Predicting Progression of Alzheimer's Disease

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Background

There is considerable variability in observed progression rates among Alzheimer's disease patients. It is not clear whether patients who start out progressing rapidly or slowly will remain consistent in their progression rate over time.

Study Objective

To determine if a simple preprogression rate index, calculated at the initial assessment, predicts whether or not patients will remain rapid, slow or intermediate progressors over time.

Setting and Population

The Baylor Alzheimer's Disease and Memory Disorders Center sees self-referred, agency-referred, and physician-referred individuals for evaluation and management of cognitive complaints. All patients are evaluated for systemic and brain disorders with laboratory testing, including neuroimaging, and psychometric tests. A diagnosis of various forms of MCI or dementia is assigned according to standardized criteria through a Consensus Conference1. Subjects seen in our center have a wide range of education and socioeconomic levels, and include 14% minority subjects. Only **Probable AD** Patients (NINCDS-ADRDA, DSM IV) were included in this study. We coded the presence or absence of **psychosis** (hallucination, delusions) and **extra-pyramidal signs** at baseline.

Methods

We included **801 probable AD patients** with an initial visit and at least one comprehensive follow-up approximately one year later. Psychometric tests given at baseline and at all annual visits included: **Mini-mental status examination (MMSE), National Adult Reading Test—American Version (AMNART), Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-Cog), Clinical Dementia Rating Scale (CDRS) sum of the boxes , Verbal Series Attention Task (VSAT) (time and errors), Lawton and Brody Activities of Daily Living (PSMS and IADL)**. Patients were classified based upon scores at their initial visit into **slow, intermediate, and rapid progressors** based upon our previously published calculated preprogression rate2 derived from the Mini-mental Status Examination score and a standardized estimate of disease duration3. We then performed a mixed effects regression analysis to determine whether the preprogression groups (slow, intermediate, rapid) remained distinct over 3.60 ± 2.4 years of follow up on the outcome measures. We adjusted for covariates previously reported to influence progression in AD (pre-morbid IQ as estimated by the AMNART, age, sex, years of education, hallucinations, delusions, extra-pyramidal signs).

Results

Baseline characteristics of the study sample: See Table 1

Relationship of covariates to each study outcome: Pre-morbid IQ and presence of delusions at baseline were significantly associated with all outcome measures. Other baseline covariates were related to some outcomes and not others (see Table 2).

Preprogression rate and change in function over time: After adjustment for significant covariates, patients in the slow preprogression group continued to decline at a slower rate than those in the intermediate or fast preprogression groups on the ADAS-Cog, the SCDR, the IADL, and the PSMS. For example the annual change in ADAS-Cog scores was 10.31 points less for slow preprogressors compared to fast preprogressors. Performance on outcome measures tended to be similar for intermediate and fast preprogressors, except for the ADAS-Cog, on which intermediate preprogressors remained distinct from the slow and fast groups. Interaction terms for time and preprogression rate indicated that the differences in rate of change in each group did not remain uniform on all measures. Table 3 contains the regression coefficients for unadjusted and adjusted linear mixed effects regression models, and Figures 1-6 reflect graphically the changes in functional scores predicted from adjusted regression models. Including the baseline MMSE severity category in the model did not alter the fundamental pattern of results.

Table 1. Patient Characteristics at Baseline

Variable	n with value	Mean ± SD or n (Percent)
Age at Diagnosis	801	73.36 ±8.66
Sex (% female)	801	261 (32.6%)
Race/Ethnic Group	801	
–White		701 (87.5%)
–Black		65 (8.1%)
–Hispanic		28 (3.5%)
–Other		7 (0.8%)
Years of Education	800	13.4±3.5
Estimated duration of disease before diagnosis (yrs)	801	3.8 ± 2.5
Pre-Progression Rate Group	801	
–Fast		211 (26.3%)
–Intermediate		371 (46.3%)
–Slow		219 (27.3%)
Baseline MMSE	801	19.0±6.8
Baseline ADAS Cog	527	24.8±12.9
CDR Sum of Boxes	716	6.8±4.7
First AMNART (estimated IQ)	599	107.7±10.3
PSMS	529	8.3±3.6
IADL	523	15.9±6.8
VSAT (time)	674	231.1±92.3
VSAT (errors)	675	16.1±15.9
Hallucinations at Baseline	801	194 (24.22%)
Delusions at Baseline	801	365 (45.6%)
Extra-pyramidal Symptoms at Baseline	775	54 (7.0%)
Years of active follow-up (first visit to last visit date)	801	3.60±2.4
Proportion deceased as of censoring date (12/31/2004)	801	373 (46.6%)
Overall survival (from first visit to death or censoring)	801	5.5±2.8

Table 2: Relationship between Pre-progression Category and Subsequent Rate of Decline on Cognitive and Functional Measures

	Progression Measures											
Independent Variables	ADAS-Cog		VSAT Time		VSAT Errors		SCDR		IADL		PSMS	
	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P	Beta	P
Unadjusted Model												
Intermediate vs. Fast	-2.81	.041	-25.25	.004	-3.55	.003	-1.19	.011	-1.63	.010	-.83	.115
Slow vs. Fast	-13.06	<.001	-78.15	<.001	-9.37	<.001	-4.80	<.001	-5.23	<.001	-2.79	<.001
Slow vs. Intermediate**	-10.25	<.001	-52.90	<.001	-5.82	<.001	-3.61	<.001	-3.60	<.001	-1.96	<.001
Years of Follow-up	3.43	<.001	11.43	<.001	1.93	<.001	1.86	<.001	1.57	<.001	2.03	<.001
Interaction 1*		NS	5.71	.055		NS	.18	.034	.28	.038	.01	.933
Interaction 2*		NS	7.64	.007		NS	-.10	.257	.27	.053	-.56	<.001
Adjusted Model¶												
Intermediate vs. Fast	-3.50	.009	-19.69	.035	-2.82	.010	-1.04	.030	-2.08	.002	-.86	.102
Slow vs. Fast	-10.31	<.001	-.52.18	<.001	-6.62	<.001	-2.62	<.001	-3.60	<.001	-.56	<.001
Slow vs Intermediate**	-6.81	<.001	-32.49	<.001	-3.80	<.001	-1.57	<.001	-1.52	.009	-.47	.291
Years of Follow-up	3.52	<.001	12.50	<.001	2.14	<.001	1.87	<.001	1.65	<.001	2.00	<.001
Interaction 1*		NS	4.035	.202		NS	.25	.012	.41	.007	.06	.625
Interaction 2*		NS	6.63	.028		NS	-.12	.207	.20	.201	-.56	<.001

Note: When all interactions terms for a measure are non-significant, the betas from models without interaction terms are reflected in the table.

* Interaction 1: Time by intermediate pre-progression group (fast=reference group)
Interaction 2: Time by slow pre-progression group (fast=reference)
**Test of hypothesis that coefficient on slow vs fast = coefficient on intermediate vs. fast
¶ Models adjusted for age at diagnosis, sex, years of education, pre-morbid IQ, and presence of hallucinations and/or delusions

Table 3: Effect of Covariates: Betas (p-values) for significant covariates*

	Covariates						
Progression Measures	Age	Sex (1=male, 0=female)	Education	AMNART	Delusions	Hallucinations	Extra-pyramidal Signs
Adas-Cog	NS	NS	.39 (.027)	-.40 (<.001)	3.74 (.001)	NS	NS
Vtime	-1.29 (.001)	NS	NS	-3.32 (<.001)	18.69 (.014)	NS	NS
Verror	-.17 (.001)	NS	NS	-.39 (<.001)	2.22 (.016)	NS	NS
SCDR	NS	NS	NS	-.08 (<.001)	1.77 (<.001)	1.33 (.005)	NS
IADL	NS	-2.58 (<.001)	NS	-.07 (.005)	3.20 (<.001)	1.60 (.014)	NS
PSMS	.042 (.042)	NS	NS	-.05 (.016)	1.76 (<.001)	1.28 (.010)	NS

*Reported betas calculated in models adjusted for the remaining covariates

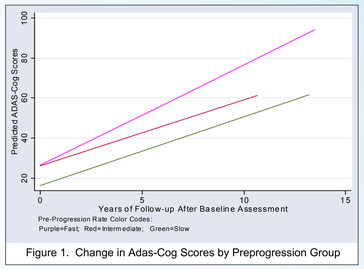

Figure 1. Change in Adas-Cog Scores by Preprogression Group

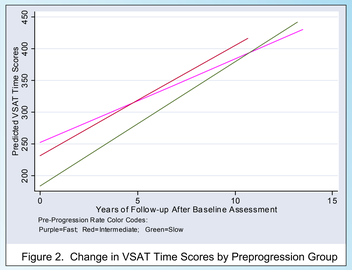

Figure 2. Change in VSAT Time Scores by Preprogression Group

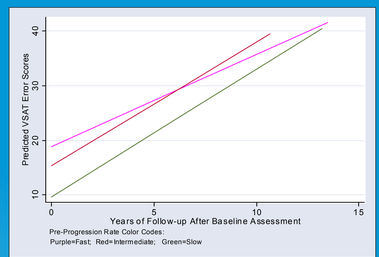

Figure 3. Change in VSAT Errors Score by Preprogression Group

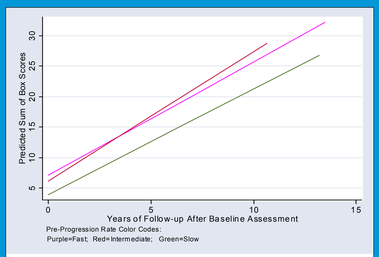

Figure 4. Change in CDRS Sum of Boxes Score by Preprogression Group

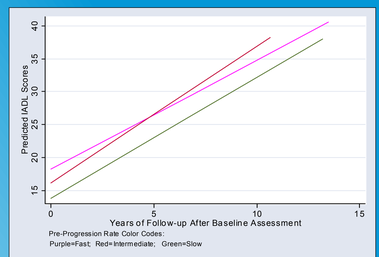

Figure 5. Change in IADL Score by Preprogression Group

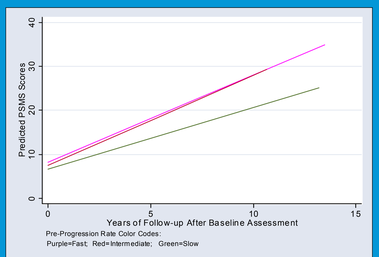

Figure 6. Change in PSMS Score by Preprogression Group

Discussion and Conclusions

A calculated preprogression rate at the initial visit is predictive of observed decline on multiple cognitive and functional measures over time. The clearest difference in functional change was observed between the slow preprogressors and those classified as intermediate and fast preprogressors. This has implications for clinical prognostication as well as for the design of clinical trials.

Subjects in this study had between 1 and 13 years of follow-up (mean=3.6, SD2.4). The graphs in Figures 1 through 6 indicate some acceleration in the rate of decline in the intermediate group after the third year of follow-up.

The presence of hallucinations or delusions (but not extrapyramidal signs) at baseline also influenced progression on some outcome measures, but the most powerful and consistent effect was attributable to pre-morbid verbal IQ as estimated by the AMNART. Further analysis of this finding is the subject of a separate report4.

References

1. Doody RS, Pavlik V, Massman P, Kenan M, Yeh S, Powell S, Cooke N, Dyer C, Demirovic J, Waring S, Chan W. Changing patient characteristics and survival experience in an Alzheimer's disease center patient cohort. Dementia and Geriatric Cognitive Disorders 2005; 20: 198-208.

2. Doody RS, Massman P, Dunn JK. A method for estimating progression rates in Alzheimer's disease. Archives of Neurology 2001; 58:449-454

3. Doody R, Dunn J, Huang E, Azher S, Kataki M. A method for estimating duration of illness in Alzheimer's disease. Dementia and Geriatric Cognitive Disorders 2003; 17: 1-4.

4. Pavlik V, Doody R, Massman P, Chan W, Yeh S. The influence of premorbid IQ and eduction on progression of Alzheimer's disease. Dementia and Geriatric Cognitive Disorders 2006, in press.

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