ORIGINAL ARTICLE

Clinical Prediction of Alzheimer Disease Dementia Across the Spectrum of Mild Cognitive Impairment

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Objective: To determine whether clinical assessment methods that grade the severity of impairments within the spectrum of mild cognitive impairment (MCI) can predict clinical course, particularly among very mildly impaired individuals who do not meet formal MCI criteria as implemented in clinical trials.

Design: Cohort.

Setting: Community volunteers.

Participants: From a longitudinal study of normal (Clinical Dementia Rating [CDR] = 0; n = 77) and mildly impaired (CDR = 0.5; n = 167) participants with 5 or more annual clinical assessments, baseline level of cognitive impairment in daily life was graded using CDR sum of boxes (CDR-SB) and level of cognitive performance impairment was graded using neuropsychological test scores.

Main Outcome Measures: Five-year outcome measures included (1) probable Alzheimer disease (AD) diagnosis and (2) clinical "decline" (CDR-SB increase ≥ 1.0). Logistic regression models were used to assess the ability of baseline measures to predict outcomes in the full sample and separately in the subjects who did not meet formal MCI criteria as implemented in a multicenter clinical trial (n = 125; "very mild cognitive impairment" [vMCI]).

Results: The presence of both higher CDR-SB and lower verbal memory and executive function at baseline predicted greater likelihood of probable AD and decline. Five-year rates of probable AD and decline in vMCI (20%, AD; 49%, decline) were intermediate between normal participants (0%, AD; 28%, decline) and participants with MCI (41%, AD; 62%, decline). Within vMCI, likelihood of probable AD was predicted by higher CDR-SB and lower executive function.

Conclusions: Even in very mildly impaired individuals who do not meet strict MCI criteria as implemented in clinical trials, the degree of cognitive impairment in daily life and performance on neuropsychological testing predict likelihood of an AD diagnosis within 5 years. The clinical determination of relative severity of impairment along the spectrum of MCI may be valuable for trials of putative disease-modifying compounds, particularly as target populations are broadened to include less impaired individuals.

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As putative disease-modifying therapies for Alzheimer disease (AD) enter clinical trials, interest is growing in identifying the disease at an early "prodromal" clinical phase prior to dementia, with the hope that therapeutic intervention can slow the progression of neuropathological features and symptoms.[1-3] This transitional continuum, when patients are no longer clinically normal but do not yet have dementia, is most commonly referred to as mild cognitive impairment (MCI).[4] At the more impaired end of this spectrum, when individuals are more likely to present for neurological or psychiatric evaluation and meet diagnostic criteria for MCI as implemented in clinical trials, substantial AD neuropathological features and neuronal loss may already be present.[5-9] It would be ideal to intervene with disease-modifying therapies even earlier, when individuals are at the less impaired end of this spectrum and presumably have a lesser degree of pathological features.

In community settings, there are many individuals who do not fully meet formal MCI criteria as they have been implemented in clinical trials but who are not

normal. At least in some cases, their mild impairments may represent the first detectable clinical evidence of AD,[10-14] which may not be diagnosed for a decade or more.[11,15] In a recent study of a longitudinal community volunteer–based cohort, a group of mildly impaired individuals who did not meet formal clinical-trial MCI criteria was shown to be more likely than normal individuals to be diagnosed in the future with AD dementia.[11] Yet many of these individuals do not demonstrate progressive decline and dementia. It is as yet unknown how the future likelihood of AD dementia can be predicted within groups of individuals at the very mildest end of the MCI spectrum (who would not meet MCI diagnostic criteria as implemented in clinical trials). It would be extremely valuable to determine whether clinical methods could be used to identify subgroups of individuals with very mild MCI at high risk of future AD dementia, with the goal of recruiting them for clinical trials of disease-modifying agents.

Previous prospective work by our group has shown that relatively greater severity of cognitive impairment in daily life (graded using the Clinical Dementia Rating [CDR] sum of boxes [CDR-SB])[12] and relatively poorer neuropsychological performance[10,16] at baseline predict the development of probable AD dementia within 3 years. We undertook the present study to focus on the individuals at the less impaired end of this spectrum over a longer period of follow-up and to consider CDR-SB and neuropsychological testing together in the prediction of AD dementia. We chose 5 years as the follow-up period because it represents a credible duration of early intervention trials. In addition to the outcome measure of probable AD, we also investigated the outcome of clinical decline ("decline," operationalized as an increase in CDR-SB of ≥ 1.0 during the follow-up period) to capture evidence of progression in this very mild group, who were generally not expected to progress to dementia in a 5-year interval.[11] In the subset of subjects with longer-term follow-up after the initial 5 years, we also provide data on whether this intermediate outcome is associated with later diagnosis of probable AD.

METHODS

PARTICIPANTS

The participants in this study were drawn from an ongoing longitudinal study (N=379) of predictors of AD.[10] For the present analyses, we included all subjects with at least 4 annual follow-up visits to obtain approximately 5 years of follow-up (n=244). The vast majority of the participants not included in the present analysis are still actively participating but have not yet been followed up over 5 visits.

Participants in the longitudinal study were recruited between 1992 and 2005 using advertisements seeking individuals with and without memory difficulty. Volunteers underwent a multistage screening procedure. To be included, participants had to be primarily English speaking, 65 years or older, without dementia, and free of significant underlying medical, neurological, or psychiatric illness (based on standard laboratory tests and a clinical evaluation). They also had to have a CDR of 0 or 0.5.[17] Individuals with major vascular risk factors or disease (ie, atrial fibrillation, insulin-dependent diabetes mellitus, cerebral infarcts, cardiac bypass graft surgery) were excluded. All subjects and informants provided informed consent in accordance with the Human Research Committee of the Massachusetts General Hospital, Boston.

ASSESSMENT AND GRADING OF FUNCTIONAL STATUS

A semistructured interview was administered annually to quantify the degree of clinical impairment, generating an overall CDR rating and the CDR-SB.[17,18] It includes a set of questions regarding functional status, asked of the subject and an informant, and a standardized neurological, psychiatric, and mental status evaluation of the subject. Each interview was administered by a skilled clinician (eg, psychiatrist, neurologist, psychologist, or physician's assistant) and took 1 to 2 hours.

DIAGNOSTIC ASSESSMENT

A consensus clinical diagnosis was assigned to participants who developed significant cognitive and functional impairment, incorporating clinical history, medical records, laboratory evaluation, mental status evaluation results obtained during the office evaluation, and neuroimaging studies.[10,19] Individuals with dementia were classified as having AD or another diagnosis (eg, frontotemporal dementia, vascular dementia) according to standard criteria.[19-21] Diagnoses were made by clinicians who were blind to the results of the neuropsychological tests described later.

To look more closely at the mildest end of the MCI spectrum, we retrospectively applied formal MCI criteria to our sample. The original MCI criteria[4] were operationalized in a manner similar to that of a multicenter MCI clinical trial[22] and a recent study of very mild MCI[11]: (1) an informant-corroborated complaint of a decline in memory (≥ 0.5 in the CDR memory category); (2) preserved general intellectual function (Mini-Mental State Examination score ≥ 24)[23]; (3) an objective memory deficit (California Verbal Learning Test [CVLT][24] delayed free recall score ≥ 1.0 SD lower than age-, sex-, and education-adjusted mean of normal individuals [CDR=0; n=121] [see later]) at baseline, similar to that used by other groups in fitting current MCI criteria to data acquired prior the development of the MCI concept[25]; (4) intact ability to perform instrumental and basic activities of daily living (ratings <1 on community affairs, home/hobbies, and personal care dimensions of the CDR); and (5) absence of dementia (CDR <1 and failure to meet *DSM-IV* criteria for dementia). Once the participants were identified who met MCI criteria (n=42), the remaining individuals with a CDR of 0.5 or lower were designated as having "very mild cognitive impairment" (vMCI) (n=125).

NEUROPSYCHOLOGICAL MEASURES

At baseline, a neuropsychological battery was administered to all subjects.[10] For the present analyses, we focused on 2 cognitive domains, verbal memory and executive function, because of previous work in this sample and others indicating that these domains are useful predictors of cognitive decline.[10,16,26] In each domain, measures from 2 tests were included: (1) verbal memory (CVLT total learning score and delayed retention score [percentage of retention at delayed free recall of last immediate learning trial][24] and the free recall measure from the Free and Cued Selective Reminding Test[27]) and (2) executive function (Trail Making Test Part B [time to completion] [Trails B][28] and Self-Ordering Test [total score]).[29] One CVLT measure was used in MCI diagnostic criteria and 2 different CVLT measures were used for prediction. The neuropsychological test battery was administered in a separate session from the clinical evaluation and was scored in a blinded fashion with respect to CDR, CDR-SB, and diagnostic information.

Table 1. Demographic, Clinical, and Neuropsychological Characteristics of Sample

Characteristic	Mean (SD)			
	Normal (CDR=0)	All (CDR=0.5)	vMCI	MCI
Sample size	77	167	125	42
Age, y	71.6 (4.5)	72.7 (5.8)	72.3 (5.6)	73.8 (6.2)
Education, y	15.4 (2.8)	15.3 (2.9)	15.3 (3.0)	15.1 (2.6)
Sex, M/F	30/47	75/92	57/68	18/24
CDR sum of boxes	0.01 (0.08)	1.33 (0.78)[a]	1.23 (0.70)[b,c]	1.61 (0.93)[a,d]
MMSE[23] score	29.5 (0.7)	29.1 (1.6)	29.2 (0.7)	28.6 (0.9)
CVLT[24] total learning score	0.13 (0.99)	−0.39 (1.03)[a]	−0.16 (0.80)	−1.50 (0.82)[a,d]
CVLT delayed retention score[e]	−0.08 (0.98)	−0.18 (1.28)	0.32 (0.86)[b,c]	−1.66 (1.18)[a,d]
Free and Cued Selective Reminding Test[27] score	0.07 (1.05)	−0.20 (1.25)	0.08 (1.02)	−1.05 (1.47)[a,d]
Trails B[28] score	−0.07 (0.99)	−0.18 (1.22)	−0.12 (1.13)	−0.35 (1.45)
Self-Ordering Test[29] score	−0.07 (1.06)	−0.49 (1.05)[c]	−0.37 (0.97)[b,f]	−0.85 (1.22)[c,d]

Abbreviations: CDR, Clinical Dementia Rating; CVLT, California Verbal Learning Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; Trails B, Trail Making Test Part B; vMCI, very mild cognitive impairment.
[a] $P<.001$.
[b] Different from normal group.
[c] $P<.005$.
[d] Different from vMCI group.
[e] CVLT delayed free recall/CVLT last immediate learning trial.
[f] $P<.05$.

We computed standardized neuropsychological test scores adjusted for age, sex, and education as follows. Using baseline data from the entire sample, we performed a linear regression for each test score using age, sex, and education as predictors and saved the residuals. Standardized scores were then calculated for all subjects by subtracting the mean of the normal individuals (CDR=0) and dividing by the standard deviation of the normal individuals.[30] Thus, a standardized score of –1.0 indicates that the subject's score was 1 SD lower than the expected mean for a cognitively intact subject of the same age, sex, and education. Because of its skewed distribution, Trails B was log transformed prior to standardization. To aid interpretation, the standardized scores for Trails B and the Self-Ordering Test were multiplied by –1 so that scores lower than zero indicated poorer performance, consistent with the other neuropsychological measures.

OUTCOME MEASURES

The primary outcome measure was a diagnosis of probable AD. Since the analyses in the present study focused on many individuals who were cognitively intact or had very mild impairment at baseline, we also chose to use clinically significant decline ("decline") as a secondary outcome measure. This was operationalized as an increase of 1.0 or more in CDR-SB.

In further analyses, the clinical significance of this secondary outcome measure was examined in subjects who had at least 5 additional annual visits of longitudinal follow-up after the initial decline end point was met (some of the subjects have participated in the study for more than 10 years). Thus, it was possible to determine what proportion of individuals who met this intermediate outcome measure went on to be diagnosed with probable AD or exhibit further decline within approximately 5 more years.

Postmortem tissue from these subjects was investigated whenever possible to evaluate for neuropathological changes of specific dementing illnesses. For individuals in this sample who came to autopsy, neuropathological diagnoses were examined using the National Institute on Aging–Reagan Institute criteria.[31]

STATISTICAL ANALYSES

Group comparisons were performed using analysis of variance with post hoc pairwise comparisons, proportions were analyzed using χ^2, and the impact of predictors on outcomes was analyzed using logistic regression. Age, sex, and education were forced into all analysis of variance or regression models. Multivariate logistic regression models, used in analyses of combinations of CDR-SB and neuropsychological measures, were performed in blocks with CDR-SB entered in the first block, verbal memory measures analyzed in the next block (using a forward conditional approach), and executive function measures analyzed in the final block, using a P value to enter of $<.05$ for independent variables. Analyses were performed using SPSS 11.0 (SPSS Inc, Chicago, Illinois).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Demographic and clinical data on the 244 subjects are presented in **Table 1**. Overall, the subjects were a well-educated group made up of more women than men. Of the group with a CDR of 0.5 (n=167), 42 subjects met MCI criteria and the remaining 125 were designated as having vMCI. The normal group (n=77) had a mean CDR-SB score slightly higher than 0 because 2 individuals had scores of 0.5 in 1 nonmemory CDR category but still carried an overall CDR of 0.[32] No differences were detectable among the groups in age, education, or sex.

LIKELIHOOD OF PROBABLE AD AND DECLINE IS ELEVATED IN THE vMCI SUBGROUP

The subjects in this study were followed up longitudinally for a mean (SD) of 4.5 (0.2) years (range, 3.8-6.9

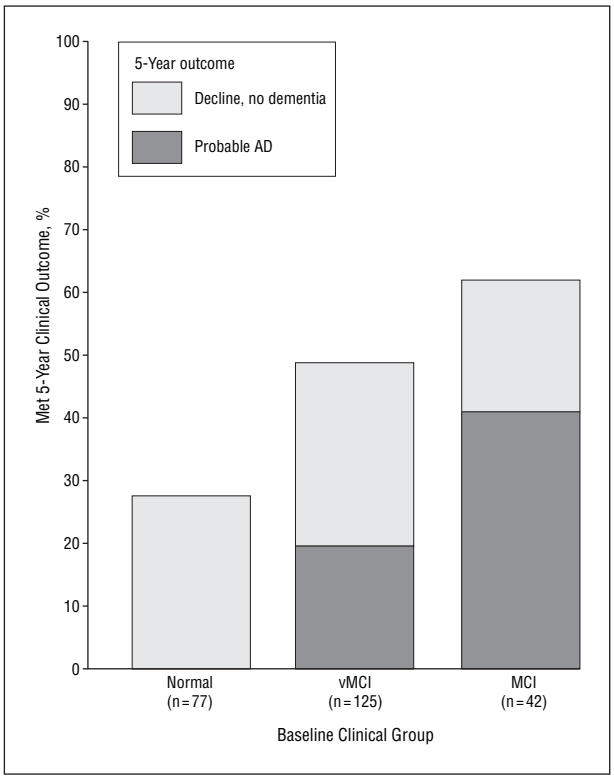

Figure. Proportion of baseline clinical groups that met outcomes of probable Alzheimer disease (AD) diagnosis and clinical decline (increase in Clinical Dementia Rating sum of boxes ≥1.0) within 5 years of follow-up. Subjects with very mild cognitive impairment (vMCI) were more likely than normal subjects to decline (χ^2_1=9.2; P<.002) and be diagnosed with AD (χ^2_1=17.6; P<.001). Subjects with mild cognitive impairment (MCI) were more likely than normal subjects to decline (χ^2_1=13.6; P<.001) and to be diagnosed with AD (χ^2_1=36.4; P<.001) and were more likely than subjects with vMCI to be diagnosed with AD (χ^2_1=7.0; P<.01). For simplicity, the 7 individuals with non-AD dementia outcomes are not illustrated.

years). Over this period, 107 of the 244 participants (44%) demonstrated clinical decline (increase in CDR-SB ≥1.0), of whom 42 (17% of the sample) were diagnosed with probable AD. Seven individuals were diagnosed with non-AD dementias and were excluded from further analyses.

We first performed analyses to determine whether individuals designated as having vMCI (n=125) were more likely to be diagnosed with probable AD dementia or to decline than normal individuals. Compared with normal individuals, members of the vMCI group were more likely to be diagnosed with probable AD (20% vs 0%; χ^2_1=36.4; P<.001) or to decline (49% vs 28%; χ^2_1=9.2; P<.002). The subjects with MCI were more likely than normal individuals to be diagnosed with AD (41%; χ^2_1=36.4; P<.001) or to decline (62%; χ^2_1=13.6; P<.001) and were more likely than subjects with vMCI to be diagnosed with AD (χ^2_1=7.0; P<.01). The **Figure** illustrates these data.

With regard to the decline end point, some individuals in each group who did not meet the end point declined by 0.5 unit on the CDR-SB (normal, 19%; vMCI, 15%; MCI, 13%), some did not change (normal, 52%; vMCI, 24%; MCI, 13%), and others improved by 0.5 or 1 unit (vMCI, 12%; MCI, 11%). Of those who met the end point, there was a range of decline over the 5-year period, with some individuals declining by 1 to 1.5 units (normal, 22%; vMCI, 21%; MCI, 10%), others declining by 2 to 3 units (normal, 6%; vMCI, 14%; MCI, 32%), and others declining by greater than 3 units (normal, 1%; vMCI, 14%; MCI, 21%).

PREDICTION OF PROBABLE AD AND DECLINE WITHIN THE ENTIRE SAMPLE

We next sought to determine whether graded measures of impairment (based on CDR-SB or neuropsychological test scores) would be useful in the assessment of the likelihood of a diagnosis of probable AD or decline in the entire sample. **Table 2** shows the results of logistic regression models predicting these outcomes. Baseline CDR-SB was strongly associated with the likelihood of probable AD; a logistic regression model predicting AD as a function of degree of baseline CDR-SB, adjusted for age, sex, and education, indicated a nearly 5-fold increase in the likelihood of AD dementia per point in baseline CDR-SB (odds ratio [OR], 4.8; 95% confidence interval [CI], 3.0-7.8; P=.001). Adjusted univariate logistic regression models also showed that the likelihood of probable AD was predicted by all neuropsychological test results examined (ORs, 0.57-0.62). Similar results, generally showing more modest effects, were observed for the decline outcome (OR, 2.25 per point of CDR-SB; OR, 0.64-0.78 for neuropsychological test measures). (For the interpretation of ORs, a higher CDR-SB indicates more prominent symptoms and is scaled in points on the CDR-SB, while higher neuropsychological test scores indicate better performance and are scaled in standard deviation units. For example, for these univariate analyses, an additional point on the CDR-SB results in nearly a 5-fold increase in likelihood, while 1 SD better performance in verbal memory results in a decrease in likelihood by nearly one-half.)

Multivariate logistic regression models demonstrated that the likelihood of probable AD was predicted by a model including CDR-SB, verbal memory, and executive function (overall model, χ^2=78.3; P<.001). Specifically, an AD diagnosis was predicted by CDR-SB (OR, 4.8; 95% CI, 2.8-8.1; P=.001), verbal memory (CVLT delayed retention, OR, 0.67; 95% CI, 0.48-0.94; P=.02), and executive function (Trails B, OR, 0.58; 95% CI, 0.39-0.88; P=.01). For the decline outcome, a multivariate model including clinical impairment (CDR-SB), verbal memory, and executive function (overall model, χ^2=53.6; P<.001) was predictive. Specifically, decline was predicted by CDR-SB (OR, 2.06; 95% CI, 1.5-2.9; P<.001), verbal memory (Free and Cued Selective Reminding Test, OR, 0.72; 95% CI, 0.54-0.95; P=.02), and executive function (Self-Ordering Test, OR, 0.75; 95% CI, 0.57-0.99; P<.05). Thus, CDR-SB, verbal memory performance, and executive function performance are useful together in the prediction of a clinical diagnosis of AD and decline.

PREDICTION OF PROBABLE AD AND DECLINE WITHIN THE vMCI SUBGROUP

We then investigated whether the grading of impairment (based on CDR-SB or neuropsychological test scores) within the vMCI subgroup would be useful for predicting AD dementia and decline. As earlier, each of the key predictors was analyzed in separate univariate logistic re-

Table 2. Adjusted Univariate Analyses of Baseline Clinical and Neuropsychological Measures Predicting Probable AD Diagnosis or Subsequent Cognitive Decline (CDR-SB Increase ≥ 1.0) Over Approximately 5-Year Follow-up Period[a]

	OR (95% CI)			
	Probable AD Diagnosis Over 5 Years		Clinically Significant Cognitive Decline Over 5 Years	
	Entire Sample	vMCI	Entire Sample	vMCI
CDR-SB	4.8 (3.0-7.8)[b]	1.65 (1.2-2.1)[c]	2.25 (1.61-3.15)[b]	1.93 (1.5-2.6)[c]
CVLT[24] total learning score	0.62 (0.45-0.87)[c]	1.2 (0.67-2.2)	0.76 (0.59-0.99)[d]	1.4 (0.89-2.3)
CVLT delayed retention score	0.61 (0.46-0.81)[c]	0.76 (0.44-1.3)	0.78 (0.62-0.98)[d]	0.81 (0.52-1.3)
Free and Cued Selective Reminding Test[27] score	0.57 (0.42-0.76)[b]	0.78 (0.50-1.2)	0.64 (0.50-0.82)[b]	0.66 (0.45-0.97)[d]
Trails B[28] score	0.57 (0.42-0.79)[c]	0.52 (0.33-0.84)[c]	0.76 (0.59-0.97)[d]	0.74 (0.51-1.1)
Self-Ordering Test[29] score	0.60 (0.43-0.83)[c]	0.76 (0.47-1.2)	0.68 (0.52-0.88)[c]	0.93 (0.63-1.4)

Abbreviations: AD, Alzheimer disease; CDR-SB, Clinical Dementia Rating sum of boxes; CI, confidence interval; CVLT, California Verbal Learning Test; OR, odds ratio; Trails B, Trail Making Test Part B; vMCI, very mild cognitive impairment.
[a] Adjusted for age, sex, and education.
[b] $P < .001$.
[c] $P < .005$.
[d] $P < .05$.

Table 3. Longer-term Outcome of Individuals Demonstrating Cognitive Decline Within First 5 Years of Follow-up by Baseline Status

	Total	Normal	vMCI	MCI
Original sample size	244	77	125	42
No. with additional 5-y follow-up[a]	27	5	18	4
No. of follow-up years after initial decline	8.8	8.5	9.2	7.6
No further decline	4	1	2	1
Further decline, without dementia	6	1	5	0
Probable AD	14	2	9	3
Non-AD dementia	3	1	2	0

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; vMCI, very mild cognitive impairment.
[a] These individuals had 5 or more additional years of follow-up after meeting the end point of cognitive decline in the present analysis.

gression models for each clinical group (Table 2). In multivariate analyses within the vMCI group, the likelihood of a diagnosis of probable AD was predicted by both CDR-SB (OR, 2.13; 95% CI, 1.08-4.18; $P = .03$) and executive function (Trails B, OR, 0.56; 95% CI, 0.35-0.91; $P = .02$). Likelihood of decline was predicted by CDR-SB (OR, 1.78; 95% CI, 1.02-3.07; $P = .04$). The CVLT was less powerful in prediction within the vMCI group because the diagnostic criteria used in defining vMCI truncated the distribution of values. Separate analyses are not presented for the MCI group because of its small sample size.

LONGER-TERM OUTCOME OF PARTICIPANTS WITH CLINICAL DECLINE

To examine the clinical significance of the intermediate outcome measure, decline, longer-term follow-up data were used to assess future clinical course in participants who met this outcome. Of the 107 subjects who met the clinical decline outcome within 5 years of initial follow-up, 27 individuals had at least 5 additional follow-up visits after the first visit, at which the decline end point had been met. Of these 27 subjects who declined, 17 (63%) ultimately were diagnosed with dementia after longer follow-up (mean time to dementia diagnosis after initial decline, 6.1 years; 14 with AD and 3 with non-AD dementias). Of the remaining 10 individuals, 6 declined by at least another 1.0 in CDR-SB but did not have dementia at last evaluation (mean follow-up time after initial decline, 9.5 years). The other 4 remained stable after having experienced the initial decline; none of these individuals improved after the initial decline (mean follow-up time after initial decline, 8.8 years). Additional details on longer-term outcome of those who declined are presented in **Table 3**.

Of the 244 subjects in the present analyses, 13 individuals died and underwent autopsy. Eight had a diagnosis of probable AD at the last clinical visit prior to death, 5 of whom had pathological changes consistent with a high probability of AD at autopsy[33]; 1 also had Lewy body pathological features. Of the remaining 3, 1 had diffuse Lewy bodies and a lesser degree of AD pathological features, 1 had both AD and cerebrovascular pathological features, and the third had mild AD changes but did not meet pathological criteria. Two of the 13 autopsied subjects had a diagnosis of vascular dementia at their last clinical visit and both demonstrated only cerebrovascular disease at autopsy. Three of the 13 autopsied subjects died with a most recent CDR of 0.5, 2 of whom showed evidence of only cerebrovascular pathological features; the other had no obvious pathological features.

COMMENT

The data presented herein demonstrate that a clinical assessment approach can identify individuals who are mildly impaired but do not meet formal MCI criteria as typically operationalized in clinical trials (vMCI), yet are more likely than normal individuals to develop AD dementia within about 5 years. We also showed that the CDR-SB and neuropsychological test performance are useful, taken separately or together, for predicting a probable AD diagnosis in a broad sample of subjects with diagnoses ranging from normal to typical MCI and within the narrower spectrum of vMCI.

The CDR-SB provides a measure of the severity of cognitive symptoms in daily life based on a structured clinical history and graded based on clinical judgment of the degree of change relative to that person's own previous baseline.[12,17,18,32] Thus, even from a single evaluation, the CDR-SB inherently provides an indication of whether the individual shows evidence of a decline in cognitive function in daily life. The grading of neuropsychological performance has the advantage of being an objective, performance-based measure but, at least when used cross-sectionally, may be challenging to interpret regarding the extent to which current performance (whether normal or impaired relative to normative data) represents a change. An approach that combines both domains of information is often part of a comprehensive clinical assessment and appears, from the present data, to be valuable in prediction of clinical course as well.

In the sample as a whole, the baseline CDR-SB and performance on verbal memory and executive function tests predicted a clinical diagnosis of probable AD over about 5 years. These same baseline measures also predicted clinically significant worsening of symptoms over the same follow-up period. The relative value of these domains of measurement will likely vary depending on the specific tools used, the setting, and the population, but they may be complementary in many situations. Even in the vMCI subgroup, both the CDR-SB and degree of neuropsychological (executive function) impairment were useful, taken either separately or together, in the prediction of a diagnosis of AD within about 5 years. Because of the criteria used to define this vMCI subgroup, the distribution of memory performance was truncated, which is the primary reason that memory measures were not useful predictors in this subgroup but were powerful predictors in the sample as a whole.

IDENTIFICATION OF INDIVIDUALS WITH vMCI

Longitudinal studies of community volunteers, like the cohort analyzed herein, identify many individuals who are not normal—some of whom have "cognitive complaints," some of whom have relatively mild impairment in 1 or more domains of psychometric testing, and others who have both.[10-12,14,34,35] A subset of individuals identified in these studies is comparable with subjects included in clinical trials for MCI, where the criteria have been implemented using cutoff scores on memory testing.[22] However, many individuals who do not meet these stricter MCI criteria do not meet criteria for normal cognition and therefore have been referred to as having "very mild" MCI. This milder end of the MCI spectrum has received less systematic study than the more severe end of the MCI spectrum, so it has been less clear whether there is a consistent intermediate phenotype between normal aging and a strictly implemented MCI diagnosis, both with respect to characteristics at the time of baseline assessment and longitudinal outcome.

We focused on a subgroup of individuals classified as having vMCI based in large part on mild symptoms of cognitive impairment in daily life, with minimal or no objective impairment on neuropsychological testing. We modeled our definitions of MCI and vMCI after those used by another group in a longitudinal community volunteer–based sample.[11] The data from the present study replicate their findings that individuals with vMCI ("pre-MCI" by their terminology) are intermediate between normal individuals and those with typical MCI in their likelihood of developing AD dementia within 5 years. As was found in the previous study, our vMCI group had a milder level of impairment in daily life (CDR-SB) and milder performance deficits on neuropsychological tests (including those not used to define MCI) than the MCI group.

In the present study, the proportion of our MCI group that "converted" to probable AD is lower than those of others, with 41% of the group receiving a diagnosis of AD by the 5-year end point, or approximately 8% per year.[11,36] The proportion of our vMCI group that progressed to an AD diagnosis within 5 years (20%, or approximately 4% per year) is also slightly lower than that of subjects with pre-MCI in the Storandt et al study[11] (about 27% at 5 years, or 5%-6% per year). Given the heterogeneity of cohorts of subjects with MCI and other "predementia" cohorts with respect to clinical outcome,[36-39] it is critical to begin to determine how to gauge the likelihood of dementia and milder forms of cognitive disability in individuals with vMCI. Our findings in this study show that, even within a group of subjects with vMCI, variation in the level of impairment in daily life (CDR-SB) and neuropsychological test performance will provide valuable indexes of the level of impairment at baseline, which can be used to compare samples for "case mix" and to predict the subsequent likelihood of developing AD dementia. It will be of great interest to compare subjects classified as having cognitive complaints with those considered to have pre-MCI or vMCI to determine the relationships between complaints or symptoms, test performance, and long-term clinical outcomes.

CLINICAL DECLINE AS A MEANINGFUL INTERMEDIATE OUTCOME MEASURE

Our secondary outcome measure, clinical decline (CDR-SB increase of ≥ 1.0), which has not been used before to our knowledge, may be useful as the focus of clinical trials shifts to individuals with milder impairments, since groups of such individuals would likely have low rates of conversion to dementia over the short-term (eg, 3-5 years). This outcome measure has both face validity, in that it is a measure of declining cognition as reflected in daily function, and predictive validity, since it appears to identify many people who are later diagnosed with probable AD or an-

other dementia. It will be illuminating to investigate the relationship of this symptom-based outcome measure to other types of outcomes used in clinical trials, including clinician- and informant-based measures of "impression of change"[40] or psychometric outcomes demonstrating declining cognitive performance on neuropsychological tests.[41]

LIMITATIONS

Several potential limitations of this study deserve mention. The participants were volunteers who may have characteristics that do not generalize well to the broader population. For example, some individuals may volunteer because they are concerned about their memory and thus may be more likely to report the presence of symptoms. In addition, the individuals in this sample are highly educated, which may also reduce generalizability in a variety of ways. Some individuals may engage in complex activities that make subtle cognitive change more apparent, and they and their informants may be more likely to observe and report these symptoms. The educational background of this sample is almost certainly reflected in better neuropsychological performance despite the presence of cognitive change in complex activities of daily life. Since many individuals in the primary care setting are not free of vascular risk factors or medical/neurological/psychiatric disease and may not have reliable informants, these issues also limit generalizability of the present results. Furthermore, it would be of interest to specifically investigate the possible contributions of subtle psychiatric symptoms in this setting. Another limitation is the retrospective application of MCI criteria; as a result, the CDR was used for both diagnostic classification of MCI and the decline outcome measure. It would be ideal in the future to perform a similar study with prospectively applied diagnostic criteria. Finally, the specific instruments used in assessment require specialized training and long administration times (the CDR evaluation and neuropsychological testing protocols used herein take about 1-2 hours each). Abbreviated screening instruments based on the CDR approach that can be applied in primary care settings are currently being developed and tested,[42] and neuropsychological batteries are being designed that may be sensitive to early signs of MCI and AD within a relatively short testing session.[43]

The CDR evaluation approach used in the present longitudinal study is particularly time and labor intensive compared with the approach typically used in clinical settings, including many clinical research settings. As the CDR-SB becomes more widely used nationally and internationally—through clinical trials, the Alzheimer's Disease Neuroimaging Initiative, and the Alzheimer's Disease Centers Uniform Data Set[44]—it will be critical to continue to refine uniform procedures for rating the CDR-SB. Efforts are currently under way at our institution to optimize the efficiency of the CDR to obtain reliable and valid ratings in a shorter time frame more consistent with practice in the Alzheimer's Disease Centers, clinical trials, and other research programs.

Despite the challenges, a comprehensive clinical approach that includes the graded assessment of both level of impairment in daily life and neuropsychological performance will likely have utility for characterizing current deficits and estimating future likelihood of dementia and decline among older individuals with very mild levels of impairment. Since data are accruing that demonstrate the presence of biological abnormalities in brain structure,[45,46] function,[47,48] brain amyloid load,[49] and cerebrospinal fluid markers[50] in individuals with the mildest symptoms of cognitive impairment, it will also be essential to integrate imaging and other biomarkers with sensitive clinical assessment methods to provide comprehensive assessments of the likelihood of subsequent cognitive disability.[51] Such risk estimates may be valuable for the purposes of recruiting and characterizing a targeted sample of mildly impaired but relatively high-risk (for future dementia) individuals for clinical trials of disease-modifying interventions and, one hopes, for screening primary care patients and community populations for individuals who might benefit from agents that prove effective.

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