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Progression of Alzheimer disease as measured by Clinical Dementia Rating sum of boxes scores

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Abstract

Background—This study examined rates of dementia progression as ascertained by the Clinical Dementia Rating sum of boxes (CDR-SB) for symptomatic Alzheimer disease (sAD) and assessed participant characteristics as predictors of CDR-SB progression.

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Dr. Martha Storandt contributed to drafting and revising the manuscript for content, study concept and design, and analysis and interpretation of data. In addition, Dr. Storandt conducted statistical analyses for the study.

Dr. Catherine Roe contributed to drafting and revising the manuscript for content, study concept and design, and interpretation of data.

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Methods—Participants (n = 792) were enrolled in longitudinal studies at an Alzheimer's Disease Research Center, received a diagnosis of sAD with a global CDR of 0.5 (n = 466) or 1 (n = 326), and had at least one follow-up assessment. Progression in CDR-SB over time as a function of baseline global CDR was examined.

Results—A longitudinal increase ($p < .0001$) in CDR-SB was observed. The annual rate of change in CDR-SB scores was 1.43 (SE=.05) in the CDR 0.5 sample and 1.91 (SE=.07) in the CDR 1 sample. For participants followed from the beginning of the CDR stage, time to progression to a higher global CDR was longer for individuals who were CDR 0.5 (3.75 years; 95% CI 3.18-4.33) than those who were CDR 1 at baseline (2.98 years; 95% CI 2.75-3.22). In the total CDR 0.5 sample, the significant predictors of progression to the next global CDR stage ($p < .01$) were age at first sAD diagnosis and apolipoprotein E4 genotype.

Conclusions—The study findings are relevant to sAD clinical trial design and accurate, reliable ascertainment of the effect of disease-modifying treatments.

Keywords

Alzheimer disease; assessment of dementia; Clinical Dementia Rating; Clinical Dementia Rating sum of boxes; cohort studies

Introduction

Growing interest in the earliest stages of symptomatic Alzheimer disease (sAD) underscores the need for a global dementia rating scale for patient care and research, including clinical trials.¹ Accurate quantification of dementia severity permits comparison across studies, assessment of dementia progression, and determination of clinically meaningful effects of antidementia medications,² including disease-modifying agents. An appropriate scale must be reliable, valid, and easily administered.

The Clinical Dementia Rating (CDR)^{3, 4} is a global dementia rating scale that assesses cognitive change, determines the presence of dementia, and quantifies dementia severity from very mild (CDR 0.5) to mild (CDR 1), moderate (CDR 2), and severe (CDR 3). The CDR's utility relates to several factors: (1) the CDR assesses intraindividual cognitive and functional change and consequently is clinically meaningful;^{5, 6} (2) the domains used to rate dementia severity are linked to validated diagnostic criteria;^{7, 8} (3) the CDR has high interrater reliability for physicians,⁹ nonphysician clinicians,¹⁰ and investigators^{11, 12} and monitors¹³ in multicenter studies; (4) the diagnostic accuracy of the CDR for sAD is confirmed by neuropathological diagnosis of AD for 92% of cases;^{14, 15} and (5) the ratings for the six domains can be summed for a CDR sum of boxes score (CDR-SB),¹⁶ providing a finer gradation of impairment.¹⁷ Based on these attributes, the CDR-SB has been nominated as a single primary endpoint for clinical trials of experimental therapies for sAD.⁶

The CDR-SB quantifies dementia severity and progression in clinical trials¹⁸⁻²¹ and AD biomarker research²² and tracks change over time, permitting ascertainment of within-stage and between-stage progression.²³ Studies have examined annual rate of change in CDR-SB.^{24, 25} However, CDR-SB progression as a function of baseline sAD severity is not characterized. Progression in CDR-SB as a function of baseline dementia severity has considerable relevance to clinical trials and patient care to assess the impact of therapeutic interventions. Our study examined rates of CDR-SB progression for participants with sAD enrolled in longitudinal studies at the Alzheimer's Disease Research Center that developed the CDR.

Methods

Participants

Participants enrolled in longitudinal studies at the Knight Alzheimer's Disease Research Center (Knight ADRC) at Washington University between July 1990 and July 2009 were included in the analyses reported here if they received a diagnosis of sAD with a global CDR score 0.5 or 1 and had at least one annual follow-up assessment. Data for individuals who initially were enrolled as CDR 0 but then progressed (n = 94) were only included for those assessments after progression. Diagnoses of sAD were made in accordance with standard criteria.⁸ Individuals with diagnoses of neurological diseases other than sAD were excluded. Participants (n = 792) were predominately women, with 466 (42% men) in the CDR 0.5 group and 326 (31% men) in the CDR 1 group. Demographic characteristics including education, race, and ethnicity were obtained by self-report. Two participants were American Indian, one was Asian American, 103 (13%) were African American, and the remainder were white. The majority had at least one apolipoprotein E (APOE) ε4 allele (59% CDR 0.5, 63% CDR 1). This prevalence of APOE4 is comparable other longitudinal dementia studies.²⁶ Other sample characteristics are shown in Table 1.

Participants were community-dwelling older adults recruited from the metropolitan St. Louis, Missouri region via word of mouth, community recruitment activities, and physician referrals. All participants were enrolled in longitudinal studies of dementia and healthy aging at the Knight ADRC. These recruitment methods and the clinical assessment protocol were consistent across the duration of the present study. Detailed information regarding recruitment and assessment methods for these studies has been published.^{14, 27} Exclusion criteria for enrollment in Knight ADRC studies were presence of a serious medical condition (e.g., end-stage renal disease requiring hemodialysis, use of insulin, depression requiring electroconvulsive therapy) that may interfere with longitudinal participation or affect cognition. All participants completed annual clinical assessments and psychometric testing unless precluded by death, refusal, or relocation far from the St. Louis area. This sample includes participants who had at least one follow-up assessment after their diagnosis of sAD; mean duration of follow-up was 4.0 years.

Recently published clinical diagnostic criteria for AD are based on a continuum of disease from a preclinical (presymptomatic) stage to an early symptomatic stage (mild cognitive impairment, or MCI) to AD dementia.²⁸⁻³⁰ For brevity, we adopt the term "sAD" to encompass both MCI caused by AD and AD dementia. Hence, many of the CDR 0.5 individuals in our sample elsewhere may be classified as MCI. We have demonstrated that a clinical diagnosis of AD at the CDR 0.5 stage in our sample is confirmed by the postmortem diagnosis of AD in 92% of cases.¹⁴

Human Research Protection

The Washington University Human Studies Committee approved all procedures. Written informed consent was obtained from all participants and collateral sources after the study was described fully.

Clinical Evaluation

At each annual clinical assessment, a clinician without knowledge of previous results evaluated the participant and interviewed the collateral source. These experienced, research-trained clinicians (neurologists, geriatricians, psychiatrists, and clinical nurse specialists) conducted semistructured interviews separately with the participant and a knowledgeable collateral source (usually the spouse, adult child, or other relative) to determine whether there was decline in the participant's cognitive abilities sufficient to interfere with the

individual's usual activities. The clinical assessment included a health history, medication and depression inventories, an aphasia battery, and a detailed neurological examination. Items from the Short Blessed Test (SBT)³¹ and Mini-Mental State Examination (MMSE)³² were interspersed throughout the participant interview and administered at each annual clinical assessment. An autobiographical memory task was conducted at every clinical assessment; the collateral source described two recent personal events experienced by the participant that the participant was later asked to recall.³³ The clinical assessment protocol assessed intraindividual cognitive change, using the participant's previously attained abilities as the control. The clinician evaluated and synthesized the data obtained in the interviews and examination to determine diagnosis and, if present, dementia severity. The determination of cognitive decline was based on the clinical assessment without reference to psychometric performance (a 1.5 hour battery was administered annually, about 2-4 weeks after the CDR was determined) or any components of previous clinical assessments, including MMSE scores, SBT scores, CDR, and the semistructured interview. The CDR was used to operationalize the clinician's judgment, determine the presence or absence of dementia and, if present, to stage its severity.

The CDR evaluates cognition and functional performance in each of six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care without reference to psychometric performance or results of previous evaluations. Information necessary to rate the domains is elicited in the semistructured interviews with the participant and collateral source. Each domain is rated using one of five levels of impairment, and only impairment due to cognition is rated. For each domain, a rating of 0 indicates no impairment, and 0.5, 1, 2, and 3 correspond to very mild, mild, moderate, and severe impairment, respectively. The scores in each of the six areas are summed to yield a *sum of box scores* ranging from 0 (no impairment) to 18 (maximal impairment). The ratings in each domain are also combined according to a standard algorithm (available on the Knight ADRC website, <http://alzheimer.wustl.edu>), to yield a *global CDR* with values of 0 (cognitively normal), 0.5 (very mild), 1 (mild), 2 (moderate), and 3 (severe) dementia.⁵

APOE Genotyping

APOE genotyping was performed on DNA extracted from peripheral blood samples using methods described previously.³⁴ Clinicians were unaware of APOE genotype results, and genotype data were not utilized diagnostically. The variable used in the analyses reported here was a dichotomy indicating whether or not an $\epsilon 4$ allele was present.

Statistical analyses

The longitudinally measured CDR-SB was examined in both the CDR 0.5 and CDR 1 samples using random coefficients analysis (PROC MIXED, SAS 9.1, Cary, NC). The primary model included the random variable time from date of first sAD diagnosis. Additional models were examined in each sample to determine if rate of change in the CDR-SB varied with participant characteristics. These included as a fixed effect one of five participant characteristics (age at first sAD diagnosis, education, gender, race [African American vs. other] and APOE status) and its interaction with time. The analyses were then repeated in subsamples of participants who were initially: (a) CDR 0 at baseline and for whom the first sAD diagnosis at CDR 0.5 occurred at a follow-up assessment or (b) CDR 0 or 0.5 at baseline and for whom the sAD diagnosis at CDR 1 occurred at follow-up. These analyses using only data from the time of the first sAD diagnosis at CDR 0.5 or CDR 1 provide estimates of the rate of change from the beginning of the global CDR stage. To determine if the rate of change in the CDR-SB accelerated after diagnosis of sAD as it does for cognitive measures,³⁵ we used the same method of latent difference scores described

previously³⁵ in the subset of CDR 0.5s who had progressed from CDR 0. Kaplan-Meier analyses were conducted to determine median time to a higher level of severity (i.e., CDR > 0.5 for the CDR 0.5 sample and CDR > 1 for the CDR 1 sample), and Cox proportional hazards analyses to determine if any participant characteristics were related to survival time.

Results

A significant ($p < .0001$) longitudinal increase in the CDR-SB scores was obtained in all analyses. The annual rate of change in CDR-SB scores was 1.43 (SE .05) in the CDR 0.5 sample and 1.91 (SE = .07) in the CDR 1 sample. The annual rates of change in CDR-SB were slightly less in the subsets followed from the beginning of the CDR stage: CDR 0.5, $n = 94$, slope = 1.36, SE = .11; CDR 1, $n = 209$, slope = 1.88, SE = .09. The rate of change in the CDR 0.5 subset did not accelerate; however, only 47 (out of 94) participants had at least 3 assessments at CDR 0.5. This null result thus may be misleading due to reduced power.

The attrition rate for the third assessment (i.e., second follow-up) was 17% (2% due to death); it was the same in CDR 0.5 and CDR 1 samples. In the CDR 0.5 sample those lost to follow-up were significantly older than the remainder of the sample (79.7 vs. 77.2 yrs, $p = .04$) and more likely to be women (77 vs. 27%; $p = .002$). These differences were not observed in the CDR 1 sample. There were no differences in education, MMSE at baseline, or presence of an APOE $\epsilon 4$ allele in either sample.

Only one significant, $F(1, 347) = 5.89$, $p = .02$, interaction between time and a participant characteristic (age at first sAD diagnosis) was observed; it occurred in the CDR 0.5 sample. To explore this interaction, the analysis was repeated using age as an ordinal scale with three levels: under 75 years, 75 through 84 years, and 85 years and above. There were too few people under age 65 to include them as a separate group. The slopes for the three age groups were 1.27 (SE = .08) for those under 75, 1.51 (SE = .08) for those aged 75 through 84 years, and 1.60 (SE = .11) for those 85 and above. Given the minimal difference in the slopes for the two oldest groups, they were combined (slope = 1.54, SE = .07). The somewhat slower rate of change in those under age 75 compared with those above age 75 is illustrated in Figure 1. Table 2 shows the annual rate of change in CDR-SB for all ages and stratified by age less than 75 years and 75 years and older.

Estimates of the median time to progression to a higher global CDR were 3.07 years (95% CI 2.76 to 3.37) for the CDR 0.5 sample and 2.41 years (95% CI 1.99 to 2.83) for the CDR 1 sample. These estimates were longer in the subsamples followed from the beginning of the CDR stage: 3.75 years (95% CI 3.18 to 4.33) for CDR 0.5 and 2.98 years (95% CI 2.75 to 3.22) for CDR 1.

The only significant ($p < .01$) predictors of survival time to the next higher global CDR were obtained in the total CDR 0.5 sample; these predictors were age at first sAD diagnosis and APOE status. Those under age 75 years had a median survival time of 3.32 years (95% CI 2.63 to 4.00) compared with 2.88 years (95% CI 2.33 to 3.42) for those aged 75 to 84 years and 3.10 years (95% CI 2.72 to 3.49) for those 85 years and older. Median survival time was shorter (2.92 years, 95% CI 2.40 to 3.45) for those with an APOE4 allele than for those without (3.33 years, 95% CI 2.67 to 3.98). The median survival time was very similar for those with 1 allele (2.95 years, 95% CI 2.38 to 3.52) or with 2 alleles (2.82, 95% CI 1.62 to 4.03). The age effect was marginally significant ($p = .07$) in the subset of the CDR 0.5 sample followed from the beginning of the stage; the APOE effect was not significant ($p = .44$).

Only the samples that progressed from a lower level were used to examine clinical features of those who then progressed to the next stage within 2 years; otherwise progression would

be related to where in the stage (e.g., CDR 0.5) the person was first seen. Of the 94 people who progressed to CDR 0.5 sAD from CDR 0 and had subsequent evaluations, 19 progressed to CDR > 0.5 within 2 years, and 42 progressed in more than 2 years (Table 3). These two groups were not significantly different in education, age, MMSE, CDR-SB, or any of the six individual box scores at the time of first diagnosis of sAD.

Among the members of the subset who had progressed to CDR 1 and who had subsequent evaluations, 67 progressed to CDR > 1 within 2 years, and 75 progressed in more than 2 years (Table 3). Those who progressed rapidly were significantly older ($M = 78.57$) than those who progressed more slowly ($M = 75.86$). They also had poorer scores on the CDR-SB and 3 of the 6 individual box scores: Judgment and Problem Solving: 1.02 vs. .88 ($p = .006$); Community Affairs: 1.08 vs. 0.87 ($p = .001$); Home and Hobbies: 1.10 vs. 0.96 ($p = .02$). The results were the same when adjusted for age.

Discussion

This study describes the natural history of sAD progression as measured by the CDR-SB for a well-characterized sample of participants with very mild and mild sAD. The findings have relevance to the design of AD clinical trials and accurate determination of the effect of disease-modifying treatments. The results of this study can provide guidance regarding the appropriate duration of proposed clinical trials and the anticipated rate of progression for very mild and mild sAD. The main findings in this study were the differing rates of progression observed for the CDR 0.5 and CDR 1 groups, the effect of older age on more rapid increase in CDR-SB for the entire CDR 0.5 sample, and the effect of the presence of an APOE4 allele for more rapid progression to a higher CDR in the entire CDR 0.5 sample. Education, gender, and race (defined as African American vs. other) were not predictors of progression. These findings are consistent with prior studies that show that dementia severity and APOE4 are associated with more rapid progression.^{15, 36-38}

The stability of dementia severity characterized by the CDR ratings has been demonstrated.²⁷ The CDR-SB can be easily derived from ratings used in assigning a global CDR and provides a more detailed quantification of clinically significant cognitive changes. The CDR-SB detects the earliest stages of sAD, including its very mildest stages, comparable to mild cognitive impairment (MCI), and even a milder stage of cognitive decline analogous to preMCI.^{15, 37}

The principal strength of this study was the sample. Participants were well-characterized, and the large ($N = 792$) sample followed longitudinally with a mean duration of follow-up of 4 years. The sample size and length of follow up permitted comparison of several covariates including demographic factors (age, race) and APOE4 status.

The study has some limitations. Our community-dwelling older adults represent a convenience sample of research volunteers rather than a population-based cohort, which may affect generalizability. The sample was recruited from one site and represents inhabitants of one metropolitan region. Use of antidementia medications was not assessed in the present study, but previous reports indicate that rates of cognitive decline for individuals treated with cholinesterase inhibitors were similar to rates of decline in historical placebo groups not treated with cholinesterase inhibitors.²¹ The sample included only participants with sAD, and the results of CDR-SB progression would be most relevant to comparable sAD samples. Additional studies examining rates of progression in nonAD dementia may be relevant, as the rates of progression may differ in other degenerative dementias.^{40, 41}

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Figure 1. Mean Change in Clinical Dementia Rating Sum of Boxes Over Time

Table 1

Sample Characteristics at First Assessment (Means and SDs)

	CDR 0.5		CDR 1	
	Total	Subset	Total	Subset
N	466	94	326	209
Age	78.00 (8.07)	83.76 (7.53)	76.86 (8.79)	77.39 (7.42)
Education (years)	13.73 (3.30)	14.26 (3.17)	2.62 (3.35)	13.80 (3.23)
MMSE	25.53 (3.13)	26.50 (3.19)	21.04 (4.05)	22.58 (4.00)
CDR-SB	2.29 (1.02)	1.82 (0.92)	5.82 (1.34)	5.44 (1.09)

Note: Subsets include only those participants who progressed to this CDR rating from a lower rating. The range of possible scores from “best” to “worst” on the MMSE is from 30 to 0 and on the CDR sum of boxes (CDR-SB) from 0 to 18.

Table 2

Annual rate of change (slope) in CDR sum of boxes

	Total diagnosed at CDR 0.5	Subset who progressed to CDR 0.5	Total diagnosed at CDR 1	Subset who progressed to CDR 1
N	466	94	326	209
Slope, all ages	1.43 (.05)	1.36 (.11)	1.91 (.07)	1.88 (.09)
95% CI	1.33 - 1.53	1.14 - 1.59	1.77 - 2.04	1.71 - 2.05
Slope, < 75 yrs	1.27 (.08)			
95% CI	1.11 - 1.42			
Slope, 75+ yrs	1.54 (.07)			
95% CI	1.41 - 1.66			

Standard errors in parentheses; CI = confidence interval.

Characteristics (Means and SDs) at First Global CDR 0.5 or 0 of Those Who Progressed to a Higher Global CDR in Less Than or More Than 2 Years

Table 3

	CDR 0.5		CDR 1	
	Less than (<i>n</i> = 19)	More than (<i>n</i> = 42)	Less than (<i>n</i> = 57)	More than (<i>n</i> = 75)
Age at diagnosis (years)	85.82 (6.66)	82.57 (7.86)	78.57 (7.40)	75.86 (7.31)
Education (years)	14.74 (3.30)	13.88 (3.28)	14.16 (3.30)	13.29 (3.23)
MMSE	25.27 (3.23)	26.41 (3.73)	21.34 (3.87)	22.69 (4.56)
CDR-SB	2.26 (1.12)	1.76 (1.00)	5.85 (1.19)	5.25 (0.96)

Note. Samples examined are from subsets who had progressed to stage from lower CDR 0 (CDR 0.5 *n* = 94, CDR 1 *n* = 209). The range of possible scores from “best” to “worst” on the MMSE is from 30 to 0 and on the CDR sum of boxes (CDR-SB) from 0 to 18.