ORIGINAL CONTRIBUTION

Mild Cognitive Impairment

Clinical Characterization and Outcome

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Background: Subjects with a mild cognitive impairment (MCI) have a memory impairment beyond that expected for age and education yet are not demented. These subjects are becoming the focus of many prediction studies and early intervention trials.

Objective: To characterize clinically subjects with MCI cross-sectionally and longitudinally.

Design: A prospective, longitudinal inception cohort.

Setting: General community clinic.

Participants: A sample of 76 consecutively evaluated subjects with MCI were compared with 234 healthy control subjects and 106 patients with mild Alzheimer disease (AD), all from a community setting as part of the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry, Rochester, Minn.

Main Outcome Measures: The 3 groups of individuals were compared on demographic factors and measures of cognitive function including the Mini-Mental State Examination, Wechsler Adult Intelligence Scale–Revised, Wechsler Memory Scale–Revised, Dementia Rating Scale, Free and Cued Selective Reminding Test, and Auditory Verbal Learning Test. Clinical classifications of dementia and AD were determined according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria, respectively.

Results: The primary distinction between control subjects and subjects with MCI was in the area of memory, while other cognitive functions were comparable. However, when the subjects with MCI were compared with the patients with very mild AD, memory performance was similar, but patients with AD were more impaired in other cognitive domains as well. Longitudinal performance demonstrated that the subjects with MCI declined at a rate greater than that of the controls but less rapidly than the patients with mild AD.

Conclusions: Patients who meet the criteria for MCI can be differentiated from healthy control subjects and those with very mild AD. They appear to constitute a clinical entity that can be characterized for treatment interventions.

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A GREAT deal of interest has been generated concerning the topic of a boundary or transitional state between normal aging and dementia, or more specifically, Alzheimer disease (AD).[1] This condition has received several descriptors including mild cognitive impairment (MCI), incipient dementia, and isolated memory impairment.[2-4] Reviews of several studies have indicated that these individuals are at an increased risk for developing AD ranging from 1% to 25% per year.[5] The variability in these rates likely reflects differing diagnostic criteria, measurement instruments, and small sample sizes.[5]

Patients with an MCI are also becoming of interest for treatment trials. The Alzheimer's Disease Cooperative Study, which is a National Institute on Aging consortium of Alzheimer's Disease research groups, is embarking on a multicenter trial of agents intended to alter the progression of patients with MCI to AD.[6] Several pharmaceutical companies are initiating large trials on this same group of individuals.

Questions can be raised as to the diagnostic criteria for MCI. Some investigators believe that virtually all these patients with mild disease have AD neuropathologically, and, therefore, this may not be a useful distinction.[7] Others[6,8,9] note that while many of these pa-

SUBJECTS AND METHODS

The subjects for this study were recruited through the Mayo Alzheimer's Disease Center/Alzheimer's Disease Patient Registry (ADC/ADPR) using a standardized clinical protocol.[8-12] The patients were derived from 2 sources: community patients in Rochester, Minn, and regional patients referred to the ADC. The community patients were recruited through the Division of Community Internal Medicine of the Mayo Clinic from Rochester residents who were receiving their general medical care at the Mayo Clinic. If during the course of their medical evaluation the patients expressed concern about their cognitive function, the patients' families expressed a concern about the patients' cognition, or the examining physician detected a cognitive change in the patients, the patient was then referred to the ADC/ADPR staff. The regional patients were derived from individuals who had come to the Mayo ADC for an evaluation of cognitive difficulties. These individuals were either referred by their personal physicians, family members, or by the patients themselves.

Patients from both the community and regional sources received an identical evaluation. On referral, the patients were seen by a behavioral neurologist who obtained a medical history from the patient and corroborating sources, performed the Short Test of Mental Status,[13,14] Hachinski Ischemic Scale,[15] and a neurologic examination. Study personnel obtained other data including the Record of Independent Living,[16] Geriatric Depression Scale,[17] and additional family history information. Laboratory studies were performed, including a chemistry group, complete blood cell count, sedimentation rate, vitamin B_{12} and folic acid levels, sensitive thyroid-stimulating hormone level, and syphilis serologic testing. All patients received a head imaging study (computed tomography or magnetic resonance imaging). Additional studies including a cerebrospinal fluid analysis, electroencephalogram, and a single-photon emission computed tomographic scan were performed as the clinical situation indicated.

Two sessions of neuropsychological testing were completed on all subjects. The first set of tests was used for diagnostic purposes and included the Wechsler Adult Intelligence Scale–Revised, Wechsler Memory Scale–Revised, Auditory Verbal Learning Test, and Wide-Range Achievement Test-III.[18] The second set of tests was used for research purposes and included the Mini-Mental State Examination (MMSE),[19] Dementia Rating Scale (DRS),[20] Free and Cued Selective Reminding Test,[21-23] Boston Naming Test,[24] Controlled Oral Word Association Test,[25] and category fluency procedures.[26]

At the completion of this evaluation a consensus committee meeting was held involving the behavioral neurologists, geriatrician, neuropsychologists, nurses, and other study personnel who had evaluated the patients. Diagnoses were made for dementia and AD according to the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*,[27] and the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders of Association criteria, respectively.[28] The diagnosis of MCI was made if the patient met the following criteria: (1) memory complaint, (2) normal activities of daily living, (3) normal general cognitive function, (4) abnormal memory for age, and (5) not demented.[8] Several studies[3,8,9] characterizing the outcome of patients with an MCI using these criteria have been reported. At the conclusion of the consensus conference, after the diagnosis had been made, the patients were staged on the Clinical Dementia Rating scale (CDR)[29,30] and the Global Deterioration Scale.[31]

Control subjects were sought from the community population of individuals receiving general medical examinations at the Mayo Clinic.[32-34] They underwent a similar evaluation as the patients described earlier including the neurologic examination and neuropsychological testing battery. They qualified as controls if, in the opinion of their clinician, they were functioning normally in the community and did not have a cognitive impairment. In addition, they could not have any active neurologic or psychiatric illnesses and could not be taking psychoactive medications. They could have comorbid illnesses such as hypertension and coronary artery disease, and they could be taking medications for these disorders. However, in the opinion of their physicians, these illnesses or their treatments did not interfere with the patients' cognitive function. These patients were also reviewed at the consensus conference and CDR scale and Global Deterioration Scale ratings were completed.

Patients and control subjects were reevaluated every 12 to 18 months and received an abbreviated neuropsychological battery at that visit. Their performance was reviewed at the consensus conference and the diagnoses were adjusted accordingly, if necessary. They were also reassessed on the CDR scale and the Global Deterioration Scale. The Mayo ADC/ADPR projects have been approved by the Mayo Institutional Review Board.

tients progress to AD, not all do, and consequently, the distinction is important.

We have been enrolling patients at the mild end of the cognitive spectrum for more than 10 years as part of a community study on aging and dementia.[8,10] Our recruitment scheme involves screening patients who are being seen by their primary care physicians for periodic general medical evaluations which affords us the opportunity to detect patients before they present to a dementia or memory disorders clinic. This study reports the clinical criteria used to diagnose these patients as well as their neuropsychological characterization, differentiation from controls and patients with mild AD, and the longitudinal course of the subjects with MCI. As such, these data provide a background for the clinician to use in evaluating these individuals in practice.

RESULTS

We have enrolled 76 subjects with the diagnosis of MCI over the last 11 years. The demographic features of these subjects as well as groups of control subjects and patients with very mild AD enrolled over the same interval grouped by CDR ratings are shown in the **Table** for comparison purposes. The Table also shows the performance of the 4 groups with respect to a sampling of cognitive measures. As would be consistent with the selection criteria, the subjects with MCI performed slightly more

poorly on these measures than the control subjects, but were superior to the patients with AD. Statistical comparisons in the Table were performed using a 1-way analysis of variance with each cognitive measure as the dependent variable comparing the 4 groups of subjects. The relevant pairwise comparisons were made between adjacent groups, eg, control vs MCI and MCI vs AD (CDR 0.5) and AD (CDR 0.5) vs AD (CDR 1), using Tukey honestly significant difference with a level of significance being set at the .01 level due to the large number of comparisons performed.

As one measure of disease severity, the CDR sum of box scores was calculated.[29,30] The CDR sum of the box scores was determined by totaling the individual box scores for a given patient (range, 0-18). For example, a control patient may have had 0 in each of the 6 boxes for the various categories. A typical patient with AD and a summary CDR score of 1 might have had the sum of the 6 having scored 1 in each of the 6 individual boxes. This statistic yielded an approximate index of severity on the CDR as well as involvement of activities of daily living.

On measures of general cognition such as the Wechsler Adult Intelligence Scale–Revised, the controls and subjects with MCI did not differ significantly. On the screening measures of general cognition, MMSE and DRS, there were small differences largely due to the memory component of those measures. In general, while the subjects with MCI did not perform as well as the control subjects, they still functioned in the normal range. However, the subjects with MCI differed from even the CDR 0.5 patients with AD on virtually all measures of general cognitive function (**Figure 1**).

The Table displays memory data among the 4 groups. Again, as would be expected from the selection criteria, the subjects with MCI were significantly impaired on all memory measures relative to control subjects and appeared similar to the patients with AD. These results were seen for virtually all measures of learning and delayed recall using word lists, paragraphs, and nonverbal materials. The differences were less dramatic between the subjects with MCI and the patients with AD; rather, the other areas of cognition and functional measures differentiated these groups.

The Boston Naming Test results paralleled those of the memory domain. These findings can be interpreted as indicating that either the linguistic function of naming is impaired early in the disease process, or that this naming test actually assesses semantic memory and therefore is consistent with the other memory data.

Figure 2 demonstrates the outcome of the subjects with MCI up to approximately 4 years of follow-up. The conversion rate was 12% per year for the 4 years. These rates are in contrast to conversion rates for the healthy control subjects in our community sample. We have enrolled and followed up more than 500 control subjects in the 10 years of the study, and these subjects tend to convert to MCI/AD at a rate of approximately 1% to 2% per year.

Figure 3 shows the mean annualized rate of change for all subjects in the comparison groups on the MMSE, DRS, and Global Deterioration Scale. On the MMSE, the subjects with MCI behaved more like control subjects than the patients with AD. Similarly, the subjects with MCI showed a slower rate of change on the DRS and Global Deterioration Scale with respect to annualized differences than did the patients with AD.

Comparison of 4 Clinical Groups on Various Cognitive Scales*

	Controls, CDR 0	MCI, CDR 0.5	AD, CDR 0.5	AD, CDR 1
N	234	76	48	58
M/F	71/163	30/46	19/29	15/43
APOE, ϵ4/non ϵ4	161/46	43/22	21/17	24/22
Age, y	79.8 ± 0.5[a]	80.9 ± 1.0[a]	75.6 ± 1.7[c]	80.5 ± 1.0[a]
Education, y	13.3 ± 0.2[a]	13.7 ± 0.4[a]	12.5 ± 0.4[b]	12.1 ± 0.4[b]
CDR sum of boxes	0.0 ± 0.0[a]	1.5 ± 0.2[b]	3.3 ± 0.1[c]	5.9 ± 0.2[d]
GDS	1.1 ± 0.0[a]	2.7 ± 0.1[b]	3.4 ± 0.1[c]	3.9 ± 0.1[d]
GDepS	2.1 ± 0.1[a]	2.8 ± 0.3[b]	3.2 ± 0.3[b]	3.4 ± 0.3[b]
MMSE	28.3 ± 0.1[a]	26.0 ± 0.3[b]	22.6 ± 0.5[c]	21.4 ± 0.4[c]
DRS	134.3 ± 0.4[a]	124.7 ± 1.1[b]	112.7 ± 1.9[c]	106.7 ± 1.9[c]
VIQ	102.5 ± 0.6[a]	99.1 ± 1.3[a]	86.6 ± 1.5[b]	85.4 ± 1.2[b]
PIQ	100.4 ± 0.8[a]	96.2 ± 1.4[b]	82.1 ± 1.7[c]	81.4 ± 1.2[c]
FSIQ	101.8 ± 0.7[a]	98.0 ± 1.3[a]	83.9 ± 1.3[b]	83.0 ± 1.0[b]
BNT	50.3 ± 0.5[a]	45.0 ± 1.2[b]	34.7 ± 1.9[c]	33.5 ± 1.4[c]
COWAT	35.1 ± 0.7[a]	29.9 ± 1.3[b]	24.4 ± 1.7[b]	20.0 ± 1.4[b]
WMS-R				
LMI	21.3 ± 0.4[a]	12.7 ± 0.6[b]	8.6 ± 0.8[c]	5.8 ± 0.6[d]
LMII	15.3 ± 0.5[a]	4.2 ± 0.6[b]	2.8 ± 0.6[b]	1.5 ± 0.5[b]
VRI	25.7 ± 0.4[a]	20.2 ± 0.7[b]	14.4 ± 0.9[c]	13.8 ± 0.7[c]
VRII	17.6 ± 0.5[a]	7.4 ± 0.9[b]	4.1 ± 0.7[c]	2.2 ± 0.4[d]
AVLT				
LNG	35.5 ± 0.6[a]	25.0 ± 0.9[b]	21.5 ± 1.1[c]	17.8 ± 0.8[d]
% RET	62.1 ± 1.6[a]	21.6 ± 2.9[b]	8.3 ± 2.8[c]	10.8 ± 3.1[c]
FCSRT				
LN	58.4 ± 0.8[a]	34.1 ± 1.7[b]	25.6 ± 2.3[c]	16.6 ± 1.6[d]
% RETN	86.7 ± 1.1[a]	59.8 ± 4.4[b]	39.5 ± 6.2[c]	31.4 ± 5.3[c]

**Analyses reflect differences at the .01 level for comparison of adjacent groups. Values are mean ± SD. CDR indicates Clinical Dementia Rating; MCI, mild cognitive impairment; AD, Alzheimer disease; APOE, ratio of apolipoprotein E ϵ4 noncarriers to carriers excluding 2/4 genotypes; GDS, Global Deterioration Scale; GDepS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; DRS, Dementia Rating Scale; VIQ, Wechsler Adult Intelligence Scale, Verbal IQ; PIQ, Wechsler Adult Intelligence Scale, Performance IQ; FSIQ, Wechsler Adult Intelligence Scale, Full-Scale IQ; BNT, Boston Naming Test; COWAT, Controlled Oral Word Association Test; WMS-R, Wechsler Memory Scale-Revised; LM, Logical Memory; VRI, Visual Reproductions; AVLT, Auditory Verbal Learning Test; LNG, sum of learning trials 1 to 5; %RET, delayed recall/trial 5 × 100; FCSRT, Free and Cued Selective Reminding Test; LN, sum of the performance across trials 1 to 6; and RETN, delayed recall/trial 6 × 100. Comparison of 4 clinical groups on various cognitive scales. Analyses reflect differences at the .01 level for comparison of adjacent group. Similar letters (ie, a, b, c, and d) indicate no significant difference between pairwise comparisons.*

COMMENT

This study was designed to quantitatively characterize and describe the clinical course of patients diagnosed as having MCI using criteria that are similar to those being adopted by several multicenter treatment trials. While the criteria for MCI can be accepted by investigators in principle, the operationalization of these criteria can be challenging. As such, these results provide cross-sectional and longitudinal data with respect to these criteria.

As expected, the subjects with MCI performed more similarly to the control subjects than the patients with

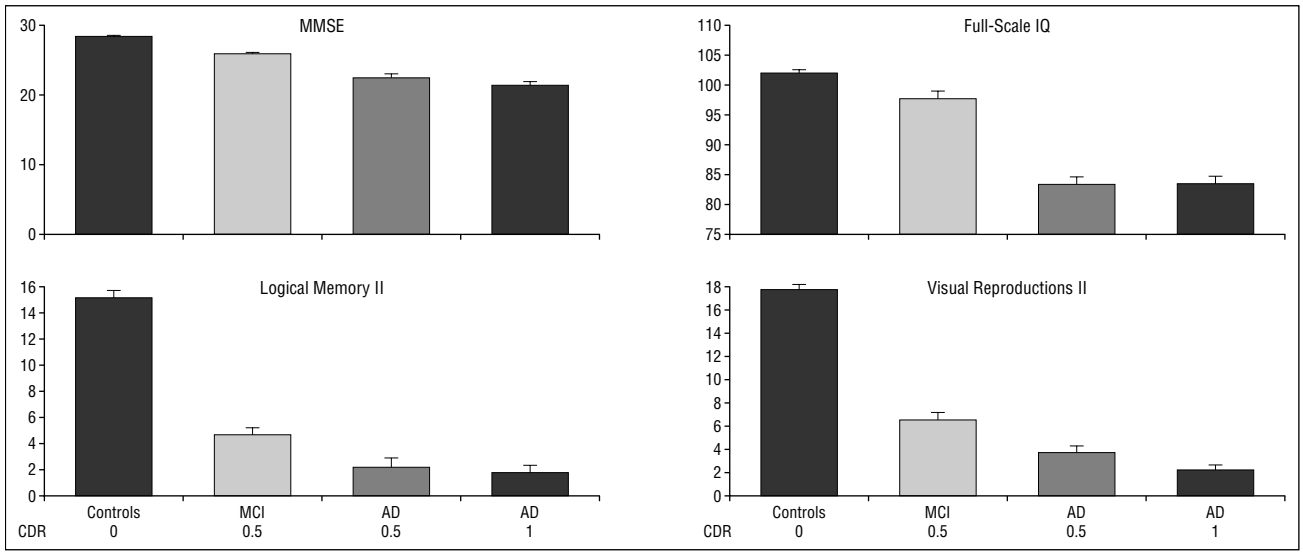

Figure 1. *Relative performance among 4 groups: controls, subjects with mild cognitive impairment (MCI) (Clinical Dementia Rating [CDR] 0.5), and patients with Alzheimer disease (AD) (CDR 0.5; CDR 1), on measures of global cognitive functioning, Mini-Mental State Examination (MMSE), and full-scale IQ compared with performance on measures of delayed recall for verbal materials (Logical Memory II) and nonverbal materials (Visual Reproductions II).*

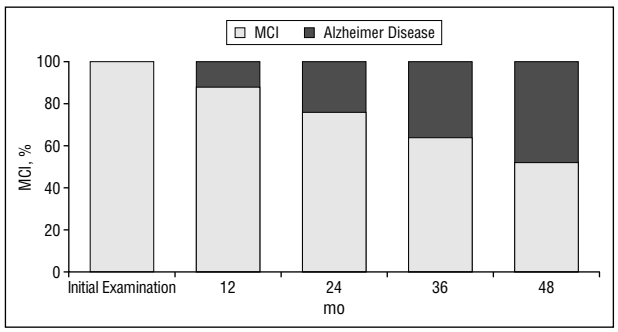

Figure 2. *Annual rates of conversion from mild cognitive impairment (MCI) to dementia over 48 months.*

AD on measures of general cognition and other nonmemory indexes. While there may have been mild impairments in some of the domains of cognition, eg, full-scale IQ, the actual raw score difference was sufficiently small, eg, a full-scale IQ of 101.8 vs 98.0 for controls and subjects with MCI, respectively, to not be clinically meaningful. That is, it is doubtful that most clinicians would say that a subject with a full-scale IQ of 98 was demented on the basis of this measure. The subjects with MCI performed more poorly than the control subjects on the Controlled Oral Word Association Test, but once again, the performance of the subjects with MCI was in the normal range for age based on our community studies.[35] This is not to say, however, that these subjects may not have incipient clinical AD; rather, most clinicians would be reluctant to make the diagnosis of AD at this stage. In addition, it is not likely that these subjects have a significant functional deficit since their mean CDR sum of box scores was 1.5 with most of the decline being accounted for by memory deficits. However, the patients with very mild AD (CDR 0.5) had a mean CDR sum of the box score of 3.3 that reflected these subjects' impairment in functional domains.

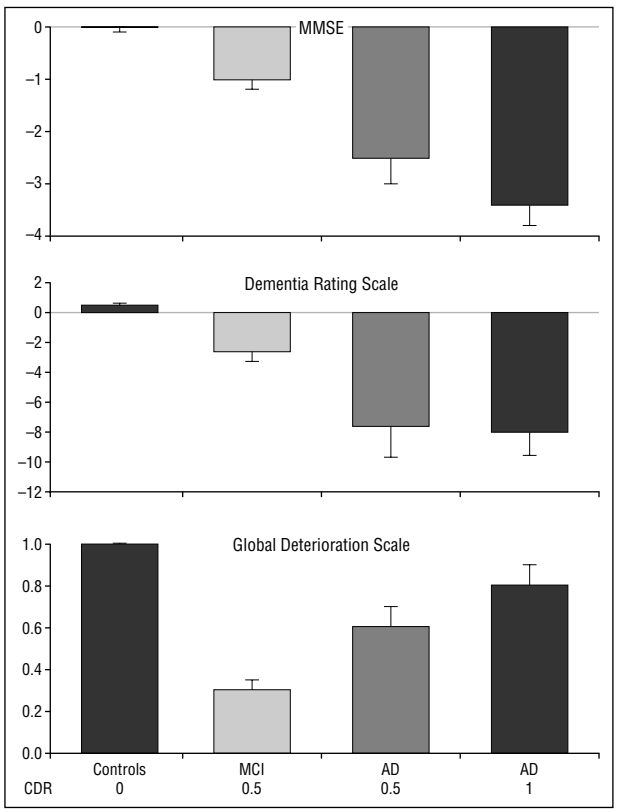

Figure 3. *Annual rates of change on 3 measures of global function for controls, subjects with mild cognitive impairment (MCI) (Clinical Dementia Rating [CDR] 0.5), and patients with Alzheimer disease (AD) (CDR 0.5; CDR 1). MMSE indicates Mini-Mental State Examination.*

From a memory perspective, the subjects with MCI appeared more like the patients with AD than the control subjects. Again, this is not surprising considering the selection criteria, but these data lend quantitation to these criteria. In fact, if the clinician sees a patient with impaired delayed recall performance or difficulty benefit-

ing from semantic cues during learning or recall in the setting of relatively preserved general cognition, the diagnosis of MCI should be entertained.

Most of the subjects received the diagnosis of MCI at entry into the study, while a few of the subjects had converted from a prior normal control status. The documentation of a memory decline was largely historical and based on the interview with the subject. With respect to the quality of the memory complaints, we asked for changes in memory function with respect to items involving recent memory. We prefer corroboration by an informant who knows the patient well. Previous work[36] has indicated that while individuals' subjective impressions of their memory function correlate best with indexes of depression, informants' assessments correlate well with objective performance.

Since the memory decline was subjective, it was necessary to corroborate memory performance as being abnormal (generally 1.5 SD below age- and education-matched control subjects) while general cognitive (Verbal IQ, Performance IQ) was within 0.5 SD of appropriate controls. The value of availability of an objectively documented decline in performance is helpful in detecting those subjects who are predisposed to develop AD.[37]

The clinical course of these subjects is important to describe. Individuals with MCI appear to be at an increased risk of developing AD at the rate of 10% to 12% per year. As Dawe et al[5] have indicated, there is variability in the literature largely due to different clinical criteria, neuropsychological measures used, and small numbers of subjects. However, several recent studies[1,8,38,39] using somewhat similar criteria, neuropsychological measures, and larger subject pools have demonstrated rates that are consistent with those reported herein.

Our previous work demonstrated that apolipoprotein E ϵ4 carrier status and features of memory function may predict who is likely to progress to AD more rapidly.[3,8,12,38,40] Magnetic resonance imaging volumetric measurements of the hippocampal formation may also be useful.[41]

There are 2 issues with respect to the classification of MCI and CDR 0.5 that need to be clarified. The first issue pertains to potential contamination of the MCI diagnosis with healthy individuals. As described earlier, it is possible that some subjects with MCI may have had long-standing poor memory function that may not progress. While the proportion of the total group of subjects with MCI who constitute long-standing poor performers is small, without longitudinal objective data, some of these individuals could be classified as MCI.

The other issue concerns the heterogeneity of the classification of a CDR score of 0.5. As Figure 1 demonstrates, some subjects with the classification of a CDR score 0.5 can be diagnosed as having MCI, while others may be designated as having AD. Essentially, those with a CDR score of 0.5 who have MCI have a significant memory impairment, but their other cognitive functions and activities of daily living are only slightly abnormal. Generally speaking, these deficits are of insufficient magnitude to constitute the diagnosis of AD by most clinicians. Those with a CDR score of 0.5 who qualify for the diagnosis of AD are more likely to be impaired in other areas of cognition (≥1.0 SD below healthy subjects on Verbal IQ, Performance IQ, MMSE, and DRS) and are functionally impaired (CDR sum of boxes, Global Deterioration Scale). These individuals meet the criteria for very mild AD and are distinguishable from the subjects with MCI.

All the classifications discussed are clinical. While the diagnoses are supported by neuropsychological data, the ultimate judgment is that of a clinician. Most clinicians would be uncomfortable at classifying subjects with MCI as having AD based on the criteria described.

The rates of change of subjects with MCI are different from control subjects and patients with AD. It is noteworthy that the control subjects improved from baseline to first follow-up on the full-scale IQ, which is a documented phenomenon.[42] This makes the decline of the MCI group meaningful, albeit small. These subjects change on the global instruments more rapidly than control subjects but not as rapidly as the clinically diagnosed patients with AD. This could reflect several factors. It is possible that the measuring instruments are not linear and are less sensitive to changes in the more mild states. It is also possible that the MCI group is "contaminated" with essentially healthy subjects who are not going to progress to AD. This difference can also be used to argue that not all subjects with MCI have AD at this point in time.

As is apparent, there are many interesting questions surrounding subjects with MCI. This study was designed to lend quantitative characterization to the clinical criteria for MCI that are being used in several multicenter trials. It also documents the clinical course of these subjects over the years with respect to their changes on standard instruments and their diagnostic outcomes. These results demonstrated that these subjects are at increased risk of progressing to AD and are useful to characterize for both theoretical and practical purposes.

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Anticardiolipin Antibodies

In their article on the prevalence of anticardiolipin antibodies in patients with idiopathic intracranial hypertension, Leker and Steiner [1] state that "the incidence of anticardiolipin antibodies in idiopathic intracranial hypertension has not been systematically studied... ." Obviously they were unaware of work carried out at this institution.[2] Sussman and colleagues [3] looked for abnormalities of coagulation in 38 patients with the syndrome of idiopathic intracranial hypertension and found evidence of antiphospholipid antibodies (anticardiolipin antibody and/or lupus anticoagulant) in 12 cases (32%), in 1 of 18 healthy obese controls, and 3 of 24 controls with other neurologic disease. The patients were similar, but not identical in the 2 studies. Only 18 of the patients studied by Sussman and colleagues had had imaging of the intracranial venous system (angiography) and 3 had evidence of dural sinus thrombosis and would have been excluded from the series reported by Leker and Steiner. Nevertheless, the results obtained by Leker and Steiner are remarkably similar to the earlier study, with 6 of their 14 patients having positive anticardiolipin antibody, and although the rates of positivity in suitable controls from the same population are not provided, this second study is further evidence that this is a real association and warrants further investigation. We need to determine how persistent antiphospholipid antibodies are in these patients, their relationship to prognosis, their relationship with other possible risk factors (the nonobese patients may be more likely to have antiphospholipid antibodies[3]) and whether they affect the response to treatments, both those conventionally used for idiopathic intrcranial hypertension and those used for other antiphospholipid antibody syndromes.

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In reply

We thank Howell for his comments regarding our article. Indeed, the series published by Sussman et al[1] adds important information to our knowledge concerning possible associations between anticardiolipin antibodies and intracranial hypertension. We appologize for our failure to cite their work that was published after our manuscript was completed but prior to its submission to the ARCHIVES. *According to Howell, Sussman et al included patients with dural sinus thrombosis in their series whereas such patients were not included in our series. Moreover, dural sinus thrombosis may present in a benign fashion mimicking benign intracranial hypertension (pseudotumor cerebri).*[2] *Neuroimaging studies, which are mandatory for the diagnosis of dural sinus thrombosis, are not reported for their patients and therefore, the true incidence of benign intracranial hypertension in the series of Sussman et al is unknown. Nevertheless, these 2 studies provide support to the association of anticardiolipin antibodies with intracranial hypertension.*

We concur with Howell that further studies investigating this association should be conducted before management issues can be answered.

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Correction

Error of Figure. In the study titled "Mild Cognitive Impairment: Clinical Characterization and Outcome" by Petersen et al published in the March issue of the ARCHIVES (1999;56:303-308), the bottom panel of **Figure 3** was incorrect. The correct version of the bottom panel of the figure is reprinted here.