Similar results have been reported by Chui et al,[10] who controlled for the initial level of impairment, as we did, by limiting their analyses to subjects with initial MMSE scores above 15. When Chui et al included all initial MMSE scores, they noted that their results were the same as those of the Drachman group, ie, that the major predictor was the initial level of impairment.

Chen et al[8] also suggested that the prevalence of such prognostic factors as EPS and psychosis increases in monotonic fashion during the course of the illness. This can also be seen in Table 2. Thus, such signs might be viewed as disease markers that emerge at different stages of a single disease. Given biologic variability, there will be variability in which different signs occur in any one individual and when they occur, in terms of both sequence of emergence and timing. Such clinical heterogeneity is often interpreted as suggestive of different subtypes, but as Chen et al indicated, they may instead reflect natural variations in the expression of a single disorder.

Thus, for example, syphilis initially appeared to be a variety of different disorders, since there were individual variations in which organs were affected, but later it became clear that this was a single disorder caused by a single infectious agent.[11] On the other hand, as was the case with diabetes mellitus, subtypes of a disorder may be initially identified by clinical heterogeneity in the course of the disease, in that case by age at onset, a finding later confirmed by findings of differential processes of the disease.

Hence, a familial subtype of AD may have a higher risk of the development of a particular disease feature than another group, or may present these features in a different sequence or with different timing. However, the identification of a subtype requires dem-
onstration not only of such heterogeneity (which may equally well indicate stage), but also of a distinct cause or process. In short, heterogeneity is necessary to the existence of clinical subtypes, but it is not sufficient. However, the identification of potential subtypes and the research necessary to identify them requires the study of heterogeneity as a first step.

For these reasons, it appears important not to assume the absence of heterogeneity in a salient disease feature, such as rate of progression, in a progressive disorder, but to document its presence or absence. If it is present, it is important to determine empirically whether there is clinical significance in terms of cause or process to such heterogeneity. The result of the present study, then, is to suggest that there appears to be substantial heterogeneity in the rate of progression in patients with AD; that, like initial degree of severity, rate of progression appears to be a strong predictor of course; and that such results should stimulate research into the relationship of rate of progression to causative and process features of AD.

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