ORIGINAL CONTRIBUTION

Mild Cognitive Impairment Represents Early-Stage Alzheimer Disease

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Background: Mild cognitive impairment (MCI) is considered to be a transitional stage between aging and Alzheimer disease (AD).

Objective: To determine whether MCI represents early-stage AD by examining its natural history and neuropathologic basis.

Design: A prospective clinical and psychometric study of community-living elderly volunteers, both nondemented and minimally cognitively impaired, followed up for up to 9.5 years. Neuropathologic examinations were performed on participants who had undergone autopsy.

Setting: An AD research center.

Participants: All participants enrolled between July 1990 and June 1997 with Clinical Dementia Rating (CDR) scores of 0 (cognitively healthy; n=177; mean age, 78.9 years) or 0.5 (equivalent to MCI; n=277; mean age, 76.9 years). Based on the degree of clinical confidence that MCI represented dementia of the Alzheimer type (DAT), 3 subgroups of individuals with CDR scores of 0.5 were identified: CDR 0.5/DAT, CDR 0.5/incipient DAT, and CDR 0.5/uncertain dementia.

Main Outcome Measure: Progression to the stage of CDR 1, which characterizes mild definite DAT.

Results: Survival analysis showed that 100% of CDR 0.5/DAT participants progressed to greater dementia severity over a 9.5-year period. At 5 years, rates of progression to a score of CDR 1 (or greater) for DAT were 60.5% (95% confidence interval [CI], 50.2%-70.8%) for the CDR 0.5/DAT group, 35.7% (95% CI, 21.0%-50.3%) for the CDR 0.5/incipient DAT group, 19.9% (95% CI, 8.0%-31.8%) for the CDR 0.5/uncertain dementia group, and 6.8% (95% CI, 2.2%-11.3%) for CDR 0/controls. Progression to greater dementia severity correlated with degree of cognitive impairment at baseline. Twenty-four of the 25 participants with scores of CDR 0.5 had a neuropathologic dementing disorder, which was AD in 21 (84%).

Conclusions: Individuals currently characterized as having MCI progress steadily to greater stages of dementia severity at rates dependent on the level of cognitive impairment at entry and they almost always have the neuropathologic features of AD. We conclude that MCI generally represents early-stage AD.

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MILD COGNITIVE impairment (MCI) is conceptualized as a boundary or transitional state between aging and dementia.[1] Memory deficit is both the usual complaint in MCI and the cardinal feature of Alzheimer disease (AD). The major focus of MCI research has been to distinguish individuals who will progress to AD from those who will not.[1-9] Interest in MCI has been stimulated by the hope that pharmacologic intervention at this stage may delay or prevent progression to AD.[10] Multicenter trials of cholinesterase inhibitor drugs and other agents with putative benefit for AD already are being conducted in individuals with MCI.

The diagnosis of MCI is established by (1) evidence of memory impairment, (2) preservation of general cognitive and functional abilities, and (3) absence of diagnosed dementia.[3] Mild cognitive impairment is staged clinically at the 0.5 level on the Clinical Dementia Rating (CDR) scale.[11] Memory deficit in MCI is quantitated by scores greater than 1.5 SDs below that of age-appropriate norms on measures of episodic memory. However, the other MCI criteria are subjective and can be difficult to operationalize. For example, scores in the normal range for age on the Mini-Mental State Examination (MMSE)[12] are assumed to indicate preserved general cognitive abilities, although brief cognitive tests such as the

SUBJECTS AND METHODS

CLINICAL DATA

Subjects were participants who enrolled in our longitudinal study (inaugurated in 1979) of healthy aging and dementia of the Alzheimer type (DAT) between July 1990 and June 1997 and were either nondemented or had very mild cognitive difficulties. The period of study reflects the initiation in our protocol in July 1990 of a classification scheme that predicts whether mildly impaired participants will progress to greater dementia severity; eligible subjects entered after June 1997 were not included to allow surveillance through December 1999. Individuals living in the greater St Louis, Mo, community were eligible for enrollment. The recruitment and assessment methods have been described previously and are based on media appeals for both healthy and cognitively impaired persons.[27,28] All participants are assessed annually unless prevented by death, refusal, or relocation far from St Louis.

Four hundred four participants who met eligibility criteria and were between the ages of 45 and 103 years were enrolled with either a CDR 0 (n=177) or a CDR 0.5 (n=227) score, where CDR 0 indicates no dementia. Clinical and neuropathologic data obtained through December 1999 were used for analysis. All procedures were approved by the Washington University Human Studies Committee. Data from some individuals reported herein have been included in previous reports from our center.[25,26,28]

The inclusionary and exclusionary clinical diagnostic criteria for DAT used in this study have been validated.[29] These criteria require the gradual onset and progression of impairment in memory and in at least 3 other cognitive and functional domains. Other known neurologic, medical, or psychiatric disorders with the potential to cause dementia must be absent. These clinical diagnostic criteria are comparable to but more stringent (because impairment in 4 domains is required) than those for "probable AD" as reported by the work group convened by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association.[30] Diagnostic accuracy for AD with these criteria is 93% (AD confirmed histologically in 193 of 207 consecutive autopsies of individuals with DAT).[28] Nondemented controls who lack known causes of dementia and have no cognitive or functional impairment also are enrolled.

The determination of DAT or control status is based solely on clinical methods, without reference to psychometric performance. Experienced neurologists, psychiatrists, geriatricians, and master's-prepared nurse clinicians conduct semistructured interviews with the participant and with a collateral source (generally the spouse or adult child) who is knowledgeable about the participant; a neurologic examination of the participant also is conducted. Clinicians are assigned randomly to each assessment. At entry and every 2 years thereafter, the assessment interviews (collateral source and participant) are videotaped for later independent review by a second randomly chosen clinician. Examiners and reviewers are not aware of findings from previous assessments.

The assessment protocol contains items from standard brief cognitive batteries, including the MMSE and the Short Blessed Test (SBT),[31] but the items are dispersed such that a score cannot be readily discerned. The diagnosis of DAT is based on the clinical information (derived primarily from the collateral source) that the participant has experienced the gradual onset and progression of memory and other cognitive problems that represent a decline from that individual's previous level of function and interfere, at least to some degree, with performance of accustomed activities in the community and at home. Support for the diagnosis is sought from the individual's responses to relevant queries, including recall of recently experienced personal events (eg, visit from an out-of-town relative) and of new material (eg, a fictitious name and address); recall of highly learned personal information (eg, name of last school attended); temporal and geographic orientation; and abstract reasoning as measured by performance on similarities and differences, calculations (eg, determining the number of quarters in $6.75), and problem solving. The assessment protocol also contains visuoconstructive tasks (eg, clock drawing), a depression inventory, aphasia battery, health history, and medication inventory.[27,29]

The CDR[11,32] is a dementia staging instrument used to rate cognitive function along 5 levels of impairment from none to maximal (rated as 0, 0.5, 1, 2, or 3) in each of 6 domains: memory, orientation, judgment and problem solving, function in community affairs, home and hobbies, and personal care. (Personal care has no 0.5 impairment level.) Only impairment caused by cognitive dysfunction is rated. Community affairs and home and hobbies assess instrumental activities of daily living relevant to the individual and hence vary according to that person's accustomed activities; examples include job performance for those who still are employed and skills in driving, home repairs, household finances, shopping, cooking, and card games. Personal care represents basic activities of daily living common to almost all individuals (dressing, bathing and grooming, eating, and continence).

Based on the collateral source and participant interviews, a global CDR score is derived from individual ratings in each domain such that CDR 0 indicates no dementia and CDR 0.5, 1, 2, and 3 represent very mild, mild, moderate, and severe dementia, respectively. Interrater reliability for the CDR has been established.[33-35] The CDR 0.5 stage originally was designated "questionable dementia."[32] With experience, we recognized that this CDR stage often represents the earliest symptomatic stage of AD ("very mild dementia").[24] Not all domains need be rated at the same level of impairment as the global CDR score; for example,

MMSE often are insensitive to early-stage dementia.[5,13,14] The perceptions of a knowledgeable informant regarding an individual's cognitive abilities in everyday functioning, on the other hand, have been shown to be sensitive and reliable for early dementia detection.[15-19]

Overdependence on cognitive test performance and underutilization of knowledgeable informants may result in failure to detect very mild dementia in many individuals who nominally meet MCI criteria. Progression of patients with MCI to "diagnosable AD" may be confounded because the threshold for dementia diagnosis[20] may vary considerably among clinicians and may require long observation periods, since the mildest forms of AD are marked by slow rates of cognitive decline.[21,22] Even so, MCI

a participant may merit a box score of 1 for memory but scores of 0.5 or 0 for other domains and still have a global CDR of 0.5. The individual ratings can be totaled to yield the sum boxes,[36] a more quantitative rating that ranges from 0 (0×6, or no impairment in any of the 6 domains) to 18 (3×6, or maximal impairment in each of the 6 domains).

Beginning in July 1990, all participants with a global CDR 0.5 score were categorized on clinical grounds into 1 of 3 groups: (1) CDR 0.5/DAT, with impairment (0.5 or greater) in memory and at least 3 of the 5 remaining CDR domains; (2) CDR 0.5/incipient DAT, with impairment in memory and 2 or fewer remaining CDR domains; and (3) CDR 0.5/uncertain dementia, generally when memory only was impaired at the 0.5 level or the impairment was doubtful (eg, in the situation where a "worried-well" individual proclaims serious memory loss that is inapparent to the collateral source and does not interfer with usual function). Diagnostic confidence for DAT at the CDR 0.5 level increased from CDR 0.5/uncertain dementia to CDR 0.5/incipient DAT to CDR 0.5/DAT. Categorization was based on the clinician's judgment following the clinical assessment that the participant had early-stage DAT (either CDR 0.5/DAT or CDR 0.5/incipient DAT, depending on the number of impaired CDR domains) or that it could not be determined whether the participant was demented or healthy (CDR 0.5/uncertain dementia). In keeping with the expectation that CDR 0.5/DAT and CDR 0.5/incipient DAT represented early-stage AD, these 2 groups were predicted to progress in dementia severity with time to CDR 1 or greater. Because the CDR 0.5/incipient DAT group was less impaired (fewer CDR domains affected), they were expected to progress at a lesser rate than the CDR 0.5/DAT group. The CDR 0.5/uncertain dementia participants were expected to be heterogeneous, some perhaps with very early-stage AD and others who were cognitively normal but mildly depressed or worried, and hence as a group were predicted not to progress or to progress only very slowly.

EXPIRATION SUMMARY

In all participants who undergo autopsy, a validated retrospective postmortem interview is conducted with the informant to assess cognitive status from time of last assessment until death.[37] Before the results of the autopsy are known, a senior clinician reviews all clinical assessments and the postmortem interview and generates an expiration summary. The expiration summary yields a final CDR score and dementia diagnosis for the participant.[28]

APOE GENOTYPING

Beginning in 1993, restriction enzyme isotyping of the apolipoprotein E (*APOE*) allele was performed as described previously.[38] Genotype results were not available to clinicians and hence were not used diagnostically.

PSYCHOMETRICS

A 1.5-hour psychometric battery is administered to all participants by trained psychometricians at each assessment as described in detail elsewhere.[39] Testing usually takes place 1 to 2 weeks after the clinical assessment; the psychometric results are unknown to the clinician and do not enter into diagnosis or CDR staging. The psychometrician is unaware of the participant's CDR score and diagnosis. The battery includes 4 measures of episodic memory: logical memory, digit span (forward and backward), and associate learning from the Wechsler Memory Scale (WMS)[40] and the Benton Visual Retention Test,[41] where form C assesses nonverbal memory (administered according to 10-second exposure recall instructions). Also included are 3 measures of semantic memory: the information subtest of the Wechsler Adult Intelligence Scale (WAIS),[42] the Boston Naming Test,[43] and Word Fluency for S and P.[44] Four speeded measures of psychomotor and visuospatial ability address executive functions: WAIS digit symbol, WAIS block design, Trail-Making Test part A,[45] and Crossing-off.[46] An attentional measure (WMS mental control) and nontimed visuospatial measure (form D of the Visual Retention Test) complete the battery. Scoring procedures for this battery have been described.[39]

NEUROPATHOLOGY

Brains were examined by standard protocol as described previously.[47,48] Following fixation with neutral phosphate-buffered 10% formalin (3.7% formaldehyde by volume), brains were sectioned (1-cm intervals) in the coronal plane, and tissue blocks taken from midfrontal, temporal, inferior parietal, and occipital calcarine and visual association neocortex, hippocampal formation, entorhinal cortex, nucleus basalis of Meynert, midbrain/substantia nigra, pons/locus ceruleus, cerebellum, and other regions. Sections (6-µm) from paraffin-embedded tissue blocks were stained routinely with hematoxylin-eosin and modified Bielschowsky methods.[47] Histologic criteria reported by Khachaturian[49] were used with modification for the neuropathologic diagnosis of AD as described previously.[28]

STATISTICAL ANALYSIS

Progression to at least mild dementia severity, defined by a score of CDR 1 or greater, was the primary outcome measure. Rate of progression was estimated as a function of the length of follow-up using the Kaplan-Meier product limit estimator. The relation of each demographic, clinical, and psychometric measure to development of CDR 1 or greater was examined using the nonparametric log-rank test. All calculations were performed by SAS statistical software (SAS Institute, Cary, NC). Means are reported with SDs or 95% confidence intervals (CIs), as appropriate.

progresses to AD at rates of 10% to 15% per year,[1,2,4-6,23] suggesting that many MCI cases actually are AD. Support for this possibility also comes from our experience with minimally impaired individuals in whom AD almost always is the responsible neuropathologic disorder.[24-26]

For these reasons, we hypothesize that most MCI cases represent unrecognized very mild AD. To test this hypothesis, we studied individuals with the CDR 0.5 level of cognitive impairment encompassed by MCI to determine their rate of progression to more overt stages of dementia over a 9.5-year period in comparison with nondemented older adults. We also examined the clinicopathologic correlates of nondemented aging, MCI, and very mild AD.

Table 1. Baseline Variables and Relation to Progression to a Clinical Dementia Rating (CDR) of 1 or Greater*

Variable	CDR 0 Controls (n = 177)	CDR 0.5 Uncertain (n = 53)	CDR 0.5 Incipient (n = 69)	CDR 0.5 DAT (n = 105)	Progression Log-Rank Test χ^2	Progression Log-Rank Test *P*
Demographics						
Age, mean (SD), y	78.9 (10.7)	76.4 (11.1)	78.0 (9.4)	76.4 (8.1)	5.7	.02
Sex, M/F	65/112	26/27	30/39	46/59	0.6	.56
Education, mean (SD), y	14.0 (3.3)	13.5 (3.4)	12.5 (3.6)	12.5 (3.2)	0.2	.65
Patients with *APOE4* alleles, %†	(n = 135)	(n = 36)	(n = 56)	(n = 85)		
0	76	64	50	36		
1	23	36	45	54	5.4	.02
2	1	0	5	10		
Clinical findings						
Informant-reported finding, %						
Memory problem	19	70	77	95	2.0	.15
Memory decline	21	70	74	93	3.6	.06
Interference	4	40	45	84	6.3	.01
Subject-reported finding, %						
Memory problem	44	79	77	81	0.02	.88
Subject						
Short Blessed Test score, mean (SD) (0-28)	1.6 (2.2)	3.3 (3.6)	4.6 (4.0)	8.0 (5.4)	13.9	<.001
MMSE score (30-0)	28.5 (1.4) (n = 24)	29.2 (0.4) (n = 6)	25.9 (3.0) (n = 10)	23.7 (2.7) (n = 13)	5.3	.02
CDR sum boxes, mean (SD)	0.07 (0.2)	1.0 (0.6)	1.3 (0.5)	3.1 (0.7)	31.3	<.001
Psychometric, mean (SD)						
WMS Logical Memory	7.4 (2.8)	6.8 (3.1)	5.1 (3.2)	3.7 (2.7)	44.9	<.001
WMS Associate Learning	12.2 (3.3)	10.9 (4.0)	10.1 (3.3)	8.7 (3.0)	25.9	<.001
Digit Span, forward	6.5 (1.1)	6.0 (1.3)	6.0 (1.1)	6.0 (1.2)	1.8	.18
Digit Span, backward	4.5 (1.2)	4.3 (1.3)	4.2 (1.1)	3.9 (1.3)	4.9	.02
Benton Visual Retention form C	5.2 (1.8)	5.0 (1.9)	4.4 (2.1)	3.5 (1.8)	22.7	<.001
Boston Naming Test	52.2 (7.4)	48.6 (10.5)	45.7 (12.0)	42.9 (11.3)	10.8	.001
Word Fluency for S and P	27.6 (9.5)	23.1 (9.4)	25.3 (10.2)	22.0 (9.8)	1.3	.24
WAIS Digit Symbol	40.8 (12.7)	37.4 (13.2)	35.3 (15.4)	28.4 (14.1)	20.2	<.001
Trail-Making Test part A, No. of seconds	53.5 (27.2)	54.9 (25.7)	61.7 (34.9)	80.4 (42.8)	13.2	<.001
WMS Mental Control	6.9 (1.9)	6.4 (2.3)	6.2 (2.4)	6.1 (2.2)	3.1	.08
WAIS Information	19.6 (4.5)	16.9 (5.1)	16.8 (5.7)	13.6 (5.4)	14.2	<.001
WAIS Block Design	27.8 (8.3)	25.5 (10.0)	24.4 (10.1)	19.7 (9.5)	13.0	<.001
Benton Copy form D	9.4 (1.0)	8.9 (2.0)	9.3 (1.3)	8.9 (1.8)	3.4	.07
Crossing-off	152.5 (41.5)	146.4 (40.2)	137.9 (39.1)	153.6 (39.0)	5.7	.02

**DAT indicates dementia of the Alzheimer type; WMS, Wechsler Memory Scale; and WAIS, Wechsler Adult Intelligence Scale. The range of possible scores from best to worst performance is shown in parentheses for the Short Blessed Test and Mini-Mental State Examination (MMSE). Higher scores on the Short Blessed Test, CDR sum boxes, and Trail-Making A indicate worse performance; for all other psychometric measures, lower scores indicate worse performance.*

†Some subjects enrolled before 1993 lack APOE *genotype data; MMSE testing was initiated only in 1997 (the last year for entry into this study). The numbers of subjects include those with* APOE *and MMSE data.*

RESULTS

BASELINE

Entry characteristics for the CDR 0/control, CDR 0.5/uncertain dementia, CDR 0.5/incipient DAT, and CDR 0.5/DAT groups are shown in **Table 1**. The mean (SD) number of prescription medications used by participants (data not shown) ranged from 2.1 (1.9) in the CDR 0/control group to 2.4 (1.9) in the CDR 0.5/uncertain dementia group and was comparable to the frequency of medication use in a community survey of similarly aged persons.[50] Major affective disorder was excluded at entry. Depressive features were defined by the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition,*[20] criteria for a major depressive episode. The number of depressive features (maximum of 9) reported by subjects was low (data not shown); the CDR 0.5/uncertain dementia participants reported a mean of 1.5 (2.3) features, whereas the mean for all other groups was less than 1. A greater frequency of the *APOE* ϵ4 allele was found in CDR 0.5 compared with CDR 0 participants and increased with diagnostic certainty for DAT across the CDR 0.5 groups.

Impairment in individual cognitive domains rated by the CDR (**Figure 1**) showed that virtually all CDR 0.5 individuals were impaired in memory (vs none of the CDR 0 individuals); the second most frequently impaired domain was judgment and problem solving. The CDR 0.5/DAT participants had impairment in multiple domains (required for DAT diagnosis) and more often had greater impairment (ie, at the 1 level) than the CDR 0.5/incipient DAT and CDR 0.5/uncertain dementia individuals; the greater impairment was especially notable for memory. The CDR sum boxes (Table 1) reflect this greater impairment. Data for personal care, which cannot be rated as 0.5, are not shown in the Figure; 0%, 7%, 0%, and 10% of the

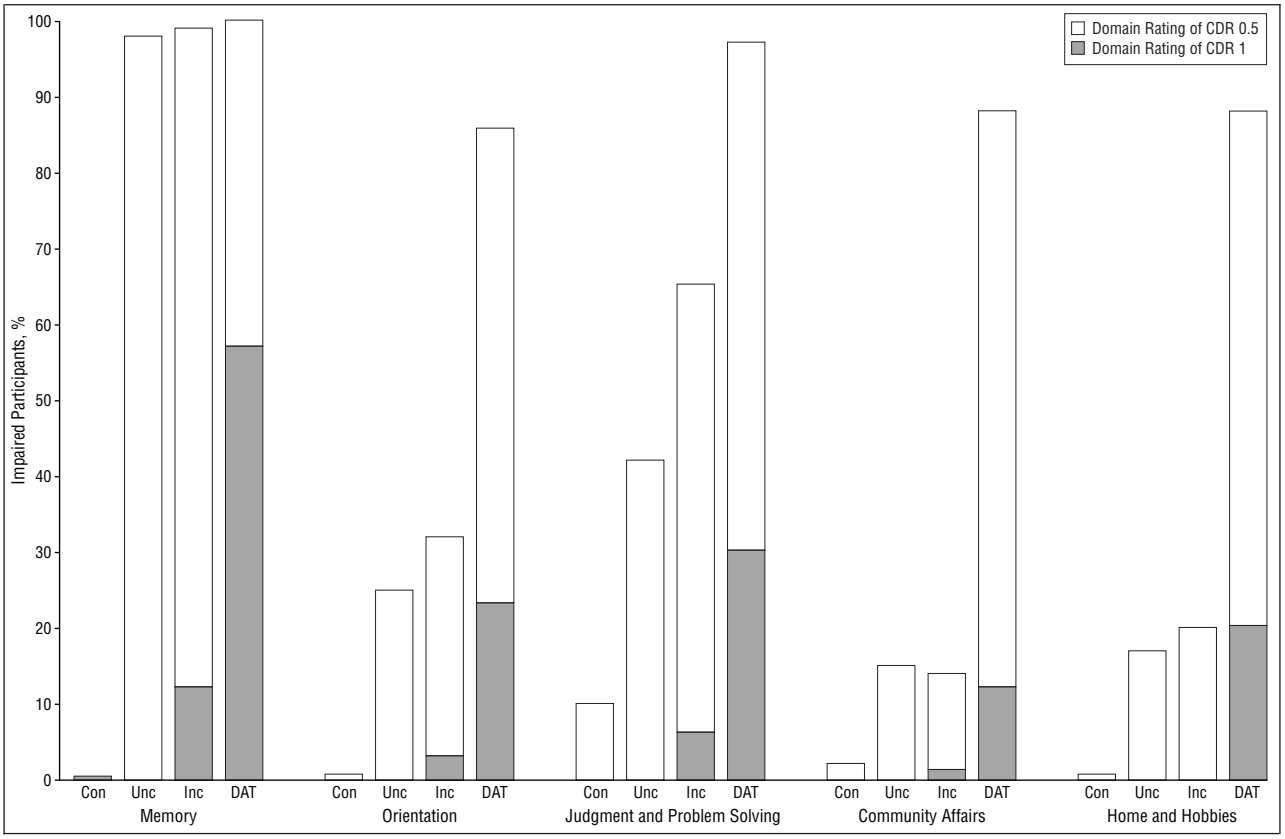

Figure 1. *Percentage of participants impaired at baseline at the 0.5 (open portion) or 1 (shaded portion) level in Clinical Dementia Rating (CDR) domains (memory, orientation, judgment and problem solving, community affairs, and home and hobbies) is shown for the 4 diagnostic groups. Con indicates CDR 0/controls; Unc, CDR 0.5/uncertain dementia group; Inc, CDR 0.5/incipient dementia of the Alzheimer type; and DAT, CDR 0.5/dementia of the Alzheimer type.*

CDR 0/control, CDR 0.5/uncertain dementia, CDR 0.5/incipient DAT, and CDR 0.5/DAT participants received a rating of 1 in personal care.

The CDR and, correspondingly, the sum boxes represent the clinician's judgment, synthesized from the informant and participant information, about the presence or absence of cognitive impairment. Informant reports of memory problems sufficient to interfere with performance of everyday functions were frequent in the CDR 0.5 participants but very unusual for CDR 0 participants (Table 1). Self-reported memory problems occurred frequently in CDR 0 participants and hence did not reliably distinguish the CDR 0 group from the CDR 0.5 groups.[17] The SBT, which incorporates a 5-item recall of a fictitious name and address, shows worse performance compared with controls in each of the CDR 0.5 groups. The overall degree of impairment on the SBT was very mild for all groups.[51] Performance on the SBT and on the MMSE corresponded with the degree of diagnostic certainty about DAT, because the CDR 0.5/incipient DAT and CDR 0.5/DAT groups performed more poorly than the CDR 0/control and CDR 0.5/uncertain dementia groups. Even the CDR 0.5/DAT group, however, had a mean MMSE score just at the lower range of "normal" cognitive status.[4,52,53]

Psychometric performance data for the 4 diagnostic groups also are shown in Table 1. In a hierarchical pattern (CDR 0.5/DAT worse than CDR 0.5/incipient DAT worse than CDR 0.5/uncertain dementia), the CDR 0.5 participants performed more poorly than CDR 0 individuals on measures of episodic memory (logical memory, associate learning, Visual Retention Test form C), semantic memory (information, Boston Naming Test), executive function (Trail-Making Test part A, digit symbol), and visuospatial abilities (block design). Immediate memory (digit span), attentional performance (mental control), and copying ability (Visual Retention Test form D) were comparable across CDR 0.5 and CDR 0 groups. The CDR 0.5 groups thus demonstrate an identical pattern of cognitive impairment, differing only in severity.

FOLLOW-UP

Figure 2 shows the survival analysis by diagnostic group for progression to CDR 1 status or greater over the 9.5-year observation period. Because enrollment was continuous, the period of observation varied for participants. The sample as a whole had a mean follow-up period of 5.1 years (2.0 years). The 5-year rates of progression to CDR 1 or greater (with 95% CIs) are 6.8% (2.2%-11.3%) for CDR 0/controls, 19.9% (8.0%-31.8%) for CDR 0.5/uncertain dementia, 35.7% (21.0%-50.3%) for CDR 0.5/incipient DAT, and 60.5% (50.2%-70.8%) for CDR 0.5/DAT groups. These rates are comparable with those reported for community samples of similarly aged controls and for patients with MCI.[1,6]

The predictive value of baseline features for progression to CDR 1 or greater status in CDR 0.5 participants is shown in Table 1. Among the clinical measures,

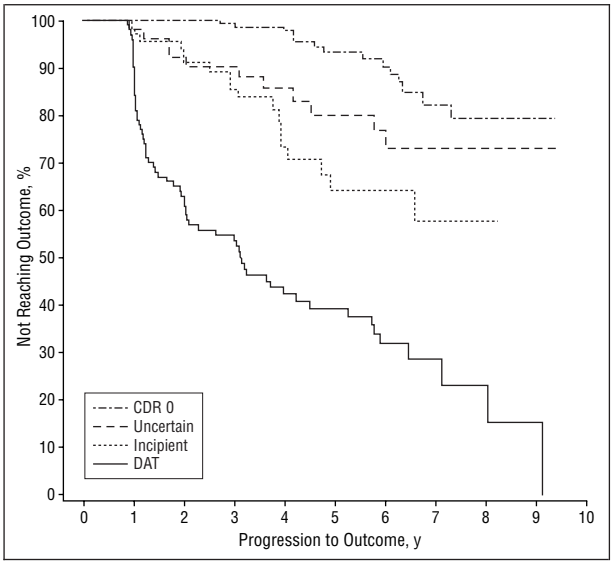

Figure 2. *Rate of progression to outcome (reaching Clinical Dementia Rating [CDR] score of ≥1) for each of the 4 diagnostic groups. CDR 0 indicates controls; Uncertain, participants with uncertain dementia; Incipient, participants with incipient dementia of the Alzheimer type; and DAT, dementia of the Alzheimer type.*

CDR sum boxes, SBT performance, and informant report of memory problem interfering with usual activities were significant predictors; CDR sum boxes had the largest χ^2 values. Most of the psychometric measures also were significant predictors. Logical memory had the largest χ^2 value, although it should be pointed out that all indicators were correlated.

NEUROPATHOLOGY

Table 2 shows the clinicopathologic correlations in all participants with postmortem examinations who died on or before December 31, 1999.

Seven of the 8 CDR 0 participants who remained nondemented at the time of the expiration summary did not meet neuropathologic criteria for AD; the remaining nondemented participant had histologic AD, consistent with preclinical AD.[26] Nine participants who were CDR 0 at baseline developed dementia at the CDR 0.5 or greater level by time of death. Of these, 8 had neuropathologic AD and the remaining participant had vascular dementia (the clinical diagnosis had been DAT).

In the CDR 0.5/uncertain dementia participants, all 6 who underwent autopsy had neuropathologic AD, including one who, while rated CDR 0.5 at entry, at expiration summary was considered to be nondemented (CDR 0). Seven of the 8 CDR 0.5/incipient DAT participants with postmortem assessments had neuropathologic AD, including 2 who remained in the incipient DAT diagnostic category at death. The remaining participant had vascular dementia; of note, this participant was the only CDR 0.5/incipient subject to have no memory impairment (rated 0 in the memory domain) at entry. Eight of the 11 CDR 0.5/DAT participants who had undergone autopsy had AD, including 8 of 10 who were considered to be demented at death (one participant was eventually considered to be nondemented and had a normal brain). The remaining neuropathologic diagnoses were frontotemporal dementia in one and vascular dementia in the other. For all participants with a CDR 0.5 score at entry, 21 (84%) had histologic AD, 2 had vascular dementia, 1 had frontotemporal dementia, and 1 had a normal brain. Thus, 24 (96%) of the 25 CDR 0.5 participants had a dementing illness. The AD cases frequently had associated neuropathologic findings, most commonly cerebral infarcts but also cortical and nigral Lewy bodies, cerebral trauma, and tumors.

COMMENT

The main finding from this study is that individuals considered by current criteria to have only MCI in fact have very mild AD. Strong evidence supports this conclusion. Cognitive impairment in individuals with MCI very often is not limited to memory but involves other cognitive domains (as assessed both clinically and psychometrically) and is sufficient to interfere with performance of activities of daily living as reported by an informant. These individuals thus satisfy criteria for dementia.[20] Predictable progression to more severe stages of DAT occurs in MCI at a rate that depends on the severity of impairment at baseline[21,22]; the more impaired individuals with MCI uniformly progress in global dementia severity within 10 years. Finally, the neuropathologic features of MCI overwhelmingly are that of AD.

How comparable is our sample to published MCI series, particularly because we equate our CDR 0.5 participants to MCI without requiring quantitative memory deficit for diagnosis? Our sample is equivalent on demographic and cognitive features to those reported by Tierney and colleagues,[4] Howieson and coworkers,[23] and Devanand and colleagues[5] except that our participants were younger than those of Howieson et al and older than those of Tierney et al and Devanand et al. Our CDR 0/control participants are equivalent for age, education, sex, *APOE* status, MMSE performance, CDR sum boxes, and risk for development of DAT to the community-based control sample of the Mayo Clinic MCI study.[1] Our CDR 0.5/DAT participants are comparable on these same features to their category of "AD, CDR 0.5," and our CDR 0.5/incipient DAT participants are similar to their category of "MCI, CDR 0.5"; the Mayo Clinic investigators did not report a category equivalent to our CDR 0.5/uncertain dementia participants. Comparison of memory deficits, as measured by WMS logical memory, for the Mayo Clinic subjects and our participants is indirect, since the Mayo Clinic group used the revised version of this measure and we used the original version; also, we measure only immediate recall, although we find performances on immediate and delayed recall to be highly correlated.[54] In our study, 7% of CDR 0, 16% of CDR 0.5/uncertain dementia, 28% of CDR 0.5/incipient DAT, and 52% of CDR 0.5/DAT participants performed 1.5 SDs below the mean of our CDR 0/control group on logical memory, whereas all of the Mayo Clinic "MCI, CDR 0.5" and "AD, CDR 0.5" subjects appear to score more than 1.5 SDs below the performance of their controls. This comparison is consistent with the slightly lower mean MMSE score (22.6) for their "AD, CDR 0.5" group vs the MMSE score (23.7) for our CDR 0.5/DAT group and may indicate that the Mayo Clinic investigators used the CDR

Table 2. Clinicopathologic Correlations in 42 Cases*

	Expiration Summary				Neuropathologic Diagnosis	
Case No.	Age at Entry, y	Age at Death, y	CDR Scores	Diagnosis	AD?	Other
CDR 0 at entry						
Remain CDR 0 at death						
1	86	88	0	Control	No	Subacute left frontal hemorrhage
2	85	91	0	Control	No	None
3	89	95	0	Control	No	None
4	88	92	0	Control	No	None
5	85	86	0	Control	No	None
6	76	80	0	Control	No	Left thalamic angioma
7	85	88	0	Control	No	None
8	80	88	0	Control	Yes	Bilateral cortical infarcts
CDR ≥0.5 at death						
9	88	95	2	DAT	Yes	None
10	87	94	3	DAT	Yes	Right occipital infarct, bilateral lacunes
11	87	93	2	DAT	Yes	Bilateral lacunes
12	93	95	0.5	DAT	Yes	Left cerebellar infarct
13	87	91	0.5	DAT	Yes	Cortical and nigral LBs, bilateral lacunes, meningiomas
14	91	92	1	DAT, VaD	Yes	Bilateral cortical infarcts
15	85	91	0.5	DAT	Yes	Left caudate lacune
16	89	89	0.5	DAT	Yes	Bilateral lacunes, right cerebellar infarct
17	94	99	0.5	DAT	No	VaD, left frontal, left thalamic infarcts
CDR 0.5/uncertain dementia at entry						
18	90	98	3	DAT	Yes	None
19	74	81	3	DAT	Yes	None
20	90	93	1	DAT, DLB	Yes	Bilateral lacunes, no LBs
21	80	83	0.5	DAT	Yes	Left cerebral hemorrhage, left thalamic lacune, meningioma
22	103	105	0.5	DAT	Yes	Cortical and cerebellar infarcts, acute
23	80	87	0	Control	Yes	Left parietal infarct, bilateral lacunes
CDR 0.5/incipient DAT at entry						
24	88	90	1	DAT	Yes	Acute left MCA infarct, right occipital and right caudate infarcts
25	81	84	2	DAT	Yes	Right frontal infarct
26	93	96	1	DAT	Yes	Right posterior cingulate infarct
27	60	64	0.5	Incipient DAT	Yes	None
28	88	90	3	DAT, DLB	Yes	Cortical and nigral LBs, temporal infarct, ventricular subependymoma
29	97	102	0.5	DAT	Yes	Cingulate infarct
30	76	78	0.5	Incipient DAT	Yes	None
31	82	82	0.5	DAT	No	VaD, multiple lacunes
32	80	86	3	DAT	Yes	None
33	73	79	3	DAT	Yes	None
34	68	74	3	DAT	Yes	None
35	85	92	3	DAT, DLB	Yes	Cortical LBs, acute frontal infarct, remote right orbital cortical contusion
36	88	92	2	DAT	Yes	None
37	73	80	3	DAT	Yes	Left thalamic infarct
38	79	81	2	DAT	Yes	None
39	79	85	3	DAT	Yes	None
40	75	88	3	DAT	No	FTD, nigral LBs, left caudate lacune
41	93	96	2	DAT	No	VaD, right MCA infarct, bilateral lacunes
42	89	95	0	Control	No	None

**CDR indicates Clinical Dementia Rating; AD, Alzheimer disease; DAT, dementia of the Alzheimer type; LBs, Lewy bodies; VaD, vascular dementia; DLB, dementia with Lewy bodies; MCA, middle cerebral artery; and FTD, frontotemporal dementia.*

0.5 designation for a slightly more cognitively impaired group than do we. Our sample thus contains many participants who meet MCI criteria (but who we already diagnose with DAT) and many others with less cognitive impairment than is required for a diagnosis of MCI.

How can we diagnose AD in such minimally impaired participants, especially since many physicians are uncomfortable in classifying patients with MCI as having AD?[1] First, we expect cognitive function in truly nondemented elderly patients to be unaccompanied by substan-

tive decline. Rather than accepting memory failure as part of aging, in the absence of disease we anticipate relatively stable performance over time; this expectation has been confirmed by us and others.[22,23,55-57] We therefore suspect even mild impairment as an abnormal rather than a benign accompaniment of age. Second, we operationalize "impairment" as the functional consequences of cognitively related interference with the performance of activities of daily living. Activities need not be relinquished to meet the interference criterion but simply performed less well than before because of cognitive loss. Third, we rely on informant observations to identify early cognitive change and functional impairment. Perhaps uniquely among programs investigating aging, MCI, and early-stage AD, we keep the clinical diagnostic process independent of neuropsychological test scores (even the SBT and MMSE) because individual performance differences on cognitive measures may obscure the distinction between nondemented aging and very mild DAT,[14,39,58] whereas informant-based detection methods contrast the current and previous cognitive abilities of the individual and are sensitive to even the mildest stages of DAT.[17]

Within the 3 CDR 0.5 groups reported herein, rate of progression to more severe stages of DAT correlated with dementia severity at entry. We predicted that the CDR 0.5/DAT and CDR 0.5/incipient DAT groups would progress over time (the incipient DAT group less so because it was less impaired at entry) and that AD would be the responsible disorder for the dementia. These predictions were correct. We predicted also that the CDR 0.5/uncertain dementia group would be heterogeneous and would not substantially progress. Although the rate of progression in this group is not much greater than that of control participants, the neuropathologic findings (all 6 decedents in this group had AD) suggest that any CDR 0.5 designation, even at the uncertain dementia diagnostic level, may predict AD. Longer periods of observation may be necessary to determine the rate of progression to more severe stages of DAT in very minimally impaired individuals, but at least for some participants it appears that the CDR 0.5/uncertain dementia classification may represent the earliest symptomatic stage of DAT.

Selective attrition may have skewed the neuropathologic findings (eg, participants in the CDR 0.5/uncertain dementia group with AD may be more likely to die and undergo autopsy than those who did not have AD). Even so, in the 11 autopsy participants from all groups who were rated CDR 0.5 at expiration summary, 9 had AD and 2 had vascular dementia. For comparison, in the 10 autopsy participants from all groups who at expiration summary were rated CDR 0, AD was absent in 8; the remaining 2 were considered to have preclinical AD.[26] These data indicate that the CDR 0 vs CDR 0.5 distinction is valid and further supports the conclusion that CDR 0.5 designates "very mild dementia" rather than "questionable dementia."

Our study has limitations. It was restricted to individuals in whom the diagnostic distinction was between nondemented aging and DAT, and thus we cannot address MCI caused by other conditions. Our informant-based assessment methods may not be applicable in all situations, such as population surveys where a reliable informant cannot be ensured for all individuals. As with any volunteer cohort, there may be selection biases in our sample. Our participants, however, were drawn from the community rather than by referral from memory disorder clinics and have attributes identical to those reported for free-living older adults, including the frequency of prescription medication use,[50] the rate at which nondemented participants develop AD,[1] and the presence of comorbid disorders at autopsy. Thus, there is no obvious reason to consider this sample as any different from other longitudinal samples of aging and very mild dementia. The unique aspects of this study relate to the long surveillance period (9.5 years) and the extensive clinicopathologic data.

The implications of our major finding, that MCI represents early-stage AD, potentially are enormous. Two large population-based studies of older adults indicate that the prevalence of MCI is more than double that of dementia. The Canadian Study of Health and Aging[59] reported the prevalence of "cognitive impairment, no dementia" to be 16.8% in individuals older than 64 years, whereas the Italian Longitudinal Study on Aging[60] found the prevalence of "cognitive impairment, no dementia" to be 10.7% and of "age related cognitive decline" to be 7.5% in subjects aged 65 to 84 years. The prevalence of dementia in these studies was 8% and 5.5%, respectively. Combined with our findings that many individuals labeled as having MCI have diagnosable DAT, these data suggest that the true prevalence of AD may be much greater than is appreciated.

This study also demonstrates that DAT can be diagnosed at earlier stages than currently is practiced. Early recognition of dementia may alleviate uncertainty by patients and their families as to the true cause of the perceived cognitive decline, permit patients to participate in planning for their future at a stage when decision-making capacity is only minimally affected, and allow early access to dementia therapy with the goal of maximizing a period of relatively good function, although it is not yet proven that currently available cholinesterase inhibitor drugs benefit very mild DAT as they do mild-moderate DAT. Finally, future clinical trial designs for antidementia agents that incorporate a placebo treatment arm will need to consider the ethical and practical implications of withholding active treatment from individuals with very mild DAT.[61]

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