MILD COGNITIVE IMPAIRMENTS PREDICT DEMENTIA IN NONDEMENTED ELDERLY PATIENTS WITH MEMORY LOSS

Andrea Bozoki, MD; Bruno Giordani, PhD; Judith L. Heidebrink, MD; Stanley Berent, PhD; Norman L. Foster, MD

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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Many 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-prevale...
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.

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 a 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.

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 9 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. 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 a immediate recall score of 6 or less on the Benton Visual Retention Test–Revised or when the sum of scores on immediate recall of logical memory 1 (LM-1) and paired associates (PA) subtests on the Wechsler Memory Scale were 19 or less. In addition, to address concerns regarding the validity of these historical AAMI criteria, we compared each subject’s scores on LM-1 and PA to age- and education-adjusted cutoffs. Because episodic memory ability generally declines with age, prevailing mild cognitive impairment (MCI) criteria make use of these adjustments as a more accurate way to identify seniors with genuine impairments.

NEUROPSYCHOLOGICAL AND NEUROLOGICAL EVALUATIONS

A neuropsychologist (B.G.) blinded to patient outcomes reviewed initial neuropsychological testing performed in each subject and archived in the MADRC database. We used age-adjusted normative criteria to identify the presence or absence of impairment in the following areas: language (Boston Naming Test), attention (WAIS-R Digit Span Forward), motor visuospatial function (WAIS-R Block Design), and verbal fluency (Controlled Oral Word Association Test; letters f, j, and l). If the Controlled Oral 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.

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 to 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 had a CDR score of 0. At 2 years, 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 6.6 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,15 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>Boston Naming Test</td>
<td>&lt;47</td>
</tr>
<tr>
<td>Attention</td>
<td>WAIS-R Digit Span</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Visuospatial function</td>
<td>WAIS-R Block Design</td>
<td>&lt;19</td>
</tr>
<tr>
<td>Frontal circuits</td>
<td>Controlled Oral Word</td>
<td>Association Test</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±7</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±13.6</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.
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 studies have demonstrated that cognitive deficits roughly parallel histopathologic abnormalities at autopsy. Consequently, we expect that M+ subjects have neuropsychological 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” 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).

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 study found that only 29 (16.5%) of 176 subjects followed up prospectively with an initial diagnosis of AAMI had pathological changes limited to 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” 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).

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rhinal cortex (Braak and Braak stages I through IV) as suggested by postmortem examinations in patients with questionable dementia. 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. 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. FDG-PET showing a more limited pathologic substrate that might account for this more widely recognized to date. A 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 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 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 similar but more benign conditions. It is interesting to note that men make up most of our cohort, both in our selected group of 48 subjects and in the total group of 196 subjects ever identified with IMI at our institution. Further studies will be needed to determine whether this represents referral bias or has biological significance. As in most dementia clinics, women constitute most of our patients overall, and the predominance of men in the IMI category is unexpected.

We adopted cutoff scores for psychological tests based on criteria recommended for AAMI by a consensus conference. The AAMI criteria were proposed to describe the “clear, age-related memory deficit” that could occur in healthy, elderly individuals. Specifically, the recommendation was to include anyone older than 50 years who had a secondary memory test performance at least 1 SD below the mean established for young adults. These criteria are rigorous and do not take into account the substantial cohort effects that can occur when different age groups are compared cross-sectionally instead of being followed longitudinally. To address this concern, we examined each subject’s memory scores (LM-I and PA) with an age- and education-adjusted cutoff, such as is used in the modern MCI definition. We found that all but 1 subject met these more lenient criteria, supporting the observation that our IMI cohort is similar to the current MCI group, despite being originally selected using AAMI criteria.

By choosing a very lenient cutoff for defining our M+ population (2 SDs below age-adjusted means), we gave subjects the “benefit of the doubt” in terms of labeling them as sufficiently cognitively impaired to be at high risk of progression (ie, marginally impaired subjects fell into the M− group). Since the null hypothesis was that the rates of conversion of the 2 groups, M− and M+, were equal, by leaving more patients in the M− group, we risked having a larger percentage of supposedly nonprogressing patients progress, approximating the rate within the M+ group. Since our results were still statistically significant, we believe that this choice of cutoff only strengthens our conclusions.

One of the goals of the clinical neurologist is to predict which mildly impaired individuals will develop a clear dementia, based on characteristics of that person’s presentation. Improving our ability to predict the appearance of dementia at an earlier stage and with greater accuracy could not only reassure many, but could also spare patients and their families the heightened anxiety that accompanies years of watchful waiting and would allow interventions targeted at secondary prevention to be applied with far better specificity and earlier in the disease process than is currently feasible. Medications currently considered too toxic or risky to be given to the very broad category of “people older than 60 years with reduced memory efficiency” might be used if the population to be treated was deemed to be more clearly at risk. Because of its significant emotional and financial implications, until reliable criteria are established, AD should only be diagnosed when dementia is clearly present.

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