Incidence of Dementia in Mild Cognitive Impairment in the Cardiovascular Health Study Cognition Study

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Objectives: To examine the incidence of dementia in subjects with mild cognitive impairment (MCI) in the Cardiovascular Health Study Cognition Study.

Design: Prospective epidemiological study.

Setting: The Cardiovascular Health Study Cognition Study of Pittsburgh, Pa, was conducted from 2002 through 2003 to determine the incidence of dementia in participants classified as having MCI in 1998 and 1999.

Subjects: There were 136 subjects with MCI. Mild cognitive impairment was subclassified as MCI amnestic type and MCI multiple cognitive deficits type (MCI-MCDT); subjects with MCI-MCDT were also grouped based on the presence of a memory impairment. Subjects with MCI were classified as possible when there were comorbidities that could explain the subjects’ cognitive deficits and as probable when there were none.

Main Outcome Measure: Dementia.

Results: The incidence of all dementias in the subjects with MCI was 147 per 1000 person-years (mean follow-up overall, 4.3 years). Of the 136 subjects with MCI, 69 (51%) in 1998 through 1999 progressed to dementia (57 [83%] to Alzheimer disease [AD]), but 25 (18%) returned to normal. Of the 10 subjects with probable MCI amnestic type, 7 (70%) progressed to dementia (all of them to AD) and none returned to normal, whereas 7 (41%) of the 17 subjects with possible MCI amnestic type became demented (6 [86%] to AD) and 3 (18%) returned to normal. Of the 40 subjects with probable MCI-MCDT, 21 (52%) progressed to dementia (17 [81%] to AD) and 2 (5%) returned to normal. Of the 69 subjects with possible MCI-MCDT, 34 (49%) progressed to dementia (28 [82%] to AD) and 20 (29%) returned to normal. Among the subjects with probable MCI-MCDT, 15 (54%) of 28 with and 6 (50%) of 12 without memory deficits progressed to dementia.

Conclusions: Subjects with MCI are at high risk for dementia. The probable MCI diagnosis identified individuals in the earliest stages of dementia, usually AD, whereas the possible MCI diagnosis identified a more heterogeneous group. However, this latter group had only a slightly lower rate of conversion to dementia than the group with probable MCI, suggesting that even with comorbid conditions, there is a high likelihood of the presence of a progressive dementing disorder.

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Mild cognitive impairment (MCI) describes elderly subjects with demonstrable cognitive deficits that are not severe enough to warrant the diagnosis of dementia. These patients have an increased risk of developing dementia, especially Alzheimer disease (AD), and can have an isolated memory deficit (eg, MCI1) or a much broader range of cognitive impairments (eg, age-associated cognitive decline). The incidence of dementia in subjects with MCI has ranged from 3.8 to 8.3 per 100 person-years after a 2- to 5-year follow-up in prospective epidemiological studies. Retrospective studies have found that 17% to 30% of patients with MCI develop dementia after 2 to 5 years of follow-up. Studies conducted in referral clinics have found that subjects with MCI progress to dementia at a rate of 10% to 15% per year.

There is accumulating clinical and pathological evidence that MCI represents the earliest form of AD. However, the data supporting this conclusion tend to come from selected cohorts (eg, referral clinics). Furthermore, the importance of the MCI syndrome as a predictor of AD has been questioned because several epidemiological studies have found that from 16% to 50% of subjects with MCI can revert to normal cognition. The purpose of the present study was to examine the incidence of dementia in MCI.
and its subgroups in a well-characterized population cohort.11

**METHODS**

**CARDIOVASCULAR HEALTH STUDY COGNITION STUDY**

The Cardiovascular Health Study Cognition Study (CHS-CS) of Pittsburgh, Pa, was conducted from 2002 through 2003 to determine the incidence of dementia in a population of normal subjects and those with MCI identified between the period of 1992 through 1994 and the period of 1998 through 1999. A total of 532 subjects were available for the present study (Figure 1). The Pittsburgh CHS-CS methods and cohort characteristics have been described previously.11,12 Details of the neuropsychological battery and normative data have been published previously.13 The adjudication committee made the determination as to whether a subject was classified as having MCI amnestic type (MCI-AT) or MCI multiple cognitive domain type (MCI-MCDT).

**MCI CRITERIA**

The MCI-AT included subjects with impairments in delayed recall of verbal material, nonverbal material, or both. Cognitive functions must otherwise fall within normal limits. The MCI-MCDT required impairments in at least 1 cognitive domain other than memory (ie, abnormal results on ≥2 tests) or abnormal results on 1 test (which could be a memory test) in at least 2 separate domains without sufficient severity or loss of instrumental activities of daily living (IADLs) to constitute dementia. These cognitive deficits may or may not affect IADLs.

Subjects were classified as having possible MCI when there were psychiatric, neurological (eg, cerebrovascular disease, history of head trauma encephalopathy, infectious diseases, or developmental disabilities), or systemic illnesses that could cause cognitive deficits or when there was insufficient information. Subjects were classified as having probable MCI when no comorbid factors were identified.

**DEMENTIA DIAGNOSIS**

The diagnosis of dementia was based on a deficit in performance in 2 or more cognitive domains that was of sufficient severity to affect the subject’s activities of daily living and on history of normal intellectual function before the onset of cognitive abnormalities. An abnormal domain was present when results of at least 2 tests of the same domain were abnormal.11,13

**ONSET OF DEMENTIA SYMPTOMS**

The adjudication committee examined the longitudinal changes from the period of 1992 through 1994 to the period of 2002 through 2003 in the Modified Mini-Mental State examination,14 the Digit Symbol Substitution Test,15 and the Benton Visual Retention Test,15 as well as information from proxies using the Informant Questionnaire for Cognitive Decline in the Elderly16 and the Dementia Questionnaire.17 This was done to identify minimal cognitive changes that may have started before 1998 to 1999. When the onset occurred before that period (11 subjects with MCI and 8 normal subjects), these subjects were excluded from the analysis of incidence rates.

**RESULTS**

The demographic characteristics of the subjects are shown in Table 1 and Table 2. The CHS-CS examined 396 normal subjects and 136 with the diagnosis of MCI in 2002 and 2003. Of the 396 normal subjects, 76 (19%) progressed to dementia (68 to AD, 5 to vascular dementia, 2 to Parkinson disease with dementia, and 1 to other dementia) and 99 (25%) to MCI over a mean follow-up of 4.6 years. Sixty-nine (51%) of the 136 subjects with MCI progressed to dementia and 25 (18%) returned to normal over a mean follow-up of 3.2 years (Figure 2).

Seven (70%) of the 10 subjects with probable MCI-AT progressed to dementia (all met criteria for AD) and none returned to normal. Seven (41%) of the 17 subjects with possible MCI-AT converted to dementia (6 to AD and 1 to Parkinson disease with dementia) and 3 (19%) returned to normal. Twenty-one (52%) of the 40 subjects with probable MCI-MCDT converted to dementia (17 to AD, 2 to Parkinson disease with dementia, and 2 to other dementia) and 2 (5%) returned to normal. Thirty-four (49%) of the 69 subjects with possible MCI-MCDT progressed to dementia (28 to AD, 1 to vascular dementia,
3 to Lewy body dementia, 1 to Parkinson disease with dementia, and 1 to other dementia) and 20 (29%) returned to normal.

Combining subtypes, of the 50 subjects with probable MCI, 28 (56%) progressed to dementia and only 2 (4%) reverted to normal. Of the 86 subjects with possible MCI, 41 (48%) progressed to dementia and 23 (27%) reverted to normal (Figure 3).

The highest rate of conversion from MCI to dementia occurred among subjects with isolated memory deficits (7 [70%] of 10 subjects). Among the remaining subjects with probable MCI, those with memory deficits (15 [54%] of 28 subjects) and those without memory deficits (6 [50%] of 12 subjects) progressed to dementia at the same rate (Figure 4).

The incidence of dementia among normal subjects was 38 per 1000 person-years (95% confidence interval [CI], 29.9-48.2), and among MCI subjects was 147 per 1000 person-years (95% CI, 113.3-189.6). Both the MCI-AT group (170/1000 person-years; 95% CI, 91.5-316.1) and the MCI-MCDT group (143/1000 person-years; 95% CI, 107.4-189.1) had similar incidence rates. In addition, the incidence of dementia was slightly higher in subjects with probable MCI (181/1000 person-years; 95% CI, 121.3-270.0) than in those with possible MCI (129/1000 person-years; 95% CI, 92.4-180.9), although it did not reach statistical significance (P > .05).

The results of this prospective epidemiological study confirm previous suggestions that MCI, in the absence of co-morbid conditions, is not a distinct clinical syndrome but...
is the earliest manifestation of dementia, most likely AD. This conclusion is supported by the principal findings of this study: (1) the incidence of dementia is higher among subjects with MCI than normal subjects; (2) the proportion of subjects with MCI without comorbid conditions who converted to dementia was higher than that of subjects with MCI with such conditions; and (3) the reversion from MCI to normal occurred mainly in the MCI cases classified as possible MCI in 1998 and 1999.

The second major finding of this study relates to subjects with a much broader range of cognitive deficits with and without memory deficits (MCDT syndrome). Both MCI-AT and MCI-MCDT had similar rates of conversion to dementia. This means that the presence of an isolated memory deficit should not be a requirement for classification of MCI and that the absence of a memory deficit does not attenuate the risk of converting to dementia. In addition, it is important to note that all subjects with probable MCI-AT, 14 (93%) of those with probable MCI-MCDT with memory deficits, and 3 (50%) of those without memory deficits who progressed to dementia had the diagnosis of AD.

Because the subjects with possible MCI had only a slightly lower rate of conversion to dementia than those with probable MCI, there appears to be an underlying progressive pathology in both the probable and possible MCI groups. This means that even with comorbid conditions, there is a high likelihood of the presence of a progressive dementing disorder. The fact that 20% of the subjects with possible MCI returned to normal demonstrates the challenge of identifying those who will progress to dementia, and risk factors such as depression or vascular disease must be considered. We should also emphasize the importance of identifying subjects with possible MCI who with the proper treatment will revert to normal.

The conceptualization of the CHS-CS MCI-AT and MCI-MCDT is similar to the MCI subgroups recently proposed by Petersen, which include 4 subgroups of MCI: amnestic (memory only), amnestic with other deficits, nonamnestic single domain, and nonamnestic multiple domain. Our MCI-AT is identical to Petersen’s amnestic MCI (ie, only memory impaired); our MCI-MCDT includes the other 3 subgroups. Our findings indicated that the majority of the subjects with MCI had MCI-MCDT with memory deficits; the “pure” memory or other cognitive domain subtypes were less frequent.

The incidence rate of dementia in the MCI cases detected here was consistent with observations from referral clinics and selected cohorts of an annual conversion of 10% to 15% from MCI to dementia. However, the rate of conversion in epidemiological studies is very heterogeneous (from 3.5% of the amnestic MCI after 2 years of follow-up to 43% of cognitive impairment with no dementia after 5 years of follow-up), and it may be influenced by the definition used to classify MCI. The other aspect that may lead to different conversion rates is how amnestic MCI is defined: pure memory deficit or memory and other cognitive test deficits. We found that there was a high rate of conversion in subjects with pure memory deficits (70%) over 4.5 years of follow-up, although the rate was lower in the MCI-MCDT group with memory deficit (54%) and in all cases with memory deficits (MCI-AT + MCDT with memory deficit) (55%).

One potential criticism of this and related studies concerns evaluation of activities of daily living. At present, there is no consensus regarding the best method for making such assessments; there is a growing sense that mild alterations in IADLs should be expected in MCI and that careful assessment of all MCI cases would reveal such changes.

The determination of impaired IADLs can be difficult at both extremes of the spectrum. For example, subjects who remain active in high-level careers (eg, attorneys) may report mild changes affecting these professional activities. By contrast, other participants may have a sedentary lifestyle after retirement or continue with lower-skill jobs that they have practiced throughout their life and may not notice (or have the opportunity to notice) mild changes in cognition or IADLs. Further, subjects
with multiple medical comorbid conditions may report significant deficits on their IADLs, although the contribution of cognition to those deficits could be minimal. Because of these problems of different sensitivities, the CHS-CS did not require normal IADLs for the diagnosis of MCI, as is done with other MCI definitions.11,12

Any study of factors associated with incident dementia must pay close attention to the timing of follow-up visits. In the CHS-CS, the first follow-up examination occurred approximately 4 years after the baseline visit. Twenty percent of the subjects classified as cognitively normal developed a diagnosable dementia in that time. Given that those subjects passed through an MCI stage during that time, it was of such short duration that we could not establish a point of incident MCI in these cases using retrospective review. Therefore, more frequent follow-up of “at-risk” individuals (defined here as normal subjects and subjects with MCI) is critical to capture MCI as part of the natural history of AD. Thus, by missing this short MCI period in many subjects, the present study likely underestimated the incidence of AD from MCI. On the other hand, some subjects progress to AD very slowly and the MCI phase is extended. These subjects may die before developing AD and thus attenuate the AD risk from MCI (see later). We are now doing annual examinations in the CHS-CS from 2002 and 2003 forward to more specifically evaluate the time from normal cognition to MCI and then to dementia as well as the incident point of MCI.

All studies of the incidence and prevalence of AD and related dementias are hampered by the lack of a biomarker that can provide perfect diagnostic accuracy. In addition, studies such as the CHS-CS also have the problem of subject mortality. Some of the subjects with MCI may not have converted to dementia because they did not live long enough after their initial cognitive decline to be classified as demented. Fortunately for both the patients and researchers, successful therapies for conditions such as heart disease, hypertension, and diabetes mellitus have resulted in longer survival after diagnosis, and this may have the paradoxical effect of apparently increasing the incidence of dementia over time owing to the increased opportunity to convert to dementia.

Despite these concerns, which are shared to a greater or lesser extent by all studies of the incidence and prevalence of dementia, one thing is becoming clear: in the absence of comorbid conditions, MCI is (early) AD. Future studies need to have sufficient cases of MCI to determine whether there are critical risk modifiers and whether those modifiers differ as a function of the MCI subgroup.

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