Mild Cognitive Impairments Predict Dementia in Nondemented Elderly Patients With Memory Loss

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**Background:** Some elderly individuals exhibit significant memory deficits but do not have dementia because their general intellect is preserved and they have no impairments in everyday activities. These symptoms are often a precursor to Alzheimer disease (AD), but sometimes dementia does not occur, even after many years of observation. There is currently no reliable way to distinguish between these 2 possible outcomes in an individual patient. We hypothesized that clear impairments in at least 1 cognitive domain in addition to memory would help identify those who will progress to AD.

**Objective:** To determine whether nondemented patients with impairments in memory and other domains are more likely than those with memory impairment alone to develop AD.

**Design and Methods:** In a retrospective study, we evaluated 48 nondemented, nondepressed patients with clinical and psychometric evidence of memory impairment who were followed up for 2 or more years. Age-adjusted normative criteria were used to identify whether additional impairments were present in language, attention, motor visuospatial function, and verbal fluency at this initial evaluation. The presence or absence of dementia after 2 years and at the most recent neurological evaluation was compared in subjects with normal scores in all 4 of these cognitive areas apart from memory (M−) and those with impairment in 1 or more of these areas (M+). Outcomes were adjusted for age, intelligence at initial evaluation, and years of education.

**Results:** Of the 48 nondemented patients with memory loss, 17 met M− criteria, leaving 31 in the M+ group. Deficits in block design were the most frequent abnormality other than memory loss. At the 2-year follow-up, 1 M− subject (6%) had progressed to AD, whereas 15 (48%) of the M+ group had progressed to AD (P=.003). At the most recent follow-up (mean±SD, 4.0±2.0 years), 4 (24%) of the M− patients progressed to AD compared with 24 (77%) of the M+ patients (P<.001).

**Conclusions:** Among nondemented elderly patients, memory loss alone rarely progresses to dementia in the subsequent 2 years. However, the risk of dementia is significantly increased among patients with clear cognitive impairments beyond memory loss. Further study is needed to determine whether patients with impairments limited to memory loss have a distinctive clinical course or pathophysiology.

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ANY OLDER adults complain of memory loss, and some show demonstrable memory impairment. For individuals with memory impairment but preserved general intellect and activities of daily living, prognosis is uncertain. In some cases, this pattern of cognitive deficits may indicate the earliest symptoms of dementia. Others will have a more benign course.

Different criteria have been used to define the features that may predict progression to dementia. In particular, researchers have focused on declines in episodic memory, since this cognitive system is known to be affected earliest and most profoundly by Alzheimer disease (AD). Memory deficits can also appear as an isolated problem in otherwise healthy older subjects, referred to in some past studies as age-associated memory impairment (AAMI).

Since the most prominent early symptom of AD is "specific, gradual and progressive memory loss," we chose to identify individuals with predominant difficulties in the areas of learning and immediate memory but with intact general intellectual function. It was believed that this classification, isolated memory impairment (IMI), would represent, in effect, a possible pre-AD state. The IMI designation was developed in 1989 when subject enrollment began, based largely on then-prevailent AAMI criteria. Corroborating this designation, the
SUBJECTS AND METHODS

SELECTION OF SUBJECTS

Of 196 subjects in the Michigan Alzheimer’s Disease Research Center (MADRC) database who were diagnosed as having IMI by a subspecialty-trained neurologist on at least 1 clinic visit, we identified 53 patients who had been evaluated for memory disturbance, met criteria for IMI at their initial evaluation, and had repeated evaluations during at least a 2-year period. The diagnosis of IMI is based on both clinical and psychometric evidence, delineated below.6 In 5 patients, additional information obtained during subsequent clinical visits indicated that an identifiable condition accounted for the cognitive deficits (1 with a history of alcoholism, 2 with psychiatric illness, and 2 with postanoxic injury). These patients were excluded, leaving 48 subjects.

Clinical evidence of IMI was based on the following: (1) the presence of a memory complaint, (2) the ability to perform all instrumental activities of daily living, (3) the absence of clinical depression, and (4) the absence of an identifiable cause of memory impairment, such as use of medication known to alter memory or a significant medical or neurological illness. Standard laboratory blood tests and structural brain imaging (computed tomography or magnetic resonance imaging) were performed as part of this evaluation.10

The neuropsychological evidence for IMI was based on the following: (1) normal orientation and general cognitive function as defined by a Mini-Mental State Examination (MMSE) score of more than 23 and maintained Wechsler Adult Intelligence Scale–Revised (WAIS-R) Full-Scale IQ (FSIQ) based on presumed premorbid estimates, (2) a score of 0 or less on the Hamilton Depression Rating Scale, and (3) diagnostic criteria and cognitive measures for clinical change based on those proposed for AAMI by a National Institute of Mental Health work group.3 These criteria used a cutoff of 1 SD below the means established for young adults as a basis for impaired memory functions. Thus, we identified memory impairment as significant when subjects had an immediate recall score of 6 or less on the Benton Visual Retention Test–Revised or when the sum of scores on immediate recall of the letter Word Association Test was unavailable, letter fluency on the letter d was substituted.) For the purposes of this study, we defined impairment as performance worse than fifth percentile or 2 SDs from the age-adjusted mean, consistent with National Institutes of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association criteria for dementia.13 (Table 1). Subjects were then categorized by this structured algorithm as having either normal scores in all 4 areas (M−) or impairment in 1 or more of these areas (M+).

The clinical outcome for each patient at 2 years and at the most recent neurological examination was determined by a neurologist (A.B.) blinded to the subject’s initial neuropsychological categorization (M− or M+). The designation of AD or continued memory impairment without dementia was based on documentation of impaired instrumental activities of daily living caused by cognitive impairment in the medical record by the patient’s treating neurologist. In some cases, repeated neuropsychological testing was available to the treating physician; however, outcome in this study was based on the physician’s clinical judgment. The choice of a clinical outcome measure simulates typical clinical decision making, given that follow-up neuropsychological data are frequently not obtained by treating clinicians.

As an additional check on the treating physician’s initial determination of IMI, we had an assistant who was certified by the Alzheimer’s Disease Cooperative Study obtain a chart review–based Clinical Dementia Rating (CDR) score for each subject’s initial diagnostic clinic visit. Since the CDR score takes into account only information from the history and physical sections of the visit note, we hoped to address concerns of possible bias on the part of the treating physician who made a determination in conjunction with neuropsychological testing in some cases.

STATISTICAL ANALYSIS

Unadjusted statistical analyses were performed using χ² analysis for dichotomous results (Fisher exact test). Logistic regression was used to compare outcomes in the 2 groups at 2 years, adjusted for other prognostic factors. Kaplan-Meier curves were compared using the log-rank (Mantel-Cox) test. To evaluate the possibility of confounding, years of education, IQ, and age were controlled for by using a Cox regression analysis. Data are presented as mean±SD.
processes other than memory could improve the predictive value of neuropsychological testing. For this study, we hypothesized that among nondemented patients with memory complaints, measurable impairments of at least 1 cognitive domain in addition to memory could help identify those who would progress to AD over a few years.

RESULTS

We identified 48 IMI patients with 210 years of clinical follow-up (mean, 4.0±2.0 years; median, 3.5 years). Their mean age was 69.4±7.2 years, and years of education was 14.7±3.7 (medians, 71 and 14.5, respectively). There were 36 men and 12 women, with an overall rate of conversion to AD of 33.3% at 2 years. In keeping with the selection criteria inherent in the diagnosis of IMI, there was no evidence of an abnormal IQ or dementia, with a mean FSIQ of 103.6±13.3 (median, 102) and mean MMSE score of 26.0±1.7. Forty-five of 48 subjects had a CDR score of 0.5 at their initial clinic visit. One subject had a CDR score of 0, and 2 subjects did not have enough documented history to calculate an initial CDR score.

Of the 48 patients, 17 were considered M− and 31 were designated M+ (Table 2). For comparison, a review of the MADRC database as a whole revealed 108 men and 88 women with IMI on at least one clinic visit (total, 196). Mean age for this group was 76.6±7.5, with an average of 14.5±3.5 years of education. The mean FSIQ was 102.6±10.6 and MMSE score was 25.5±2.3. When we examined the IMI group’s initial LM-I and PA scores and compared them with age- and education-adjusted means, we found that all M+ and all but 1 M− subject were more than 1 SD below these more restrictive measures, currently in use for the designation of MCI. This would suggest that despite using slightly different entry criteria, our IMI cohort is similar to MCI.

At 2-year follow-up, 1 M− subject (6%) had progressed to AD, and 15 (48%) of the M+ group had progressed to AD (P=.003). In the logistic regression analysis adjusting for age, years of education, and FSIQ, M+ patients were 15.7 times as likely as M− patients to progress to dementia at 2 years (P=.02) (Figure 1). According to Kaplan-Meier estimates, at 3 years of follow-up, the probability of progression to AD in the M+ group was 69% compared with only 15% in the M− group. Similarly, at 5 years, the M+ groups had a 91% probability of progression, whereas the M− group reached a plateau at 44% (Figure 2). A log-rank test confirmed a significantly different rate of progression in the 2 groups (P<.001). A Cox proportional hazards model was then constructed to take into account differences in age, years of education, and FSIQ. Group differences were once again significant, with those in the M+ group having 4.6 times the risk of progression to AD (P=.01). Age (P=.84), education (P=.90), and FSIQ (P=.85) were not significant independent predictors of progression; the survival estimates by group after adjusting for these variables were essentially identical to the Kaplan-Meier estimates.

The overall progression rate of our sample was one third at 2 years, somewhat higher than that found in several other studies14-16 of nondemented, memory-impaired subjects. (Another retrospective study, by Bowen et al, found 19% progression at 2 years, and 2 prospective studies14,16 found 22% and 24% progression at 2 years.) Our higher rate of progression is attributable to slightly different entry criteria and elimination of any subjects who were subsequently found to have another explanation for their cognitive impairment. When we consider the M+ group separately, the progression rate was almost 50%, whereas the M− group had only a single subject progress to dementia during that same period. Of subjects who were followed up for at least 3 years, more than two thirds of the M+ group had converted to AD, and at 5 years, more than 90% had. This is in stark contrast to the M− group, in which progression occurs later and levels off at less than 50% by the same 5 years.

The FSIQ and WMS–Memory Quotient differed between the 2 groups but were within normal limits in both.

Table 1. Neuropsychological Tests Used to Categorize Nondemented Subjects With Memory Impairment

<table>
<thead>
<tr>
<th>Cognitive Function</th>
<th>Test*</th>
<th>Cut Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language</td>
<td>WAIS-R Digit Span</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Attention</td>
<td>WAIS-R Block Design</td>
<td>&lt;19</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>Controlled Oral Word</td>
<td>&lt;18</td>
</tr>
<tr>
<td>Frontal circuits</td>
<td>Association Test</td>
<td></td>
</tr>
</tbody>
</table>

* WAIS-R indicates Wechsler Adult Intelligence Scale–Revised.
† Cut scores represent values 2 SDs below age-adjusted means.

Table 2. Summary Characteristics for Patient Groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>M−</th>
<th>M+</th>
<th>Total IMI</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>17</td>
<td>31</td>
<td>48</td>
<td>...</td>
</tr>
<tr>
<td>Age, y</td>
<td>69.7±7</td>
<td>69.3±75</td>
<td>69.4±72</td>
<td>t = −0.203, P = .84</td>
</tr>
<tr>
<td>Education, y</td>
<td>14.9±3.4</td>
<td>14.6±4.0</td>
<td>14.7±3.7</td>
<td>t = −0.208, P = .84</td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>3.6±1.8</td>
<td>4.2±2.1</td>
<td>4.0±2.0</td>
<td>t = 0.843, P = .40</td>
</tr>
<tr>
<td>MMSE score</td>
<td>26.4±1.5</td>
<td>25.7±1.7</td>
<td>26.0±1.7</td>
<td>t = −1.47, P = .15</td>
</tr>
<tr>
<td>MQ score</td>
<td>106.7±14.2</td>
<td>99.4±12.7</td>
<td>102.1±16.6</td>
<td>t = −1.8, P = .08</td>
</tr>
<tr>
<td>FSIQ</td>
<td>110.0±10.0</td>
<td>100.3±13.6</td>
<td>103.6±13.3</td>
<td>t = −2.52, P = .02</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD. M− indicates normal scores in all 4 cognitive areas apart from memory; M+, impairment in 1 or more cognitive areas; IMI, isolated memory impairment; MMSE, Mini-Mental State Examination; MQ, Memory Quotient; FSIQ, Full-Scale IQ; and ellipses, data not applicable.
Since digit span and block design are both WAIS subtests, on which the FSIQ is partially based, the difference in FSIQ is understandable; in fact, no change at all from premorbid estimates would be hard to explain in the M+ group. Because the 2 groups did not differ in educational age at presentation, or average duration of follow-up, neither demographic differences nor the cognitive reserve hypothesis17 is a sufficient explanation for the difference in outcome.

We compared performance on the 4 tests used to discriminate M− from M+ to examine differences between M+ patients who converted to AD during follow-up and those who did not. Of these, block design was the most frequently abnormal in both groups (63% in converters and 57% in nonconverters). The most discriminating test was the Boston Naming Test, on which 42% of converters had abnormal results, but only 14% of nonconverters had abnormal results.

However, no single test was able to distinguish those among the M+ group who progressed to AD from those who did not. Only when the results of 2 or more tests were abnormal could the groups be distinguished (P=.03) (Table 3).

Our results demonstrate that consideration of cognitive domains other than memory can significantly improve the predictive value of neuropsychological testing in nondemented patients with a memory complaint. These results follow from the hypothesis that subjects with evidence of impairments extending beyond memory are more likely to have AD than those with only memory deficits. Several studies18,19 have demonstrated that cognitive deficits roughly parallel histopathologic abnormalities at autopsy. Consequently, we expect that M+ subjects have neuropathological changes whose functional consequences already extend beyond the hippocampus and entorhinal cortex. In this study, we chose tests looking at 4 anatomically separate domains to maximize the likelihood of capturing a region clinically affected by the distribution of neuronal pathologic features, should that subject actually have early AD. By this method, we determined that nondemented patients with mild cognitive impairments in several domains including memory were more than twice as likely as those with memory impairment alone to develop AD over a period of 2 to 5 years. Furthermore, 50% of this group progressed from the category of M+ to AD at 2 years. This figure was significantly higher than any previously clinically identified “at-risk” population3,14 and similar to the yield obtained with expensive and frequently unavailable fluorine 18–labeled deoxyglucose (FDG)–PET imaging in a similar population (70% at 3 years).6 Our results are also significantly different from those found in studies of AAMI patients, due to the more inclusive nature of the original AAMI criteria, which have since been criticized for a high “misidentification rate” of healthy elderly patients. One study7 found that only 29 (16.5%) of 176 of subjects followed previously clinically identified “at-risk” population, and similar to the yield obtained with expensive and frequently unavailable fluorine 18–labeled deoxyglucose (FDG)–PET imaging in a similar population (70% at 3 years).6 Our results are also significantly different from those found in studies of AAMI patients, due to the more inclusive nature of the original AAMI criteria, which have since been criticized for a high “misidentification rate” of healthy elderly patients. One study7 found that only 29 (16.5%) of 176 of subjects followed up prospectively with an initial diagnosis of AAMI who had progressed to dementia or MCI at an average of 3.6 years of follow-up.

The corollary to our hypothesis that subjects classified as M+ are more likely to have AD than those classified as M− is that patients presenting with memory deficits alone are less likely to have neuronal pathologic features of the AD type, at least outside limbic regions. Certainly, many of these subjects simply have neuro-pathological changes limited to hippocampus and ento-

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Table 3. M+ Subjects With Abnormal Results on Each of the 4 Tests

<table>
<thead>
<tr>
<th>Subtest</th>
<th>Converters</th>
<th>Nonconverters</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>COWAT</td>
<td>5 (21)</td>
<td>1 (14)</td>
<td>.92</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>10 (42)</td>
<td>1 (14)</td>
<td>.16</td>
</tr>
<tr>
<td>WAIS-R Block Design</td>
<td>15 (63)</td>
<td>4 (57)</td>
<td>.70</td>
</tr>
<tr>
<td>WAIS-R Digit Span</td>
<td>7 (29)</td>
<td>1 (14)</td>
<td>.50</td>
</tr>
<tr>
<td>≥2 Abnormal tests</td>
<td>11 (46)</td>
<td>0</td>
<td>.03</td>
</tr>
</tbody>
</table>

* M+ indicates impairment in 1 or more cognitive areas; COWAT, Controlled Oral Word Association Test; and WAIS-R, Wechsler Adult Intelligence Scale–Revised.
rhinal cortex (Braak and Braak stages I through IV) as suggested by postmortem examinations in patients with questionable dementia. 20,21 However, a subset of these patients may have a fundamentally different response to the process that in others more rapidly evolves to AD, such as resistance to disease progression or a better ability to compensate for deficits. In other cases, the M− group may have a form of cognitive reserve not accounted for by controlling for age, education, and FSIQ. Still others may have a disorder distinct from AD or have no significant brain pathologic condition, merely meeting IMI criteria on the basis of memory scores that are different than those of young adults.

The most convincing evidence that some M− subjects do not have AD is the strikingly different clinical course many experience. As in some prospective studies, we found that some who develop clear-cut memory impairment in later life maintain a circumscribed memory deficit without dementia throughout many years. 3 Since it should be easier to develop impairment of a single cognitive domain on the basis of factors other than degenerative disease, the consideration of additional domains acts as a “check” on the diagnosis of incipient dementia. We note that although these patients do not become demented, progressive amnesia may ensue, eventually leading to a complete inability to learn new information or to recall previously learned information. This is difficult to differentiate from AD on a clinical examination and may explain why it has not been widely recognized to date. Hippocampal sclerosis is one pathologic substrate that might account for this more benign course. 22,23 FDG-PET showing a more limited pathologic substrate that might account for this more widely recognized to date. Hippocampal sclerosis is one pathology that might account for this more AD.

In our study, the subset of subjects who were followed up for more than 5 years is too small to determine whether there is truly a plateau in the number of M− subjects who develop AD, although the trend is clearly in that direction. Further studies are needed to determine whether this group that does not develop dementia represents a completely different disease process from that affecting the M+ group. Psychological criteria such as we have used have not been applied in available autopsy studies of nondemented but memory-impaired individuals. These studies 18,20 have primarily found pathologic features typical of AD.

Our study has the typical shortcomings of a retrospective study, with concerns regarding enrollment, selective loss to follow-up, and inherent limitations in the measures of change. A larger, prospective study extending 5 years or longer is needed. Clinical definitions that include information gained with longitudinal observation may better define both the mildest forms of AD and compensatory mechanisms. In other cases, the M− group may compensate for deficits. In other cases, the M− group may compensate for deficits. In other cases, the M− group may compensate for deficits.
REFERENCES


