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Progression of Alzheimer's 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's disease (sAD), and assessed participant characteristics as predictors of CDR-SB progression.

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 (standard error [SE] = 0.05) in the CDR 0.5 sample and 1.91 (SE = 0.07) 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% confidence interval [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's disease; Assessment of dementia; Clinical Dementia Rating; Clinical Dementia Rating Sum of Boxes; Cohort studies

1. Introduction

Growing interest in the earliest stages of 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 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

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monitors [13] in multicenter studies; (4) the diagnostic accuracy of the CDR for sAD is confirmed by neuropathological diagnosis of Alzheimer's disease (AD) for 92% of cases [14,15]; and (5) the ratings for the six domains can be summed for a Clinical Dementia Rating 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 end point for clinical trials of experimental therapies for sAD [6].

The CDR-SB quantifies dementia severity and progression in clinical trials [18–21] and AD biomarker research [22] 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.

2. Methods

2.1. 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 (CDR 0.5: 59%; CDR 1: 63%). This prevalence of *APOE* ε4 is comparable with 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 through 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 criterion for enrollment in Knight ADRC studies was 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.

Table 1
Sample characteristics at first assessment (means and SDs)

	CDR 0.5		CDR 1	
Variable	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)

Abbreviations: SD, standard deviation; CDR-SB, Clinical Dementia Rating Sum of Boxes; MMSE, Mini-Mental State Examination.

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-SB from 0 to 18.

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 may be classified as MCI elsewhere. 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].

2.2. 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.

2.3. 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