Original Research Article

Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord 2005;19:383–389
DOI: 10.1159/000084709

Accepted: November 1, 2004
Published online: March 30, 2005

Mild Cognitive Impairment: An Operational Definition and Its Conversion Rate to Alzheimer's Disease

Daphne M. Geslani[a] Mary C. Tierney[a, d] Nathan Herrmann[b, e] John P. Szalai[c, f]

[a]Geriatric Research, [b]Department of Psychiatry, and [c]Clinical Epidemiology and Health Services Research, Sunnybrook and Women's College Health Sciences Centre, [d]Department of Family and Community Medicine, [e]Department of Psychiatry, and [f]Department of Public Health Sciences, University of Toronto, Toronto, Canada

Key Words
Mild cognitive impairment · Conversion rate · Alzheimer's disease · Prediction

Abstract
Objective: Because of discrepant findings regarding the accuracy of mild cognitive impairment (MCI) in predicting Alzheimer's disease (AD), further study of this construct and conversion rates is essential before use in clinical settings. We aimed to develop an operational definition of MCI consistent with criteria proposed by the Mayo Alzheimer's Disease Center, and to examine its conversion rate to AD. ***Methods:*** Patients were identified from an inception cohort of patients with at least a 3-month history of memory problems, and referred to a 2-year university teaching hospital investigation by primary care physicians. We classified 161 nondemented patients at baseline using MCI criteria. Diagnostic work-ups were completed annually, and patients were classified as meeting criteria for AD or showing no evidence of dementia after 1 and 2 years. ***Results:*** Of 161 patients, 35% met MCI criteria at baseline. Conversion rates to AD were 41% after 1 year, and 64% after 2 years. Logistic regression analyses to examine predictive accuracy of MCI after 1 and 2 years, with age and education as covariates, were significant ($p < 0.0001$). After 1 year, MCI showed an optimal sensitivity of 91% and specificity of 79%, and after 2 years, these values were 88 and 83%, respectively. ***Conclusions:*** MCI is an accurate predictor of AD over 1 and 2 years in patients referred by their primary care physicians. Discrepancies in conversion rates may be due to the manner in which patients are recruited to studies as well as the use of different measures to operationalize the construct.

Introduction

Mild cognitive impairment (MCI) has been defined as a transition state between healthy aging and Alzheimer's disease (AD) [1, 2]. The Quality Standards Subcommittee of the American Academy of Neurology deemed MCI, as defined by Petersen et al. [2], worthy of further study because if preventive treatments for AD become available, it will be important to identify persons at risk for this disease [3]. Petersen et al. [2] found that 12% of MCI patients

This research was completed by Daphne M. Geslani as part of the requirements for the Master of Science degree, Institute of Medical Science, University of Toronto, under supervision of Dr. M.C. Tierney.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/05/0196–0383$22.00/0

Accessible online at:
www.karger.com/dem

Daphne M. Geslani
Geriatric Research, A1 45, Sunnybrook and Women's College Health Sciences Centre
2075 Bayview Avenue, Toronto, Ont., M4N 3M5 (Canada)
Fax +1 416 480 6776
E-Mail daphne.geslani@utoronto.ca

converted to AD per year over 4 years, compared with 1–2% per year for those with normal cognition. Other studies found conversion rates ranging from 3 to 12% per year [4–6]. In a large epidemiology study, MCI was a poor predictor of dementia, with only 11% converting to senile dementia after 3 years [7]. Furthermore, reversion rates to normal cognition for MCI patients were reported at 93 [7] and 40% [4] after 1 year. Clearly the manner in which the construct has been operationally defined needs further refinement [7, 8], particularly if it is to be used in clinical settings. Greater consensus is needed to standardize definitions and research methodology for MCI so as to make future studies more comparable and useful for designing effective treatments [9].

Our purpose was to take an important step in this direction by developing an operational definition of MCI consistent with the criteria formulated by the Mayo Alzheimer's Disease Center, and prospectively examine its conversion rate to AD [2]. As we were interested in the usefulness of this construct in the primary care setting, we used a sample of older nondemented patients referred by their primary care physicians because of concerns about memory impairment.

Materials and Methods

Patients and Procedures

Patients included in this study were part of a larger investigation examining the predictive accuracy of several cognitive, behavioral, and genetic indices in the diagnosis of AD [10, 11]. Community-residing patients with symptoms suggestive of memory impairment were referred by their primary care physicians to this research investigation at a large teaching hospital in Toronto, Ont., Canada. Physicians referred patients with at least a 3-month history of memory problems defined as stage 2 or 3 on the Global Deterioration Scale [12], but who did not meet criteria for dementia. Patients were required to be fluent in English, and have adequate hearing and vision to complete cognitive testing. This project was approved by the Research Ethics Board of Sunnybrook and Women's College Health Sciences Centre. Written informed consent was obtained after complete description of the study.

Of the 183 referred, we excluded (1) those who showed evidence of any neurological conditions that could cause memory impairment, and (2) those who met the criteria for dementia of the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) [13]. All patients underwent a workup consisting of a thorough physical examination, CT, SPECT, and laboratory tests including hematologic, renal, hepatic, and metabolic function tests that was conducted by one of four experienced geriatricians. The geriatrician also administered the Mini Mental State Examination (MMSE) [14] and evaluated the activities of daily living (ADL) of each participant. Caregivers were present at the geriatrician examination to corroborate details provided by the patient. As part of the first exclusion criteria, 8 patients were excluded because there was evidence of chronic alcohol or other drug abuse, stroke, hypoxia, intracranial mass lesions, psychoses, brain trauma, or other neurological diseases including Parkinson and Huntington diseases.

Next, patients who met medical criteria for the study were administered a diagnostic neuropsychological battery [10, 11, 15] by a psychometrist who was unaware of the geriatrician's diagnosis. Tests included were: Wechsler Memory Scale, information and orientation subtests [16]; Wechsler Memory Scale Revised Visual Reproduction, immediate and delayed recall [17]; California Verbal Learning Test (CVLT) [18]; Boston Naming Test (BNT), odd-even version [19, 20]; Controlled Oral Word Association Test (COWAT) (letters P, R, W); Category Fluency Test (animal names) [21]; Wechsler Adult Intelligence Scale-Revised (WAIS-R), digit span, similarities, and digit symbol subtests [22]; Read Perceptual Closure Test [23]; Finger Tapping Test [24], and Tokens Test [25].

After formulating diagnostic judgements independently, an experienced board-certified neuropsychologist and geriatrician met to decide whether the patient fulfilled DSM-III-R criteria for dementia. Fourteen participants met criteria for dementia and were excluded. Thus, 161 nondemented participants were eligible at baseline.

Next we applied an operational definition for MCI to each of these 161 patients based on the definition proposed by Petersen et al. [2] in their original study in which they examined conversion rates over 4 years. Although we attempted to follow their criteria as closely as possible, there were several differences between the two studies. As shown in table 1, our criterion of memory complaint differed from the definition of Petersen et al. [2], as we characterized memory complaint by at least a 3-month history of memory problems corroborated by the primary care physician. In contrast, in the sample from which they derived conversion rates, Petersen et al. [2] did not require corroboration of the memory complaint. For the second criterion of normal ADL, Petersen et al. [2] did not specify measures to assess ADL nor acceptable performance levels. In the present study, to operationalize this criterion, we stipulated that participants must not meet DSM-III-R criteria for dementia and that disturbances in their memory could not significantly interfere with social activities or relationships. In addition, we defined normal ADL as a rating of 'no difficulty' by a geriatrician on four specific activities: dressing, grooming, bathing, toileting. Each of the four activities was rated on a three-point scale: difficulty, questionable difficulty, and no difficulty. Similarly, Petersen et al. [2] did not specify which tests should be used to measure verbal or performance IQ, but only that performance must be within 0.5 SD. We explicitly stated, however, that two subtests of the WAIS-R were used to operationalize the third criterion of normal cognition. For the fourth criterion of abnormal memory, the Mayo definition suggests a cutoff that is 'generally' 1.5 SD below age-appropriate norms. In our study, this cutoff is rigorously applied. The CVLT delayed recall trial was used to assess memory because it is widely used in clinical neuropsychological assessment, has readily available norms and also because measures of verbal delayed recall have been found to be highly predictive of AD [26–30].

Ritchie et al. [7] reported discrepant findings in MCI conversion rates using a different cutoff score of 1.0 SD below the mean on a memory test. Thus, we also used this lower cutoff, in conjunction with the other four MCI criteria (table 1), to examine the effect of this criterion for memory impairment on conversion rates to AD.

Table 1. Diagnostic criteria for MCI used in the Petersen study and the present Toronto study

MCI criteria	Petersen study criteria for MCI	Toronto study criteria for MCI
Memory complaint	may or may not be corroborated by an informant[1]	memory complaint with at least a 3-month history of memory problems, corroborated by the patient's primary care physician
Normal ADL	no ADL measures specified	cognitive impairment did not interfere with social activities or relationships (DSM-III-R), and rating by the study geriatrician on a three-point scale (difficulty, questionable difficulty, no difficulty) measuring dressing, grooming, bathing, toileting
Normal general cognitive function	verbal or performance IQ within 0.5 SD	WAIS-R similarities or digit symbol age equivalent score ≥ 8.5 (this value is within 0.5 SD)
Abnormal memory	'generally' 1.5 SD below age-appropriate norms	performance on the CVLT delayed free recall trial ≤ -1.5 SD below age- and sex-adjusted norms
Not demented	DSM-III-R consensus diagnosis with behavioral neurologists, geriatricians, neuropsychologists, nurses, and other study personnel following neurologic examination, laboratory tests, head CT scan, other necessary medical tests, and neuropsychological diagnostic battery	DSM-III-R consensus diagnosis with geriatrician and neuropsychologist following neurological examination, laboratory tests, head CT scan, and neuropsychological diagnostic battery

[1] In later studies, Petersen et al. stipulated 'memory complaint, corroborated by an informant', but in the original study in which conversion rates to AD over 4 years were established, the definition used was 'memory complaint' without the requirement of corroboration from an informant.

Patients were followed for 2 years, with annual assessments to determine conversion rates to AD. At each visit, patients underwent the same medical diagnostic evaluation with the geriatrician. Patients were also administered the diagnostic neuropsychological test battery by a psychometrist blinded to all diagnostic information. A consensus diagnosis of AD was determined by the geriatrician and neuropsychologist if patients met both DSM-III-R [13] criteria for dementia and the Workgroup of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association [31] criteria for probable AD. To maintain independence between diagnoses and baseline MCI classification, the diagnostician did not have access to baseline scores on the neuropsychological tests. If the patient was diagnosed as demented or found to have new clinical evidence of a neurological condition other than AD by either diagnostician, a radiological and laboratory workup was conducted as previously described. Those who did not convert to AD or other dementia were classified as *MCI, normal, other,* or *new neurological condition.*

Patients were classified as *MCI* if they continued to meet all the criteria outlined in table 1. They were classified as *normal* if they met all MCI criteria except the criterion for abnormal memory. Memory performance in the *normal* group was defined as a score of 0.5 SD below the mean or better on the CVLT delayed free recall test. Patients were assigned to the *other* group if they were not demented and did not meet criteria for *normal, MCI* or *AD* at the annual follow-up assessment. The *other* category included those whose performance on the CVLT delayed free recall test was in the range between the *MCI* group and the *normal* group. Thus, those in the *other* category performed better than the *MCI* group (at least –1.5 SD or worse on the CLVT) but not as well as the *normal* group (–0.5 SD or better on the CVLT), therefore achieving a score between 1.4 SD and 0.6 SD below the mean on the CVLT delayed free recall test. The *other* group also included patients who demonstrated memory impairment (i.e. satisfied criterion 4) but did not meet criterion 3 for normal general cognitive function (table 1). Those who developed new neurological conditions, i.e. stroke, were classified as *new neurological conditions.* Annual diagnostic assessments were completed with no knowledge of patients' baseline classification.

Statistical Analyses

The accuracy of the MCI construct in predicting future diagnosis of AD was examined with logistic regression analyses [32]. We entered the classification of patients as either meeting criteria for MCI or not meeting these criteria at baseline to determine how well this classification predicted conversion to AD after 1 year and 2 years. Because age and education are known to influence cognitive performance, both were included in all analyses as covariates.

Although the CVLT and WAIS-R tests (used to define MCI) were normed for age and education, these factors were included as covariates in our model because both were significantly correlated with MCI classification. Therefore, age and education will play a role in determining the strength of the relationship between the outcome measure (conversion to AD) and MCI classification at baseline, and should be incorporated into the model.

Table 2. Baseline characteristics of the Toronto MCI sample compared to the Petersen MCI sample

Baseline characteristics	Toronto MCI sample (n = 57)	Petersen MCI sample (n = 76)
Age (mean ± SD), years	73.07 ± 7.72	80.9 ± 1.0
Education (mean ± SD), years	12.67 ± 3.24	13.7 ± 0.4
Male, %	36.84	39.5
MMSE (mean ± SD)	26.58 ± 2.20	26.0 ± 0.3
CVLT delayed free recall (mean ± SD)	2.42 ± 1.97	[a]
WAIS-R similarities (mean ± SD)	11.02 ± 2.36	[a]
WAIS-R digit symbol (mean ± SD)	9.54 ± 2.33	[a]
COWAT (mean ± SD)	32.80 ± 9.44	29.9 ± 1.3
BNT (mean ± SD)	47.92 ± 4.70	45.0 ± 1.2

Education and age are expressed in years and represent patients' status at entry to the study.

[a] These tests were not administered or only partial subtests were available for comparison.

Results

We applied the MCI construct to the 161 patients who did not meet criteria for dementia at baseline, which resulted in 57 patients (35%) meeting all five criteria for MCI. The remaining 104 patients were not classified as MCI at baseline because they failed to satisfy either our third criterion (they did not have normal cognitive function, n = 3) or our fourth criterion (they did not have abnormal memory, n = 101).

Table 2 shows the baseline characteristics for the 57 patients classified as MCI. For comparison of our sample with the sample in Petersen et al. [2], we have included values for those tests that were administered in both studies. As can be seen, performance on these tests is very similar between the two MCI samples.

Of the 57 patients who met criteria for MCI at baseline, 54 returned for follow-up at year 1. At year 2, we followed those 30 patients who had not converted to AD at year 1, and 28 of them returned. Figure 1 details changes in patients' classification over time. As can be seen in figure 1, 21 patients converted to AD at year 1. At year 2, 9 new patients converted to AD, bringing the total number of patients who converted to AD over the 2-year period to 30.

The conversion rate to AD for patients in the *MCI* group was 41% (n = 21) after 1 year, and 64% (n = 30) after 2 years. Reversion to *normal* for patients in the *MCI* group was 6% (n = 3) after 1 year, and 2% (n = 1) after 2 years.

Classification of patients as either meeting or not meeting criteria for MCI at their baseline assessment was entered into logistic regression analyses to examine the accuracy of the MCI construct in predicting the emergence of AD 1 year and 2 years later. Because MCI classification was significantly correlated with age and education, these factors were included in all analyses as covariates. Table 3 shows the χ^2 values, the sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR–) for each regression analysis. In every instance, we optimized both sensitivity and specificity by selecting the point on the receiver operating characteristic curve that was closest to the upper left-hand corner. According to the guidelines of Sackett et al. for LRs [33], we observed a small-to-moderate change from pretest to posttest probability with regard to the accuracy of MCI in predicting AD after year 1 and year 2. The 95% confidence limits for LR+ and LR– were calculated using equations from Simel et al. [34].

We also applied a different cutoff for the fourth criterion of abnormal memory, i.e., a cutoff of 1.0 SD below the mean on the same memory test, to the 161 nondemented patients at baseline. This was done because Ritchie et al. [7] reported highly discrepant conversion rates using this cutoff. Using this cutoff score resulted in 25 additional subjects, or 51% (n = 82) meeting all 5 criteria for MCI at baseline. Of 82 patients who met the –1.0 SD cutoff at baseline, 73 returned for follow-up at year 1 and 66 at year 2. Conversion rates to AD were 30% (n = 22) after 1 year. At year 2, an additional 10 patients converted to AD, yielding a conversion rate of 48% (n = 32) over 2 years. Reversion rate to the normal group for these patients was 16% (n = 12) after 1 year, and 9% (n = 6) after 2 years. Table 3 shows evidence-based parameters (sensitivity, specificity, LRs) for comparison with the MCI definition operationalized according to the –1.5 SD criterion for abnormal memory.

Discussion

We developed an operational definition for MCI, based on the criteria of Petersen et al. [2] and examined its conversion rate to AD in a sample of nondemented patients referred by their primary care physicians. We found a baseline MCI sample very similar to that of the Mayo Clinic sample. Our results, however, showed that this definition of MCI in our primary care patients re-

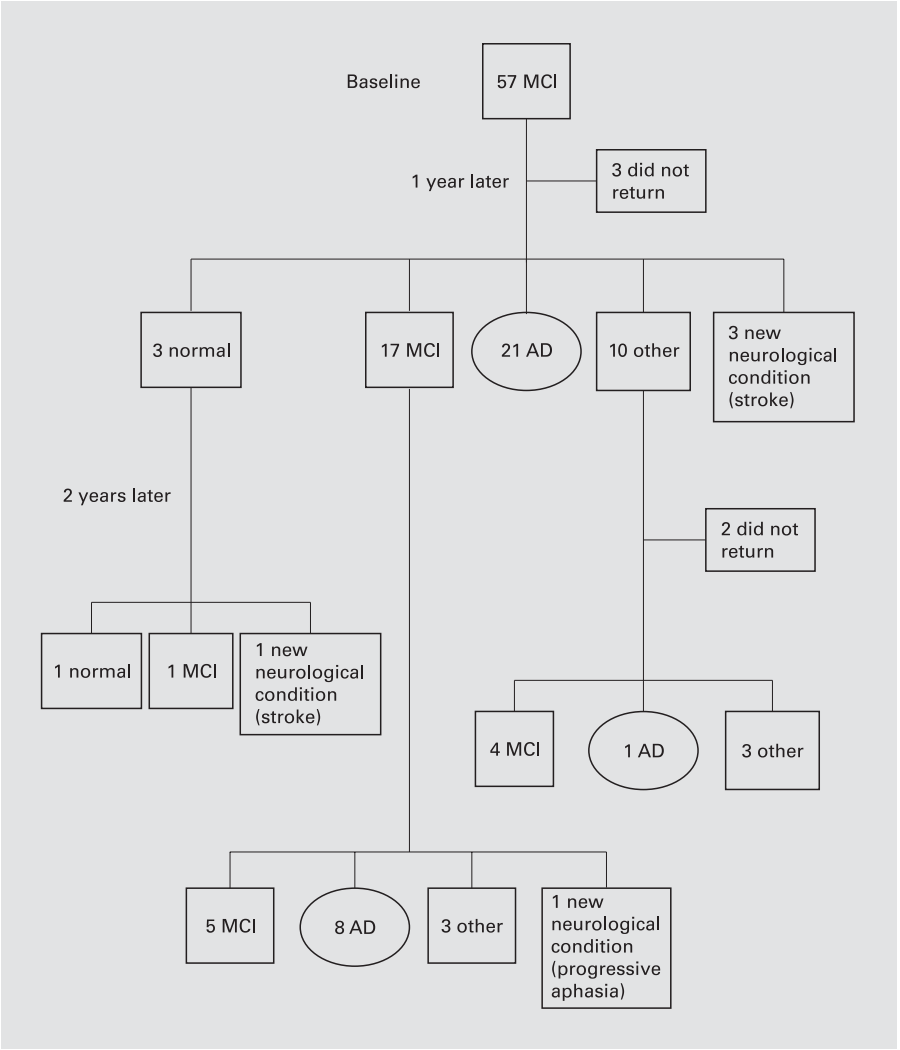

Fig. 1. Patient flow diagram for MCI patients followed over 1 and 2 years. Normal = Memory test –0.5 SD or better; other = memory test –1.4 SD to –0.6 SD, or, test score at least –1.5 SD, but general cognition performance better than –0.5 SD below mean.

Table 3. Prediction of AD (year 1, 2): Sensitivity, specificity, and LRs for baseline MCI classification

	χ^2; d.f.	Sensitivity, %	Specificity, %	LR+	LR–
MCI operationalized according to –1.5 SD criterion for abnormal memory					
One-year follow-up	20.79; 3	91	79	4.33 (s)	0.11 (m)
	(p < 0.0001)	(70–98)	(70–85)	(3.08–6.11)	(0.03–0.43)
Two-year follow-up	35.20; 3	88	83	5.18 (m)	0.14 (m)
	(p < 0.0001)	(72–96)	(74–90)	(3.37–7.94)	(0.06–0.36)
MCI operationalized according to –1.0 SD criterion for abnormal memory					
One-year follow-up	11.05; 3	87	66	2.56 (s)	0.20 (s)
	(p = 0.0115)	(65–97)	(57–75)	(1.96–3.35)	(0.03–1.23)
Two-year follow-up	22.33; 3	88	75	3.52 (s)	0.16 (m)
	(p < 0.0001)	(72–96)	(65–82)	(2.57–4.82)	(0.04–0.59)

Logistic regression analyses were completed with age and education as covariates. s = Small but meaningful change; m = moderate but meaningful change from pretest to posttest probability of developing the disease. Figures in parentheses indicate 95% confidence limits.

sulted in higher conversion rates than previously reported. Our conversion rate was 41% after 1 year and 64% after 2 years. These rates were higher than those found by Petersen et al. [2], who reported a rate of 12% per year over 4 years. These different conversion rates cannot be attributed to greater baseline cognitive impairment in the present sample because performance was similar to that of the patients in the study by Petersen et al. [2] on several cognitive measures including the MMSE, COWAT, and BNT (table 2).

One difference between participants in our study and those in the study of Petersen et al. [2] was that our patients with at least a 3-month history of memory problems were referred by their primary care physicians. In contrast, both self- and physician-referred patients from the community were accepted into the study of Peterson et al. [2]. This inclusion of patients who were not referred by their physicians may have lowered the conversion rate because patients with only self-referred memory impairment may be higher functioning than those with memory decline corroborated by a family member or physician. Even lower conversion rates (8.3% per year) were reported in another study using an epidemiological sample randomly selected from the population [4]. Thus, our inclusion of patients who have been referred by their primary care physicians with a documented history of memory problems for at least 3 months may have been one factor contributing to the higher rate of conversion to AD in this study.

Another factor contributing to our higher rate of conversion may have been our strict application of the criterion of 1.5 SD below the age-appropriate norms as a definition of abnormal memory. Peterson et al. [2] used this criterion 'generally' and thus may have included higher functioning individuals at baseline.

Ritchie et al. [7] reported a lower conversion rate to AD of 11% over 3 years and a prevalence of 3% in their sample of subjects taken from an epidemiological sample in southern France. They also found that subjects with MCI constituted an unstable group over time, with 93% of MCI patients reverting to normal cognition after 1 year, and 83% after 2 years. Rather than setting the cutoff for memory impairment at 1.5 SD below age-appropriate norms [2], Ritchie's group used –1.0 SD. Because this lower cutoff for abnormal memory included an increased number of higher functioning people in the MCI group, this may have accounted for the poor conversion rate in the French sample and increased rate of reversion to normal cognition. We examined the effect of the –1.0 SD cutoff on our conversion rates. This reduced our conversion rate to 30% in the first year and 48% in the second year. Our conversion rates decreased, but were not as low as those of Ritchie et al. [7] and were still more than twice as high as those of Petersen et al. (12% in the first year and 24% in the second year) [2]. Thus, even the more liberal cutoff of 1.0 SD below norms resulted in higher conversion rates in our sample. This suggests that while the cutoff for abnormal memory has implications for conversion rates to AD, physician referral and history of memory decline may be more important contributors to this outcome. Therefore, prediction may not be as accurate in epidemiological samples where selection is based on test scores and other performance indices, as compared to samples based on referrals by physicians who have observed change over time.

Another factor contributing to our higher conversion rates may have been the use of different neuropsychological tests to operationalize MCI. In this study, we used the WAIS-R similarities or digit symbol subtests [22] to measure general cognition, based on the suggestion by Petersen et al. [2], and the CVLT delayed free recall test [18] to assess memory for the MCI construct. While Petersen et al. [2] also used the WAIS-R for general cognition, they reported using two different tests for memory without specifying which one was included in the operational criteria for MCI, i.e. the Auditory Verbal Learning Test or Wechsler Memory Scale-Revised. In contrast, Ritchie et al. [7] used a computerized neuropsychological exam, Examen Cognitif par Ordinateur, previously developed by their group, and Larrieu et al. [4] used the Benton's Visual Retention Test to measure memory. The effect of different neuropsychological tests on conversion rates is not known and clearly needs to be examined in further studies of the MCI construct.

Another aspect of the MCI construct that needs further refinement is the assessment of ADL. Petersen et al. [2] did not specify how to measure this criterion nor what aspects of ADL should be included. The criterion states only that MCI patients must demonstrate 'normal ADL' [2]. In this study, therefore, to operationalize this criterion, we stipulated that participants must not meet DSM-III-R criteria for dementia and that disturbances in their memory could not significantly interfere with social activities or relationships. In addition, we stipulated that participants had to have normal abilities in four ADL areas assessed by the geriatrician: dressing, grooming, bathing and toileting. While it is possible that the use of other operational criteria for the measurement of basic ADL, or instrumental ADL, may result in different conversion rates, the results of a large population-based study

[35] indicated that intact instrumental ADL may be unnecessary for case definition of MCI as it did not alter the conversion rate.

The results of this study can only be generalized to nondemented patients who have been identified by their primary care physicians as having at least a 3-month history of memory problems and who meet our operational definition for MCI. Replication of these findings in other primary care and tertiary care practices is required to ensure their generalizability.

Acknowledgements

This is to acknowledge the contributions of neuropsychologist Dr. W.G. Snow and geriatricians Drs. R.H. Fisher and G. Nadon to the formulations of diagnostic decisions. We also acknowledge the contribution of Dr. Alex Kiss to the statistical analyses.

References

1 Petersen RC: Aging, mild cognitive impairment, and Alzheimer's disease. Neurol Clin 2000;18:789–805.
2 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: Mild cognitive impairment: Clinical characterization and outcome. Arch Neurol 1999;56:303–308.
3 Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST: Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001;56:1133–1142.
4 Larrieu S, Letenneur L, Orgogozo JM, et al: Incidence and outcome of mild cognitive impairment in a population-based prospective cohort. Neurology 2002;59:1594–1599.
5 Bozoki A, Giordani B, Heidebrink JL, Berent S, Foster NL: Mild cognitive impairments predict dementia in nondemented elderly patients with memory loss. Arch Neurol 2001;58:411–416.
6 Morris JC, Storandt M, Miller JP, et al: Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397–405.
7 Ritchie K, Artero S, Touchon J: Classification criteria for mild cognitive impairment: A population-based validation study. Neurology 2001;56:37–42.
8 Burns A, Zaudig M: Mild cognitive impairment in older people. Lancet 2002;360:1963–1965.
9 Luis CA, Loewenstein DA, Acevedo A, Barker WW, Duara R: Mild cognitive impairment: Directions for future research. Neurology 2003;61:438–444.
10 Tierney MC, Szalai JP, Snow WG, Fisher RH: The prediction of Alzheimer disease: The role of patient and informant perceptions of cognitive deficits. Arch Neurol 1996;53:423–427.
11 Tierney MC, Szalai JP, Snow WG, et al: Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. Neurology 1996;46:661–665.
12 Reisberg B, Ferris S, DeLeon M, Crook T: The global deterioration scale for assessment of primary degenerative dementia. Am J Psychiatry 1982;139:1136–1139.
13 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 3 revised. Washington, American Psychiatric Association, 1987.
14 Folstein M, Folstein S, McHugh S: 'Mini-mental state'. A practical method for updgrading the cognitive status of patients for the clinician. J Psychiatr Res 1975;12:189–198.
15 Tierney MC, Szalai JP, Snow WG: A prospective study of the clinical utility of ApoE genotype in the prediction of outcome in patients with memory impairment. Neurology 1996;46:149–154.
16 Wechsler D, Stone CP: Wechsler Memory Scale. New York, Psychological Corp, 1973.
17 Wechsler D: Wechsler Memory Scale-Revised. San Antonio, Psychological Corp, 1987.
18 Delis D, Massman P, Butters N, Salmon D: Profiles of demented and amnesic patients on the California Verbal Learning Test: Implications for the assessment of memory disorders. Psychol Assess 1991;3:19–26.
19 Kaplan E, Goodglass H, Weintraub S: Boston Naming Test. Philadelphia, Lea & Febiger, 1983.
20 Fisher N, Tierney MC, Snow WG, Szalai JP: Odd/even short forms of the Boston Naming Test: Preliminary geriatric norms. Clin Neuropsychol 1999;13:359–364.
21 Spreen O, Benton AL: Neurosensory Center Comprehensive Examination for Aphasia. Victoria, Neuropsychology Laboratory, 1969.
22 Wechsler D: Wechsler Adult Intelligence Scale-Revised. New York, Psychological Corp, 1981.
23 Read DE: Age-related changes in performance on a visual-closure test. J Clin Exp Neuropsychol 1988;10:451–466.
24 Reitan RM: Manual of Administration of Neuropsychological Test Batteries for Adults and Children. Tucson, Neuropsychology Laboratories, 1977.
25 Benton A, Hamsher K: Multilingual Aphasia Examination. Iowa, AJA Associates, 1983.
26 Estevez-Gonzalez A, Kulisevsky J, Boltes A, Otermin P, Garcia-Sanchez C: Rey verbal learning test is a useful tool for differential diagnosis in the preclinical phase of Alzheimer's disease: Comparison with mild cognitive impairment and normal aging. Int J Geriatr Psychiatry 2003;18:1021–1028.
27 Grober E, Lipton RB, Hall C, Crystal H: Memory impairment on free and cued selective reminding predicts dementia. Neurology 2000;54:827–832.
28 Lange KL, Bondi MW, Salmon DP, et al: Decline in verbal memory during preclinical Alzheimer's disease: Examination of the effect of the APOE genotype. J Int Neuropsychol Soc 2002;8:943–955.
29 Chen JG, Edwards CL, Vidyarthi S, et al: Learning and recall in subjects at genetic risk for Alzheimer's disease. J Neuropsychiatry Clin Neurosci 2002;14:58–63.
30 Fox LS, Olin JT, Erblich J, Ippen CG, Schneider LS: Severity of cognitive impairment in Alzheimer's disease affects list learning using the California Verbal Learning Test (CVLT). Int J Geriatr Psychiatry 1998;13:544–549.
31 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS/ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
32 Hosmer D, Lemeshow SF: Applied Logistic Regression. New York, Wiley, 1989.
33 Sackett DL, Haynes RB, Guyatt GH, Tugwell P: Clinical Epidemiology: A Basic Science For Clinical Medicine, ed 2. Boston, Little, Brown and Company, 1991.
34 Simel DL, Samsa GP, Matchar DB: Likelihood ratios with confidence: Sample size estimation for diagnostic test studies. J Clin Epidemiol 1991;44:763–770.
35 Fisk JD, Merry HR, Rockwood K: Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. Neurology 2003;61:1179–1184.