Multiple Cognitive Deficits in Amnestic Mild Cognitive Impairment

Joel H. Kramer^a Adam Nelson^a Julene K. Johnson^a Kristine Yaffe^{a,b}
Shenly Glenn^a Howard J. Rosen^a Bruce L. Miller^a

^aSan Francisco Medical Center, University of California, and ^bSan Francisco VA Medical Center, San Francisco, Calif., USA

Key Words

Amnestic mild cognitive impairment · Alzheimer's disease · Executive function · Fluency

Abstract

Objective: To determine if more widespread cognitive deficits are present in a narrowly defined group of patients with the amnestic form of mild cognitive impairment (MCI). **Methods:** From a larger sample of patients clinically diagnosed as meeting the criteria of Petersen et al. for amnestic MCI, we selected 22 subjects who had Clinical Dementia Rating scores of zero on all domains besides memory and orientation. These MCI subjects with presumably isolated memory impairments were compared to 35 age-matched normal controls and 33 very mild Alzheimer's disease (AD) patients on a battery of neuropsychological tests. **Result:** In addition to the expected deficits in episodic memory, the amnestic MCI group performed less well than the controls but better than the AD group on design fluency, category fluency, a set shifting task and the Stroop interference condition. Over half the amnestic MCI group (vs. none of the normal controls) scored at least 1 standard deviation below control means on 4 or more of the nonmemory cognitive

tasks. **Conclusions:** Isolated memory impairment may be fairly uncommon in clinically diagnosed amnestic MCI patients, even when the criteria for amnestic MCI are fairly narrow. Additional cognitive impairments are likely to include fluency and executive functioning. These more diffuse deficits argue for comprehensive cognitive assessments, even when the patient and family are reporting only memory decline, and are consistent with the increase in attention paid to the heterogeneity of MCI.

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Mild cognitive impairment (MCI) lies intermediate between normal aging and dementia [1]. Despite variability in how MCI is operationally defined, elderly individuals with MCI are consistently shown to have a higher rate of progression to dementia [2–5].

Although subtypes of MCI have been reported [6–8], the amnestic form is most frequently studied, and criteria for MCI typically emphasize memory deficits. Among the most widely cited criteria for MCI are those proposed by Petersen et al. [9], which require memory complaint, normal activities of daily living, normal general cognitive function, abnormal memory for age and absence of dementia. How normal general cognitive function is deter-

mined, however, varies across studies and includes clinical impression, Mini Mental State Examination (MMSE), Clinical Dementia Rating Scale (CDR) [10] and cognitive testing. Petersen et al. [9], for example, used the intelligence quotient as a measure of general cognitive abilities and reported no differences between their MCI and normal control cohorts.

One important unanswered question is whether amnesic MCI patients are, in fact, free of the widespread cognitive deficits characteristic of early Alzheimer's disease (AD). Global measures of cognition such as the intelligence quotient and memory-oriented tasks like the MMSE can obscure focal deficits in domains such as language, visuospatial ability, working memory and executive functioning. In addition, even CDR scores of 0 or 0.5 do not rule out deficits in judgment or declining participation in community affairs. In the study of Petersen et al. [9], for example, their MCI cohort had a mean sum of box scores on the CDR of 1.5, implying that despite average intelligence quotient scores, some nonmemory domains of functioning may have been abnormal.

Studies of amnesic MCI typically define their cohort somewhat broadly, either on the basis of clinical complaint or a CDR score of 0.5. This leaves unanswered the clinically relevant question of whether subtle nonmemory deficits are going undetected. While some recent studies have suggested that nonmemory deficits are often present [2, 11], their subjects were drawn from a general population of MCI patients without any specific methods to select subjects with isolated memory impairment. The goal of the present study was to determine whether MCI patients who present with 'isolated' memory deficits have more diffuse cognitive impairment. To accomplish this, we began with a cohort of patients with CDR scores of 0.5 who met the criteria of Petersen et al. [9] for amnesic MCI. To create a sample with presumed isolated memory impairment, we then excluded cases with more widespread functional decline by requiring that all nonmemory domains assessed by the CDR were zero. This approach enabled the creation of a cohort that, per an informant, had no nonmemory functional deficits.

Methods

Subjects

The initial sample of subjects consisted of 86 patients diagnosed as having MCI at the UCSF Memory and Aging Center with a CDR total score of less than 1.0. The diagnostic evaluation consisted of a complete history and physical examination, interviews with an informant, completion of the CDR and any appropriate laboratory

and neuroimaging assessments to rule out identifiable causes for cognitive change. The CDR was completed by a clinic nurse who completed the Brief Training and Reliability Protocol offered by the Washington University Alzheimer's Disease Research Center. Subjects also received bedside neurocognitive testing blind to clinical diagnosis. The diagnosis was made by consensus conference where all clinicians who participated in the evaluation were present. A diagnosis of amnesic MCI was made using the criteria of Petersen et al. [9], which require memory complaint, typically corroborated by an informant, normal activities of daily living, normal general cognitive function, abnormal memory for age and absence of dementia. The determination of amnesic MCI was based on clinical grounds, and, as in the original paper of Petersen et al. [9], psychometric cut-off scores were not used. Individual CDR domain scores were then examined to select only those cases that were rated as a zero on the CDR domains of 'judgment', 'community affairs', 'home and hobbies' and 'personal care'. Twenty-two cases met this criterion. Of these 22 cases, 20 were rated as 0.5 on 'memory' and 2 were rated 0. Only 1 of these 22 subjects received a 0.5 for 'orientation'; the other 21 cases had ratings of 0 on orientation. One subject was rated as zero for memory and orientation.

The cognitive performance of our amnesic MCI was compared to two control groups, normal controls and patients with very mild AD. Both control groups were drawn from the Memory and Aging Center. The mild AD control group consisted of 33 patients who met NINCDS-ADRDA criteria for probable AD, had CDR total scores of 1 or less and MMSE scores greater than 23. The normal control group consisted of 35 normal elderly subjects over the age of 64 years recruited for research by the Memory and Aging Center. Inclusion into the normal control cohort required a CDR of 0, absence of significant cognitive complaints from the subject and informant, and a normal neurological examination.

Subjects in all three groups underwent laboratory testing and neuroimaging to rule out other medical conditions that can cause cognitive impairment. Exclusion criteria included abrupt onset of cognitive impairment, evidence for significant CNS effects of cerebrovascular disease, specifically the presence of severe periventricular white matter disease, large confluent white matter lesions, or grade 4 white matter lesions as described by Scheltens et al. [12], more than 1 lacunar infarct, any cortical strokes, CNS lesions on neuroimaging, including parenchymal mass lesion or extra-axial mass lesion with visible compression of the brain parenchyma, communicating or noncommunicating hydrocephalus or evidence of demyelinating disease, focal inflammatory or infectious disease or recent or remote intracerebral hemorrhage, substance abuse (including alcohol) or dependence, history of head trauma with loss of consciousness greater than 30 min, metabolic or systemic abnormalities with possible impact on cognition including uncorrected B₁₂ deficiency, uncorrected hypothyroidism, renal insufficiency requiring dialysis, significant liver dysfunction (with deficiency in synthetic function), respiratory insufficiency requiring oxygen or HIV positive status.

Demographic data are summarized in table 1. There were no group differences in age or education.

Neuropsychological Assessment

All subjects completed a brief neuropsychological screening designed to quickly and reliably assess episodic memory, working memory, executive functioning, fluency, naming, spatial ability and abstract reasoning [13]. The screening typically required

Table 1. Mean demographic and neuropsychological data in the normal control (NC), MCI and mild AD groups

	NC		Amnesic MCI		AD		MCI versus NC	MC versus AD
	mean	SD	mean	SD	mean	SD		
Age	73.0	5.3	75.0	6.1	73.4	9.2	n.s.	n.s.
Education	16.6	2.8	16.5	3.2	15.7	3.3	n.s.	n.s.
MMSE	29.5	0.8	28.5	1.5	25.2	1.3	<0.05	<0.001
Delayed verbal memory	7.3	1.8	4.5	2.8	1.6	1.9	<0.001	<0.001
Delayed visual memory	11.4	3.0	8.6	4.6	3.6	3.7	<0.05	<0.001
Digits backward	5.0	1.2	4.7	1.0	4.0	1.0	n.s.	n.s.
Modified trails	3.3	0.5	2.7	0.9	2.0	0.8	<0.005	<0.005
Stroop	49.7	9.7	38.8	10.4	19.9	10.2	<0.001	<0.001
Design fluency	10.1	2.9	8.0	2.9	5.3	2.2	<0.05	<0.05
d-Word generation	15.3	5.7	13.3	5.4	10.6	4.4	n.s.	n.s.
Animal fluency	21.5	5.9	15.6	5.0	9.6	5.1	<0.001	<0.001
Boston naming	14.5	0.8	13.5	1.3	11.4	3.3	n.s.	<0.05
Modified Rey copy	15.4	1.4	15.2	1.7	14.2	2.8	n.s.	n.s.
Abstract reasoning	4.8	1.0	4.5	1.3	2.9	1.5	n.s.	<0.001
GDS	4.3	3.7	6.3	3.9	7.7	6.7	n.s.	n.s.

n.s. = Not significant; GDS = Geriatric Depression Scale.

45 min to complete. Verbal episodic memory was evaluated with the California Verbal Learning Test – Short Form [14]. Visual memory was assessed by having subjects draw from memory a geometric figure they had copied 10 min earlier. Recall of the figure was scored on a 17-point scale. Working memory was measured using backward digit span length. Executive functioning tasks included cognitive flexibility and response inhibition. Cognitive flexibility was assessed using a modification of the Trail-Making Test that required subjects to serially alternate between numbers and days of the week. To adjust for the fact that some subjects did not complete the task within the 2-min time limit, the dependent measure was the number of correct connections made per minute (log transformed to normalize the distribution). Response inhibition was assessed by the interference condition of the Stroop test; their final score was the total number of correct responses in 60 s. Verbal fluency was number of words beginning with the letter ‘d’ in 1 min and number of animals in 1 min. Design fluency was assessed using condition 1 of the Delis-Kaplan Executive Functioning System Design Fluency subtest that required subjects to generate novel designs with 4 lines. Confrontation naming was assessed with a 15-item short form of the Boston Naming Test. Spatial ability was assessed by having subjects copy a complex geometric figure [13]. Interpretation of proverbs and determining conceptual similarities between word pairs served as the measure of abstract reasoning.

Statistical Procedures

Group differences on the cognitive measures were evaluated using one-way ANOVA with Tukey’s post hoc contrasts, with the contrasts of primary interest being MCI versus control and MCI versus AD.

Results

Mean scores on the neuropsychological test for the AD, MCI and normal control groups are listed in table 1. There were no group differences in age or education. On the MMSE, the MCI group’s mean score of 28.5 (range = 26–30) was well within normal limits but below that of the normal controls and higher than that of the AD patients. As expected, the MCI group also performed less well than the control group but better than the AD group on measures of delayed verbal and visual memory.

Significant group differences were found for all of the neuropsychological variables except design copying, with the AD group performing less well than controls on all measures.

There were significant differences between the MCI and normal control groups on several fluency and executive tasks. The MCI group performed less well than the normal control group but better than the AD group on design fluency, category fluency, modified trails and the Stroop interference condition. The MCI subjects performed comparably to both the normal controls and AD subjects on d-word generation. There were no differences between the MCI subjects and normal controls on Boston naming, backward digit span and abstract reasoning; both groups obtained higher scores than the AD group.

Table 2. Number of MCI, AD and normal subjects scoring in the impaired range

Number of nonmemory tests in the impaired range	Amnesic MCI	AD	Normal controls
Using cut-off of 1 standard deviation below the mean			
0	1	0	16
1	6	1	7
2	0	1	7
3	3	3	5
4	8	4	0
5+	4	24	0
Using cut-off of 1.5 standard deviations below the mean			
0	6	1	21
1	4	2	10
2	3	3	2
3	5	3	2
4	2	5	0
5+	2	19	0

To rule out the possibility that MCI subjects did less well on the fluency tasks because of poor memory (and a related increase in perseverative responses), the analyses for category and design fluency were repeated using the total number of responses (correct + perseverative). Results were unchanged.

We also tabulated the number of amnesic MCI subjects who performed in the impaired range on the non-memory tasks (table 2). Two different cut-offs for impairment were used: worse than 1 standard deviation below the mean and worse than 1.5 standard deviations below the mean. When 1 standard deviation below the mean was used as the cut-off, 4 of the 22 MCI subjects performed below this threshold on 5 of the cognitive tasks, 8 subjects scored below the threshold on 4 tasks, 3 subjects scored below this threshold on 3 tasks, and 6 subjects scored below the threshold on 2 tasks. Only 1 of the amnesic MCI subjects scored within a standard deviation of the normal control mean on all nonmemory cognitive tasks. In contrast, only 5 of the normal controls had 3 or more performances below the 1 standard deviation cut-off. When the more conservative 1.5 standard deviation cut-off was used, 4 MCI subjects scored in the impaired range of 4 or more nonmemory tests, whereas none of the normal controls did.

Discussion

One of the major findings of the present study is that non-memory deficits were found in a narrowly defined group of amnesic MCI subjects. To be included in this cohort, scores on the nonmemory domains of the CDR had to be zero, implying intact judgment and normal functioning at home and in the community. Nonetheless, these subjects scored significantly lower than normal age-matched controls on 4 of the 9 nonmemory cognitive tasks, performing less well on measures of executive functioning, category fluency and design fluency. Over half the amnesic MCI group scored at least 1 standard deviation below control means on at least 4 of the nonmemory cognitive tasks.

This study further demonstrates the low prevalence of MCI cases with isolated memory deficits. We began with a cohort of 86 MCI subjects who met the criteria of Petersen et al. [9] for amnesic MCI. Of these 86 cases, 64 had evidence for dysfunction in nonmemory domains on the CDR. Only 22 cases, approximately 25%, had CDR scores of zero in all the nonmemory domains. In addition, only 1 of the 22 amnesic-MCI subjects in our final sample scored within 1 standard deviation of the mean of our normal controls on all of the nonmemory cognitive tasks, whereas 16 of the normal controls performed at this level. This low incidence of isolated memory impairment is consistent with other reports in the literature. Lopez et al. [8], for example, reported on 130 participants from the Cardiovascular Health Study with MCI. Using neuropsychological test scores to classify subjects, they found that about 28% had isolated memory impairment, whereas the remaining 72% had deterioration in at least 1 non-memory cognitive domain. This percentage is highly concordant with our CDR data that showed that only 25% of clinically diagnosed amnesic MCI cases had isolated memory dysfunction. A study of retirement community residents also showed that 25–35% of memory-impaired subjects also had executive impairment [15].

Morris et al. [16] have argued that MCI generally represents early-stage AD and that MCI patients almost always have the neuropathological features of AD [17, 18]. If this is the case, we might expect incipient cognitive changes in an MCI cohort that parallel those found in early AD. Neuropsychological studies demonstrate that in addition to memory, cognitive tasks particularly sensitive to early AD include category fluency and executive functioning [19–23]. Other studies of patients with questionable dementia also reported diminished category fluency [24]. Our findings of fluency and executive deficits

in MCI are consistent with the view that amnesic MCI frequently represents a prodrome of AD. The more widespread cognitive difficulties in our amnesic MCI cohort suggest that they are at greater risk for conversion to dementia. Among nondemented elderly individuals, the risk of dementia significantly increased among patients with clear cognitive impairments beyond memory loss [25–27] whereas memory loss alone progressed to dementia less often over a 2-year period [26].

General cognition in our amnesic MCI subjects was clinically determined to be normal. Although the mean MMSE score in the amnesic MCI group was lower than that of the normal controls, a mean MMSE of 28.5 is not only entirely within normal limits, it is actually higher than the mean MMSE score (mean = 28.3) of the normal controls used in the original study of Petersen et al. [9]. The MCI group's MMSE was also higher than the 24 that several groups use as a cut-off [28] for indicating global impairment, and none of the subjects in our sample had an MMSE below 26. Normal general functioning was also reflected in our subjects' CDR scores, where the mean sum of box scores was quite low.

One of the ongoing issues in MCI research is how to best define constructs like amnesic MCI and normal general cognitive function [28, 29]. The issue of diagnostic criteria is critically important, since how subjects are categorized can shift with even minor changes in the criteria. Some studies take a psychometric approach to both constructs. Abnormal memory or other cognitive ability is often defined as 1.5 standard deviations below the mean or below a particular cut-off score on a neuropsychological test [8, 30]. Alternately, diagnosis of amnesic MCI has been based on patient complaints [9] or clinician impression [31]. Both approaches have their strengths and weaknesses. Clinical impression is often difficult to operationalize, and establishing reliability across groups of clinicians is challenging. On the other hand, relying on psychometric tests alone can also be problematic. Performance on neuropsychological tests is affected by many factors, including education, age, cultural background, sensorimotor deficits and illnesses other than AD [1]. In addition, many standardized neuropsychological tests have small normative samples of elderly subjects that may not be representative of the population, and skewed distributions can affect the number of cases falling outside a given standard deviation cut-off. Finally, there is no consensus on which tests or what types of scores (e.g. immediate recall, delayed recall, savings scores, recognition) should be used. The approach taken in the present study was to use a combination of clinical impression and

the CDR, a standardized metric widely used for staging dementia severity, reserving the neuropsychological test scores for outcome measures. One of the advantages of this approach is that it more closely parallels what occurs in a clinic setting where formal neuropsychological testing may not be available.

This study relied on the CDR, an informant-based measure, for identifying MCI cases with isolated memory deficits. The quality of these data, however, depends on the insightfulness and accuracy of the informant. It remains possible that informants were not aware of extant nonmemory deficits, although collateral sources tend to be fairly accurate when describing the cognitive impairments in patients with even very early dementia [32].

In sum, the majority of patients that met fairly narrow criteria for amnesic MCI in a memory disorders clinic had evidence for more widespread cognitive deficits on formal neuropsychological testing. The pattern of neuropsychological deficits, characterized by poor episodic memory and difficulties with executive and fluency tasks, parallels those found in mild AD. These findings have several important clinical implications. Terms like 'MCI' and 'amnesic MCI' are not consistently defined, blurring their prognostic value and making these important patient groups more difficult to study. Our data suggest that amnesic MCI patients may be a heterogeneous group. Greater evolution of diagnostic criteria is needed, particularly as nonamnesic variants of MCI are more extensively studied. Finally, clinicians should consider the possibility that patients complaining of isolated memory changes may in fact have more diffuse cognitive difficulties suggestive of a neurodegenerative disease and target these patients for early interventions.

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