Course and etiology of dysexecutive MCI in a community sample

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Abstract

Background: Amnestic mild cognitive impairment (aMCI) is associated with an elevated risk of progressing to Alzheimer's disease. Much less is known about the course of dysexecutive mild cognitive impairment (dMCI). The goals of this study were to determine how the profile of cognitive deficits differs over time between patients with dMCI and aMCI, and control subjects; if the type of dementia differs between dMCI and aMCI in patients who progress to dementia; and if dMCI is more associated with stroke and white matter hyperintensity on magnetic resonance imaging (MRI) than aMCI.

Methods: The authors undertook a prospective evaluation of an inception cohort of 1167 ethnically diverse elders recruited from an urban community-based sample monitored with clinical and neuropsychological testing for an average of 4.5 years (standard deviation, 0.8 year). A subset of the subjects underwent MRI. We compared four groups of MCI patients: single-domain amnestic and dysexecutive MCI, and multiple-domain MCI with and without executive dysfunction.

Results: Compared with aMCI, dMCI was less likely to involve other areas of cognition over time and progress to dementia. None of the 33 single-domain dMCI patients progressed to dementia. The presence of executive dysfunction in multiple-domain MCI did not increase risk of progression to dementia. Patients with multiple-domain MCI with executive dysfunction who progressed to dementia were less likely to have an Alzheimer's–type dementia than MCI patients without executive dysfunction. Patients with dMCI were more likely to experience stroke, but not white matter hyperintensity, detected via MRI than patients with aMCI.

Conclusions: dMCI appears to follow a different course, and is less associated with Alzheimer's disease and more associated with stroke than aMCI.

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Keywords: Mild cognitive impairment; Dementia; Executive function; MRI

1. Introduction

Mild cognitive impairment (MCI) commonly occurs as a transitional state from normal cognition to dementia [1].

Deficits in MCI can involve separate areas of cognition, either in isolation or in combination. Amnestic MCI (aMCI) is the most common type of single-domain MCI, but MCI can involve other domains such as executive function (or dysexecutive MCI [dMCI]) [1,2]. In a previous study [1], we determined the relative prevalence and risk of progressing to dementia of the different subtypes of MCI in a multiethnic, community-based sample. In the current study, we

expand on these findings by addressing the following questions: How does the profile of cognitive deficits change over time between aMCI and dMCI? If dementia develops, does the type of dementia differ in these two conditions? Is dMCI associated more with cerebrovascular disease than aMCI?

We focused on dMCI because much less is known about the course and progression of dMCI than of aMCI. More than 20 studies have already been performed to determine the rates of conversion from MCI to dementia (see Mitchell and Shiri-Feshki [3] for a review of 15 of these studies). These studies have revealed that, contrary to initial supposition, nonamnestic single-domain MCI is as common or more common than single-domain aMCI in community-based samples [4–6]. They also indicate that nonamnestic single-domain MCI is significantly less likely to progress to dementia than aMCI. With the possible exception of nonamnestic multiple-domain MCI [6], all the subtypes of MCI are more likely to progress to Alzheimer's disease (AD) compared with other types of dementia [4,5]. However these studies did not subdivide nonamnestic single-domain MCI into its component cognitive domains, as we have done in the current study. The current study compares the changes in the pattern of cognitive deficits over time between aMCI and dMCI. Of the longitudinal studies that examined subtypes of MCI [1,6–8], only the previous study from our group [1] and the current study were performed using a community-based ethnically diverse sample. Of note, several of the large, multicenter studies currently underway, including the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the Alzheimer's Disease Research Centers, are poorly suited to determine the prevalence and course dMCI because they recruit subjects with aMCI selectively, but not other subtypes of MCI, in restricted clinical settings rather than the broader home-dwelling community.

In epidemiologic studies, MCI is associated with an annual conversion rate to dementia of 4.2% [3], although this rate varies considerably across studies [9]. Among the subtypes of MCI, aMCI and multidomain MCI with memory impairment appear to be at highest risk for progression to AD [1]. It has been hypothesized that nonamnestic types of MCI are more likely to progress to non-Alzheimer's dementias (eg, vascular dementia and frontotemporal lobar degeneration); however, this has not yet been demonstrated [9,10]. Vascular risk factors are associated with both executive dysfunction in nondemented elderly [11,12] and a worsening of the symptoms of AD [13]. Vascular dementia is more likely to have deficits in executive function than AD [14]. In the current study, we contrasted the course and etiology of MCI with and without executive dysfunction by comparing four MCI groups: single-domain amnestic and dysexecutive type and multiple domain with or without executive dysfunction.

The diagnoses of aMCI and dMCI are commonly used. Multiple-domain MCI with and without executive dysfunction are uncommon categories of MCI, but we used them because our main goal was to explore the effects of executive dysfunction on progression of MCI and conversion to dementia in both single- and multiple-domain MCI. To address these questions we compared four MCI groups: single-domain amnestic and dysexecutive type and multiple domain with or without executive dysfunction. The diagnoses of aMCI and dMCI are commonly used. Multiple-domain MCI with and without executive dysfunction are uncommon categories of MCI, but we used them because our main goal was to explore the effects of executive dysfunction on progression of MCI and conversion to dementia in both single- and multiple-domain MCI.

2. Methods

2.1. Subjects

The Columbia University institutional review board approved this project. All subjects discussed the study with an investigator and provided informed consent. This study was performed in a multiethnic, community-based sample in northern Manhattan [1]. The sampling strategy, detailed in previous publications [15–17], was designed to assemble an ethnically diverse sample representative of the community in which participants lived, and not enriched for particular characteristics or diagnoses. Medicare recipients age 65 or older residing in three contiguous census tracts in the neighborhoods of Washington Heights and Inwood were invited to participate in the study (the Washington Heights-Inwood Columbia Aging Project study). Subjects were excluded from the study if they did not speak English or Spanish. There were two recruitment efforts, one beginning in 1992 and the other in 1999. Ethnic group was determined by self-report using the format of the 2000 U.S. Census [18].

Subjects were diagnosed on their initial visit and categorized for the current analyses based on this initial diagnosis. See Fig. 1 for a flow diagram of enrollment. Participants were revaluated approximately every 18 to 30 months. The mean total follow-up was 4.5 years, with a standard deviation (SD) of 0.8 year. Only subjects who completed three sequential visits were used for this study (ie, if subjects dropped out or missed a visit, they were excluded from the entire analysis). Although this criterion reduced the number of subjects we could include in the longitudinal analysis, it ensured that the same subjects were compared at all time points.

We performed *t* tests between the subjects that were included and excluded to assess whether there were any systematic differences between the two groups. Age, education, Short Blessed Exam total [19], and the Blessed Functional Activity Scale [20] were compared between the two groups. A Bonferroni–corrected *P* value less than .05 was used to determine significance.

2.2. MCI and neuropsychological testing

The method for diagnosing MCI was identical to that used in our previous study [1], in which expanded Petersen
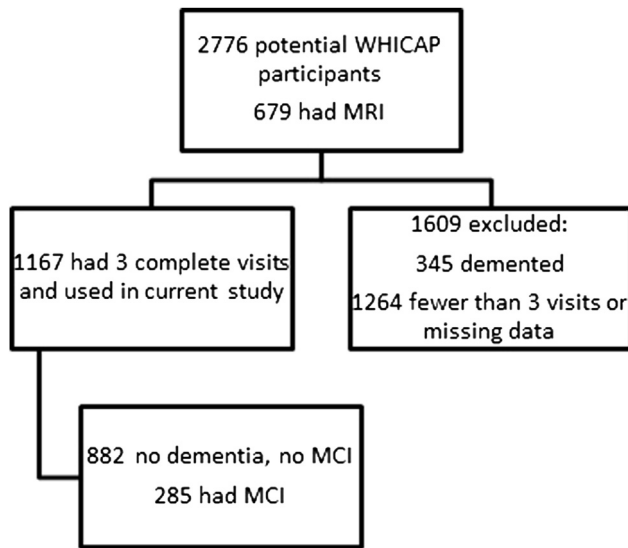
Fig. 1. Flow diagram of study enrollment. WHICAP, Washington Heights-Inwood Columbia Aging Project; MRI, magnetic resonance imaging; MCI, mild cognitive impairment.

criteria were used to include other subtypes of MCI besides aMCI [21]. MCI was diagnosed in a consensus conference by a group of physicians and psychologists based on a review of all the neuropsychological, clinical, neurological, psychiatric, and functional data. The consensus was blinded to the previous consensus diagnosis. The expanded Petersen MCI criteria used in this study for single-domain MCI were (*i*) a cognitive complaint; (*ii*) essentially preserved activities of daily living (defined later); (*iii*) objective impairment in one area of cognition defined as below 1.5 SD on an average composite measure (defined later) of memory, executive function, language, or visuospatial function; (*iv*) all other composite scores ≥1.5 SD below the demographically corrected mean; and (*v*) not demented (as diagnosed in the consensus conference by the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition, revised, criteria) [22]. Essentially preserved activities of daily living were defined as self- or caregiver report of difficulty on less than three of six items from the Disability and Functional Limitations Scale as specified in Manly and colleagues [1]. This cutoff was used because it captured 95% of the normative sample.

For the MCI criterion of objective impairment in an area of cognition, composite measures of four domains of cognition (memory, executive function, language, and visuospatial) were constructed by converting the scores for the tests listed here into z scores and then calculating the mean as detailed in Manly and colleagues [1]. The memory measure was the average composite of the total recall and delayed free recall from the Selective Reminding Test, and recognition from the Benton Visual Retention Test. The executive function measure was the average composite of letter fluency, category fluency, and the Wechsler Adult Intelligence Scale–Revised Similarities subtest. The language measure was the average composite of the Boston Naming Test,

and the Boston Diagnostic Aphasia Evaluation Repetition and Comprehension tests. The visuospatial measure was the average composite of Rosen Drawing and Benton Visual Retention Test matching. Each study participant was judged as having a deficit in one of these domains of cognition if their composite score fell below 1.5 SD of the age, years of education, ethnicity, and sex-adjusted prediction as calculated in a robust normative sample of nondemented older adults [15].

Two types of multiple-domain MCI were used in this study: MCI-multiple cognitive domains with executive impairment (MCI-MCDE) and without executive impairment (MCI-MCDN). MCI-MCDE was defined as meeting criteria for dMCI as noted earlier, with further impairment in at least one additional cognitive domain. MCI-MCDN was defined as impairment in two or more of the three nonexecutive cognitive domains (memory, language, visuospatial) without executive impairment. The categories of MCI are mutually exclusive.

2.3. Data analyses

Generalized estimating equations (GEEs) were used to compare the slope of cognitive change in memory, executive function, visuospatial, and language between the subjects without dementia or MCI and the subjects in the following four groups: aMCI, dMCI, MCI-MCDE, and MCI-MCDN. GEE is a semiparametric regression technique that, unlike logistic regression, which assumes independence, takes into account that data from the multiple visits of a subject are likely to be correlated [23,24]. Separate GEE analyses were performed on the factor scores for each of the four cognitive domains listed previously. In the GEE model, the dependent variable was the composite neuropsychological score for each domain and the predictors were the subtype of MCI and the time elapsed since entry into the study. The nondemented non-MCI group was used as the reference group to which the MCI subjects were compared. Main effects and interactions between the MCI subgroups (diagnosis) and the time elapsed (duration) were calculated. A significant interaction between the MCI subgroups and time elapsed in the GEE analysis reflects a significant difference between the change in the neuropsychological score over time (ie, the slope) between the MCI subgroup and the nondemented non-MCI group. Conversion to different types of dementia between the MCI subgroups was compared with a Kaplan-Meier survival analysis.

There were no significant differences in the included and excluded dMCI and MCI-MCDN patients on age, education, Short Blessed Exam total score [19], or the Blessed Functional Activity Scale [20]. In the aMCI group, subjects who were excluded were 1.4 years older on average than subjects who were included. In the MCI-MCDE group, the subjects who were excluded were an average of 2.6 years older and had a Short Blessed Exam total score that was

0.28 point (of 28 points) higher than those who were included (although their mean Short Blessed Exam total scored was 0.66, which is well within normal limits for this test). We concluded that the cognitive differences between the included and excluded groups were minimal, and that the MCI patients we included in our analyses were representative of the larger sample, albeit that the included aMCI and MCI-MCDE patients were slightly younger than the not-included patients.

2.4. Imaging analyses

Of the 2776 Washington Heights-Inwood Columbia Aging Project active study participants, 769 underwent magnetic resonance imaging as part of the study. The image was usually acquired during the subject's third visit. The mean time elapsed between entry into the study and imaging was 4.4 years (SD, 0.9 year)—very close to the mean time for the third evaluation (4.5 years). Image acquisition was performed on a 1.5-T scanner at Columbia University Medical Center. Fluid-attenuated inversion recovery (FLAIR)-weighted images (repetition time, 11,000 ms; echo time, 144.0 ms; inversion time, 2800 ms; field of view, 25 cm; number of excitations, 2; matrix size, 256 × 192; slice thickness, 3 mm) were acquired in the axial orientation, as were T1-weighted images (repetition time, 20 ms; echo time, 2.1 ms; field of view, 240 cm; matrix size, 256 × 160; slice thickness, 1.3 mm). Magnetic resonance images were transferred electronically to the University of California at Davis for analysis in the Imaging of Dementia and Aging Laboratory. The presence or absence of brain infarction on MRI was determined using all available images, including T1-weighted images, T2-weighted FLAIR images, and proton density/T2-weighted double-echo images. Lesions had to be larger than 3 mm to be considered an infarction. Infarcts of 1 cm or less were defined as small, and infarcts of more than 1 cm were defined as large. Two raters determined the presence of cerebral infarction on MRI. Previously published j values for agreement among raters has been generally good, ranging from 0.73 to 0.90 [25,26]. White matter hyperintensities were measured by isolating the brain on FLAIR images, identifying the voxels with intensity 3.5 SD or greater above the mean intensity value of the image, and multiplying these voxels by voxel dimensions and section thickness (see publications by others [27–30] for details of this procedure). The number of infarcts and volume of white matter hyperintensities were compared among the MCI groups using analyses of variance.

3. Results

3.1. Cognitive testing

Separate GEE analyses were performed on the four cognitive domains and Bonferroni corrected for four comparisons. For all of the cognitive domains tested, there were significant main effects of duration and diagnosis, indicating that—in each cognitive domain—cognitive scores differed among the patients with different MCI diagnoses, and those scores changed over time. We were most interested in the interaction of duration and diagnosis to determine whether the MCI groups had different changes in cognitive scores over time. For memory, there was no significant interaction between duration and diagnosis (Fig. 2A). In the language domain, the aMCI patients had a significant decline (B = −0.029, P = .003) and the dMCI patients had a significant improvement (B = 0.042, P = .001) compared with the subjects without dementia or MCI (Fig. 2B). In the visuospatial domain, patients with MCI-MCDN had less of a decline than the subjects without dementia or MCI (B = 0.043, P = .047), but this effect did not survive correction for multiple comparisons (Fig. 2C). The MCI-MCDE patients had significantly greater executive function decline than the subjects without dementia or MCI (B = −0.108, P = .002; Fig. 2D). All other interactions were not significant.

3.2. Progression to dementia

The patients were monitored for an average of 4.5 years (SD, 0.8 year). See Table 1 for subjects who received a diagnosis of dementia at any point during the 4-year follow-up. Of note, none of the patients with dMCI developed dementia. The proportion of patients with aMCI (21%), dMCI (0%), MCI-MCDE (25%), and MCI-MCDN (39%) who developed dementia was significantly different ($\chi^2[1] = 17.55$, $P < .001$). Kaplan-Meier analysis showed that the MCI groups had significantly different rates of progression to dementia (log-rank Mantel-Cox, $\chi^2[1] = 142$, $P < .001$; Fig. 3). See Table 1 for mean and median survival times to dementia from the Kaplan-Meier analysis.

3.3. Imaging

The mean amount of white matter intensity volume did not vary significantly by diagnostic group ($F_{(6,703)} = 1.39$, $P = .218$). The mean numbers of infarcts varied significantly by diagnostic group ($F_{(6,712)} = 4.83$, $P < .001$). See Fig. 4 for significant ($P < .05$) group differences revealed by post hoc analyses. The proportion of subjects with stroke that affected the frontal gray or white matter was calculated for each diagnostic group: no dementia no MCI, 9%; aMCI, 12%; dMCI, 19%; MCI-MCDE, 12%; and MCI-MCDN, 15%. When MCI patients progressed to dementia, 76% of aMCI, 70% of MCI-MCDN, and 46% of MCI-MCDE patients were given probable AD as the sole diagnosis (Table 1).

4. Discussion

In our longitudinal data, several trends emerged. First, patients with aMCI appeared to have more extension of cognitive deficits into nonamnestic cognitive domains, such as language, over 4.5 years than patients with dMCI. Second,
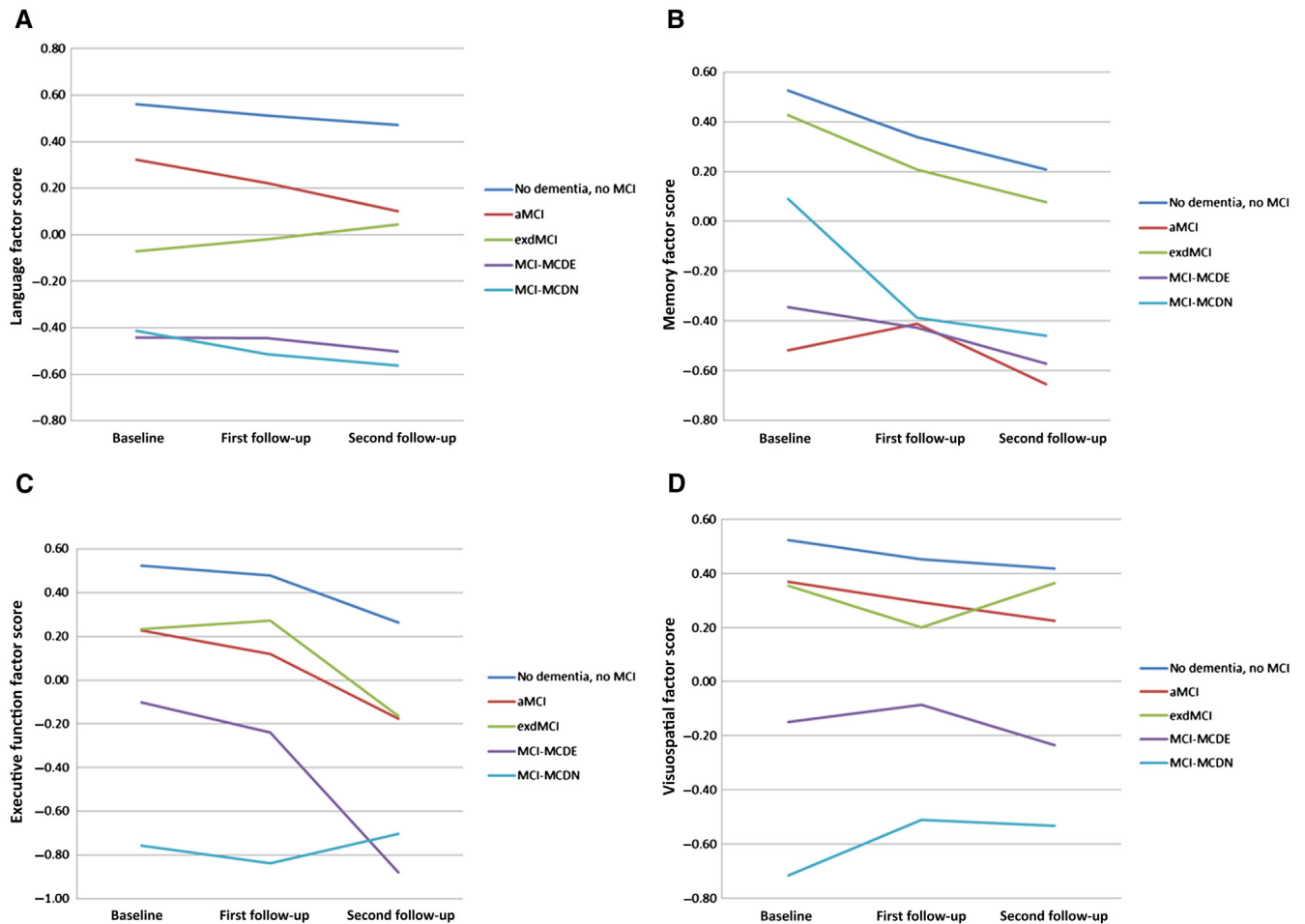
Fig. 2. (A–D) Changes in cognitive performance over time in different domains of cognition in patients with aMCI, dMCI, MCI-MCDE, and MCI-MCDN, and in patients without dementia or MCI. MCI, mild cognitive impairment; aMCI, amnestic MCI; exdMCI, dysexecutive MCI; MCI-MCDE, multidomain MCI with executive dysfunction; MCI-MCDN, multidomain MCI without executive dysfunction. (A) Language factor score. (B) Memory factor score. (C) Executive function factor score. (D) Visuospatial factor score.

as expected, patients with MCI affecting multiple domains generally had the lowest scores across all cognitive domains, and may be demonstrating a floor effect on some of the measures, but they are more likely to progress to dementia than those with single-domain MCI. These findings agree with the previously published finding that patients with aMCI have a greater risk of progressing to dementia than patients with dMCI, and that those with multidomain MCI are at higher risk of progressing to dementia than those with single-domain MCI [1].

Our findings on progression to dementia are consistent with our analysis of the neuropsychological data. dMCI tends to remain more isolated and less likely to progress to dementia than aMCI. Not only did none of the dMCI patients progress to dementia over 4.5 years, but a lower proportion of those with MCI-MCDE than those with MCI-MCDN progressed to dementia. This result is surprising given that MCI-MCDE patients actually have impairment in an additional domain—executive function—compared with MCI-MCDN patients. That no patients with dMCI progressed to dementia

is likely related to the small sample size of this group. When the MCI-MCDE patients did progress to dementia, the proportion of probable AD as the sole diagnosis was less than for aMCI or MCI-MCDN (Table 1). The most common other diagnoses besides probable AD were mixed dementia (AD plus stroke) or AD with other concomitant disease, and vascular dementia.

The imaging results demonstrate that patients with dMCI are more likely to have had a stroke than patients with aMCI. Preliminary evidence suggests that these strokes are more likely to be in the frontal gray and white matter in patients with dMCI. However, white matter hyperintensity (WMH) volume was not associated with dMCI compared with aMCI. Our findings on WMH replicate those of Luchsinger and associates in the same cohort [31]. These results suggest that dMCI is associated with infarcts larger than 3 mm, but not WMH, compared with aMCI. We do not have an explanation for this apparent paradox. One hypothesis is that WMH might be associated selectively with AD [13].

Table 1
Demographic and clinical characteristics of the subjects

Characteristic	No dementia or MCI	aMCI	dMCI	MCI-MCDE	MCI-MCDN
n	882	98	33	103	51
Mean age, years, n (SD)	76 (6.2)	77 (5.3)	74 (5.7)	76 (6.3)	80 (8.2)
Mean education, years, n (SD)	11 (4.5)	11 (4.6)	12 (3.4)	11 (3.4)	7 (5.1)
White, %	35	34	24	34	14
Black, %	32	34	39	37	27
Hispanic, %	32	32	36	29	59
Women, %	69	67	76	67	65
Mean no. of vascular risk factors (SD)	1.0 (0.72)	1.1 (0.75)	1.2 (0.86)	1.2 (0.76)	1.3 (0.63)
Short Blessed exam total mean (SD)	1.3 (1.7)	2.7 (2.7)	2.2 (3.3)	3.4 (2.6)	3.8 (3.4)
Blessed Functional Activity Scale mean (SD)	0.47 (0.79)	0.71 (1.0)	0.65 (1.1)	0.97 (1.3)	1.2 (1.6)
Progressed to dementia, n (%)	38 (4.3)	21 (21)	0 (0)	26 (25)	20 (39)
Of those progressed to dementia, sole cause assigned to probable AD, n (%)	23 (60)	16 (76)	NA	12 (46)	14 (70)
Mean survival time to dementia, years, n (SE)	6.3 (0.05)	5.7 (0.12)	NA	5.4 (0.16)	4.9 (0.21)
Median survival time to dementia, years, n (SE)	6.5 (0.10)	6.1 (0.17)	NA	5.8 (0.21)	5.5 (0.56)

Abbreviations: MCI, mild cognitive impairment; aMCI, amnestic MCI; dMCI, dysexecutive MCI; MCDE, multidomain MCI with executive dysfunction; MCDN, multidomain MCI without executive dysfunction; SD, standard deviation; SE, standard error of the mean; AD, Alzheimer's disease; NA, not applicable.

NOTE. Subjects had a baseline visit and two biannual follow-up visits for a total of 4 to 6 years of follow-up after the initial visit. See Methods for details of diagnosis of MCI and dementia. The mean and median survival times to dementia were calculated from the Kaplan-Meier curve (see Methods). A vascular risk score was calculated for each subject at the initial visit, which consisted of assigning the value of one to the presence of each of the following vascular risk factors: hypertension, diabetes mellitus, history of stroke, history of myocardial infarction, and history of peripheral vascular disease. Thus, each subject was assigned a score of 0 point (no vascular risk factors) to 5 points (all of the vascular risk factors).

These findings suggest that the etiology of cognitive impairment in dMCI patients has a larger ischemic component than for aMCI. This hypothesis has face validity because memory is an early and necessary symptom of AD, and

so one would expect MCI patients who have underlying AD pathology to be more likely to have memory symptoms. Because AD has a progressive course, the lower rates of extension of cognitive deficits and progression to dementia in dMCI patients also suggests that processes other than
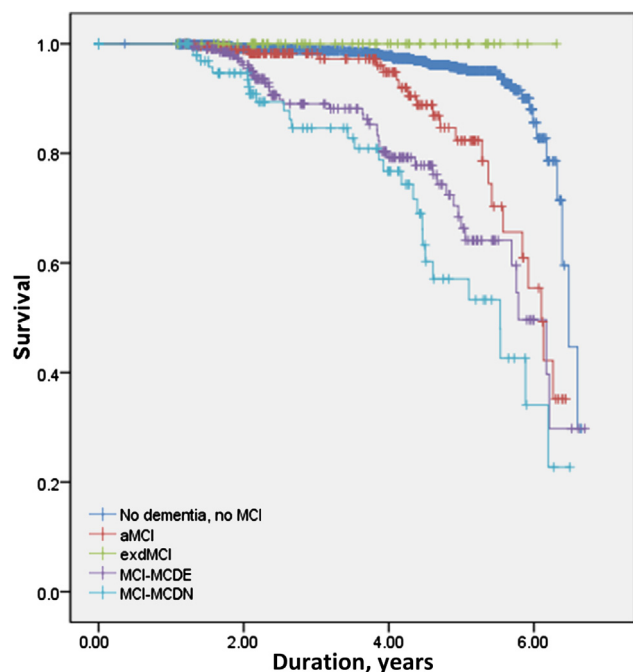

Fig. 3. Survival curve for development of dementia in patients with aMCI, dMCI, MCI-MCDE, and MCI-MCDN, and patients without dementia or MCI. MCI, mild cognitive impairment; aMCI, amnestic MCI; exdMCI, dysexecutive MCI; MCI-MCDE, multidomain MCI with executive dysfunction; MCI-MCDN, multidomain MCI without executive dysfunction.
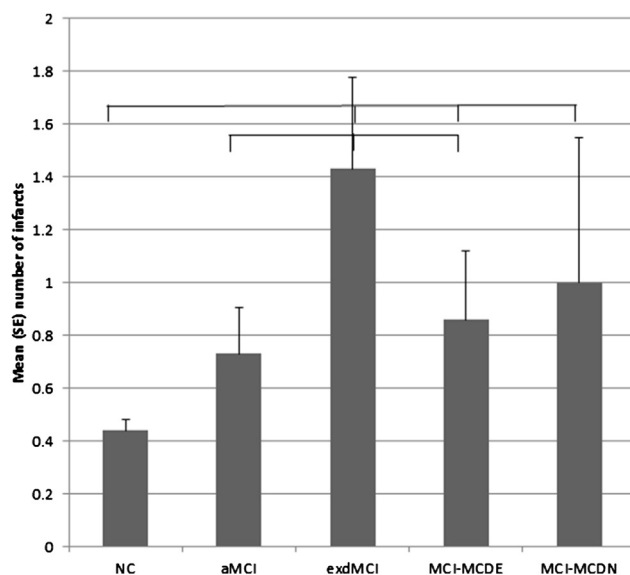

Fig. 4. Differences in mean (SE) number of infarcts as a function of diagnostic group. Lines show groups that are significantly different from each other ($P < .05$). SE, standard error; NC, normal control; aMCI, amnestic mild cognitive impairment; exdMCI, dysexecutive MCI; MCI-MCDE, multidomain MCI with executive dysfunction; MCI-MCDN, multidomain MCI without executive dysfunction.

AD, such as vascular disease, are more commonly responsible for cognitive impairment in dMCI than in aMCI. This hypothesis is consistent with previous findings that vascular risk factors are associated with executive dysfunction in healthy elderly [11,12] and that vascular dementia is more likely to be an executive-predominant dementia than AD [14]. In fact, one could criticize the findings of the current study, that dMCI is more associated with stroke and less likely to progress to involve other domains of cognition than aMCI, as obvious. However, to our knowledge, these findings have never been demonstrated longitudinally in aMCI and dMCI in an ethnically diverse community sample. Weaknesses of the current study include the relatively small sample size of the dMCI group and the lack of extensive executive function testing or autopsy data. The small sample size of some of the groups likely reduces the power of the analyses to detect differences among the groups. Future studies should evaluate whether patients with dMCI have other symptoms associated with frontal dysfunction, including behavioral, emotional, and social cognitive symptoms, and whether they are more likely to progress to frontotemporal lobar degeneration than patients with aMCI [32].

These findings are clinically relevant. Our results suggest that the cognitive dysfunction of dMCI is more likely to remain isolated and less likely to be caused by AD than aMCI. Executive dysfunction in the context of multidomain MCI does not appear to increase risk of progression to dementia. These findings are in an ethnically diverse group of subjects and may differ in another population with, for example, a different prevalence of vascular illness [33,34]. The proportion of aMCI patients that progressed to dementia in our sample is less than that found in the Alzheimer's Disease Neuroimaging Initiative (approximately 16% per year) [35]. The reasons for this are unclear, but could reflect the difficulties in diagnosing MCI in a population with relatively low levels of education. One study of 31 older adults with dMCI demonstrated that 12 progressed and 19 remained stable over 2 years—a significantly higher rate of progression than in the current study [36]. However, in that study, decline was defined as an increase in the Global Clinical Dementia Rating Score sum of boxes, whereas in the current study we examined the more extreme change of conversion to dementia. Also, the other study excluded subjects with vascular disease at baseline, which likely enriched their sample for patients with neurodegenerative illness.

In conclusion, we have shown that cognitive impairment in dMCI is more likely to remain isolated whereas aMCI is more likely to involve other cognitive areas and progress to dementia. dMCI appears to be less likely to be caused by AD than aMCI and is more associated with cerebrovascular disease. A recent set of consensus criteria for MCI has advocated that the focus on MCI shift from descriptive to assigning underlying etiologies [10]. We hope this study is a step in that direction.

Acknowledgments

RESEARCH IN CONTEXT

1. Systematic review: Amnestic mild cognitive impairment (MCI) is associated with an elevated risk of progressing to Alzheimer's disease. Much less is known about the course of dysexecutive MCI.

2. Interpretation: We found that dysexecutive MCI was less likely to progress to dementia than amnestic MCI, and when the MCI patients with executive dysfunction did progress, it was less likely to present as Alzheimer's disease and more likely to be associated with stroke.

3. Future directions: Future work will involve elucidating further the course and etiology of dysexecutive MCI.

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