Clinical Features of Mild Cognitive Impairment Differ in the Research and Tertiary Clinic Settings

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Key Words

Mild cognitive impairment • Alzheimer's disease • Cognitive domain

Abstract

Objective: Comparative analysis of subjects with mild cognitive impairment (MCI) diagnosed in a primary research setting and those seen in a tertiary care memory disorders clinic. **Methods:** Subjects who received a diagnosis of MCI between July 1, 2005, and December 31, 2006, in a longitudinal research study of normal cognition (n = 48) and patients diagnosed in a tertiary care referral clinic (n = 34) were evaluated using similar methodologies. Comparative analyses of detailed medical, neurological and neuropsychological data are presented. **Results:** The diagnosis of MCI was not accepted by 13 of 48 subjects (27%) classified as MCI in the primary research setting. Nondegenerative, potentially treatable causes of cognitive decline were found in 3 of 34 subjects (9%) seen in the tertiary referral clinic and in 11 of 35 subjects (31%) identified as MCI in the primary research setting (p = 0.02, Fisher's exact test). MCI subjects identified in the primary research setting were older than those referred to the memory clinic (mean ± SD, 79.7 ± 7.0 vs. 71.5 ± 9.0 years, p < 0.0001, t test) and had more years of education (16.0 ± 3.2 vs. 13.6 ± 4.2 years, p < 0.01, t test). MCI subjects in the primary research setting appeared to be in a

milder stage of disease, characterized by higher Mini-Mental State Examination scores (28.2 ± 1.8 vs. 25.7 ± 1.8, p < 0.0001), and a tendency towards single domain involvement, predominantly memory (mean number of domains involved, 1.0 vs. 2.5, p < 0.0001). More advanced stages of MCI, seen in the tertiary referral population, had additional involvement of attention (p < 0.0001, Fisher's exact test) and visuospatial domains (p < 0.0002, Fisher's exact test). Semi-quantitative grading of hippocampal and medial temporal lobe atrophy did not differ between groups (p = 0.81, Mann-Whitney U test). **Conclusions:** The diagnosis of MCI may be unwelcome in naïve persons. Remedial causes of MCI should be actively investigated. Demographic and clinical characteristics of MCI differ between research subjects and patients referred to a tertiary care clinic.

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Introduction

Clinical and demographic characteristics of subjects with mild cognitive impairment (MCI) often differ between studies [1–14]. The variability in clinical and demographic features of MCI reported in the literature in part reflects a combination of inconsistency in the operational definitions of MCI and the study protocols used by different centers [1–14]. Sources of recruitment

for different studies may also contribute to the inconsistencies between studies reported in the literature [1–14]. Increased understanding of these variables is essential for reconciliation of the often disparate findings reported in the literature [1, 3, 7–11, 13]. We present a comparative analysis of MCI subjects identified in the context of tertiary referral to the Memory Disorders Clinic of the Alzheimer's Disease Center at the University of Kentucky (UK ADC) and those identified as transitioning from normal cognition in a primary research setting at the UK ADC. Data presented include: (1) acceptance of the diagnosis of MCI, (2) medical causes for MCI, and (3) clinical and demographic descriptions of these disparate groups.

Objective confirmation of subjective memory complaints in the memory clinic setting may be openly received, whereas the diagnosis of MCI may be less welcome in naïve persons in the community. Evaluation of medical causes for mild cognitive decline is often performed in the primary care setting and typically precedes referral to a tertiary care memory disorders clinic. This perhaps leads to an underestimate of the influence of medical factors in the development of MCI reported in the literature in research studies recruiting subjects for study from such sources [3, 6, 15]. Persons with MCI recruited from memory disorders clinics often present with memory complaints and may be in a more advanced stage of disease than a more naïve group identified as transitioning to MCI from normal cognition in a primary research setting. Future attempts focused on developing population- or community-based screening methods for early cognitive decline or MCI may be critically dependent on a clearer understanding of these variables and how they relate to the diagnosis and possible treatment of MCI in a naïve population.

Methods

Research Clinic

The UK ADC longitudinal research program follows 500 subjects with normal cognition who undergo annual medical, neurological and neuropsychological examination (table 1) [16]. All subjects presented here were required to have undergone a previous examination, with a consensus diagnosis of 'normal'. All subjects transitioning from normal cognition to MCI in the period from July 1, 2005, to December 31, 2006 ($n = 48$) were included in the analysis. The diagnosis of MCI in this study was based on the examining physician's review of each case, including all available current and longitudinal data.

Subjects given the diagnosis of MCI were contacted by a study physician who conveyed this diagnosis to each participant using

a standardized protocol. This communication included disclosure of the diagnosis, as well as a systematic explanation of its prognostic value for predicting future cognitive decline and the possible development of a degenerative dementia. All subjects were invited and encouraged to undergo a medical workup for reversible causes of cognitive decline according to the American Academy of Neurology practice parameter on the initial diagnosis and workup of dementia [17].

Demographic variables recorded included: age, education, gender, duration of MCI (<1 year in all cases) and willingness to undergo diagnostic medical workup for reversible causes of memory decline. Clinical variables included: laboratory testing (complete blood count; comprehensive metabolic panel including electrolytes, glucose, liver and renal functions; rapid plasma reagent; sensitive thyroid-stimulating hormone; vitamin B₁₂, and folate), MRI or CT scan of the brain (including semiquantitative estimates of hippocampal and cortical atrophy [18, 19]), cognitive domain involvement (memory, attention, language, executive and visuospatial), Folstein Mini-Mental State Examination (MMSE) [20, 21], and Clinical Dementia Rating scale (CDR) global and sum-of-boxes (CDR-SOB) scores [22].

UK ADC Memory Disorders Clinic

The UK ADC Memory Disorders Clinic is staffed by the neurologists from the UK ADC longitudinal research program. Patients are referred there by their primary care or other physicians for evaluation. All subjects undergo a full medical, neurological and neuropsychological examination, as outlined above for the research clinic subjects (table 1). All subjects who received a diagnosis of MCI in the period from July 1, 2005, to December 31, 2006 ($n = 34$) are included in the analysis. All subjects underwent a medical workup for reversible causes of cognitive decline according to the American Academy of Neurology practice parameter on the initial diagnosis and workup of dementia [17]. Diagnosis was performed by the examining neurologist and included a review of each case, taking account of all available current and longitudinal data. Demographic and clinical variables recorded are identical to those outlined above for the research clinic subjects.

These studies were approved by the University of Kentucky College of Medicine Institutional Review Board.

MCI Diagnosis

For both groups, the diagnosis of MCI followed the current consensus guidelines on MCI developed by the second International Working Group on MCI [13]. The diagnosis guidelines included:

- (1) a cognitive complaint, preferably corroborated by an informant, or evidence for longitudinal decline on cognitive test performance (at least 1.5 SD decline for UK ADC research subjects);
- (2) generally intact global cognition;
- (3) no or minimal functional impairment (insufficient to meet current diagnostic criteria for DSM-IV diagnosis of dementia);
- (4) not demented by DSM-IV criteria.

The criterion of no medically identifiable cause for cognitive decline was not included, which allowed an assessment of these factors in the development of MCI.

Cognitive domain involvement was determined by neuropsychological test profile to allow classification of MCI by subtype

Table 1. Neuropsychological tests used to assess cognitive domain function

MMSE
National adult reading test
WMS logical memory I and II
California verbal learning test
Benton visual retention test
Trailmaking A and B
WAIS-R digit span and digit symbol
Stroop test
WAIS-3 similarities
WAIS-3 matrix reasoning
WAIS-3 letter-number sequencing
COWAT
Animal and vegetable fluency
Boston naming
CERAD figures
Clockdraw test

CERAD = Consortium to Establish a Registry for Alzheimer's Disease; COWAT = Controlled Oral Word Association Task; WAIS = Wechsler Adult Intelligence Scale (R = its revised version); WMS = Wechsler Memory Scale.

(amnesic single domain, amnesic multidomain, nonamnesic single domain, nonamnesic multidomain), as proposed by the second International Working Group on MCI [13], adopted by the National Alzheimer's Coordinating Center and the Alzheimer's Disease Neuroimaging Initiative.

Statistical Analysis

Analyses were conducted to ascertain significant differences between the research setting subjects who elected to undergo further medical examination after the diagnosis of MCI and those who did not (table 2). Analyses to compare the research setting subjects who underwent further examination and the memory clinic subjects were also carried out (table 3). Where variables were assumed to be normally distributed (i.e. age, years of education, and MMSE score), means were compared using Student's t test. Proportions (e.g. gender distribution, MCI subtype distributions) were compared using the χ^2 test of independence and Fisher's exact test, where appropriate. Nonparametric measures (e.g. CDR global and CDR-SOB scores) were compared using the Mann-Whitney U test. To correct for multiple comparisons, the p value for statistical significance was set at 0.003 using the Bonferroni method. Statistical analyses were performed using SAS 9.1.3®.

Results

After they had received disclosure of the diagnosis of MCI and a systematic explanation of its prognostic implications, 13 of the 48 subjects identified in the research

Table 2. Demographic and clinical variables in MCI subjects identified in the research setting that either refused or underwent evaluation for medically reversible causes of memory decline

Variable	Refused workup (n = 13)	Underwent workup (n = 35)	p value
Age, years	83.9 $\pm$ 7.4	79.7 $\pm$ 7.0	0.08 ^a
Gender (M:F), n	4:9	17:18	0.27 ^c
Education, years	15.7 $\pm$ 2.7	16.0 $\pm$ 3.2	0.78 ^a
MMSE score	28.7 $\pm$ 1.4	28.2 $\pm$ 1.8	0.36 ^a
CDR global score (mode)	0.5	0.5	0.72 ^b
CDR-SOB score (mode)	0.5	0.5	0.38 ^b
Total number of domains involved (median)	1.0	1.0	0.93 ^b

Data are means $\pm$ standard deviation, unless otherwise indicated.

^a Student's t test. ^b Mann-Whitney U test. ^c χ^2 test.

setting refused to undergo further medical evaluation for reversible causes of memory decline (27%). Each subject declining this invitation was then systematically queried on their reasoning. One subject had recently been diagnosed as having bladder cancer and felt that this additional medical evaluation was inappropriate at the current time. The 12 remaining subjects (25% of the total group) stated their reason for forgoing further medical evaluation was a lack of acceptance of the diagnosis of MCI. All 12 of these subjects believed they retained normal cognition and did not require any further evaluation.

Demographic and clinical variables did not differ between subjects refusing further evaluation and those identified in the research setting who underwent this evaluation (table 2). Age, gender, education, MMSE, CDR global and CDR-SOB scores, and extent of cognitive domain involvement were not significantly associated with a subject's willingness to consider the validity of the diagnosis of MCI and undergo medical evaluation.

Workup for nondegenerative causes of memory decline in the 35 subjects identified in the research setting revealed evidence for hypothyroidism (11%), vitamin B₁₂ deficiency (9%), vascular disease (6%), normal pressure hydrocephalus (3%) and subdural hematoma (3%). In total, 11 of 35 subjects (31%) undergoing medical workup revealed nondegenerative causes for cognitive decline in this group. In contrast, only 3 of 34 subjects (9%) seen in the memory clinic were found to have a nondegenerative cause for the cognitive decline seen. Two subjects were

Table 3. Demographic and clinical variables in MCI subjects identified in the primary research setting or in the memory clinic

Variable	Research setting (n = 35)	Memory clinic (n = 34)	p value
Age (mean $\pm$ SD), years	79.7 $\pm$ 7.0	71.5 $\pm$ 9.0	<0.0001 ^a
Gender (M:F)	17:18	13:21	0.39 ^c
Education (mean $\pm$ SD), years	16.0 $\pm$ 3.2	13.6 $\pm$ 4.2	0.01 ^a
MMSE score (mean $\pm$ SD)	28.2 $\pm$ 1.8	25.7 $\pm$ 1.8	<0.0001 ^a
CDR global score (mode)	0.5	0.5	0.03 ^b
CDR-SOB score (mode)	0.5	0.5	0.13 ^b
Hippocampal atrophy (median)	2.0	1.5	0.81 ^b
Memory involvement, %	89	85	0.73 ^c
Attention involvement, %	14	71	<0.0001 ^c
Language involvement, %	20	29	0.36 ^c
Executive involvement, %	14	18	0.70 ^c
Visuospatial involvement, %	6	47	<0.0001 ^c
Total number of domains involved (median)	1.0	2.5	<0.0001 ^b
MCI subtype, %			
ASD	63	21	0.0004 ^c
AMD	29	65	0.0026 ^c
NSD	9	0	0.24 ^c
NMD	0	15	0.025 ^c

AMD = Amnesic multiple domain; ASD = amnesic single domain; NMD = nonamnesic multiple domain; NSD = nonamnesic single domain.

^a Student's t test. ^b Mann-Whitney U test. ^c χ^2 or Fisher's exact test.

found with vitamin B₁₂ deficiency and 1 subject had a known history of seizure disorder with evidence for hippocampal sclerosis found on MRI (hippocampal atrophy with increased T₂ signal on fluid-attenuated inversion recovery imaging). The difference in frequencies of non-degenerative causes for cognitive decline in the 2 groups did not reach significance after Bonferroni correction for multiple comparisons ($p = 0.02$, Fisher's exact test).

Demographic and clinical comparisons between subjects identified in the primary research setting and those seen in the memory clinic revealed distinct profiles (table 3). Subjects referred for evaluation in the memory clinic were less educated, significantly younger, and showed significantly poorer performance on the MMSE and more extensive cognitive domain involvement than those subjects identified as having MCI in the primary research setting. The majority of cases (63%) diagnosed in the primary research setting were classified as amnesic single domain MCI, whereas the majority of cases (65%) diagnosed with MCI in the memory clinic were classified as amnesic multidomain MCI. Increases in the frequency of both attention and visuospatial domain involvement, in addition to primary memory domain involvement, were seen in the group diagnosed in the memory clinic.

Discussion

The reluctance of over one fourth of the individuals diagnosed as having MCI in the primary research setting to accept the diagnosis and undergo further workup for nondegenerative causes of memory decline was not expected. Participants in this group are highly motivated research subjects, undergoing extensive 2- to 3-hour annual longitudinal evaluations with consent to brain donation at death [16]. Over half of these subjects have a family history of Alzheimer's disease and an approximately equal number are positive for the apolipoprotein E $\epsilon 4$ allele, a documented risk factor for the disease [16]. These data call into question the practical utility of screening for predementia disease states, such as MCI, in a naïve population. Further efforts aimed at educating the general public about the importance of early detection of degenerative disease states, such as Alzheimer's disease, are warranted.

Identification of nondegenerative potentially reversible causes for memory decline is rare in the setting of a tertiary care clinic referral population (<10% in this series, as expected). In contrast, the present data demonstrate that a significant proportion of persons identified

with early memory decline in a naïve population may have identifiable nondegenerative potentially reversible medical causes for the cognitive decline detected with intensive screening methods (31% of subjects). While the difference in frequency of nondegenerative causes of cognitive decline did not reach statistical significance in this study (after correction for multiple comparisons), these data demonstrate the importance of a thorough workup for medical causes of MCI or predementia cognitive decline, as suggested by others [6, 15, 23]. While the current American Academy of Neurology practice parameter on the detection of MCI details the need for close observation and continued follow-up, given the risk for future transition to dementia, it does not highlight the importance of medical evaluation in this setting [24]. Our data suggest that such evaluation is critical, even at this early point in the development of cognitive decline.

Subjects evaluated in the memory clinic were younger and less educated than those seen in the primary research setting, although the difference in education was not significant in this study. This may reflect a bias toward research participation in older more highly educated persons, rather than an intrinsic characteristic of the population seen in the memory clinic. The advanced age of subjects in the primary research population may be responsible for the observation of increased frequency of nondegenerative medical causes for cognitive decline in this population. Therefore, this observation may not solely reflect a bias of prereferral diagnostic evaluation for subjects referred to the memory clinic.

Comparisons of subjects diagnosed as having MCI in the primary research setting and those seen in a tertiary care referral clinic demonstrate other important differences. As expected, longitudinal assessment of subjects with normal cognition allows the opportunity to identify persons transitioning to MCI at a much earlier stage than those seen in a tertiary referral clinic. Staging of the severity of MCI has been proposed by others in the field and appears to have diagnostic and prognostic utility [5]. The milder stage of disease in these individuals is attested to by significantly higher MMSE scores and involvement of fewer cognitive domains at presentation. This observation is also supported by the finding of decreased median hippocampal atrophy (semiquantitative analysis [18, 19]) in these subjects, although this finding was not statistically significant.

The vast majority of cases classified as MCI in the primary research setting met diagnostic criteria for amnesic single domain involvement. In contrast, cases classi-

fied as MCI in the memory clinic most often met criteria for amnesic multidomain involvement, again suggesting that these subjects were in a more advanced state of disease. Several previous studies investigating the heterogeneity of MCI subtypes have suggested that amnesic multidomain MCI may be the most prevalent subtype [5, 14]. The present data are not inconsistent with these previous observations, but instead suggest that MCI is a dynamic state. Isolated memory involvement appears first, followed by attention and visuospatial deficits [4]. The development of multiple domain involvement suggests a progression of the underlying disease state and may be a harbinger of impending dementia, as defined by the DSM-IV criteria (of which such multidomain involvement is one of the core requirements).

The strengths of this study lie in the uniform clinical assessment and detailed evaluations performed on subjects in each study group, as well as the uniform application of the diagnostic criteria for MCI in these 2 distinct clinical populations. Similar studies are lacking in the present literature.

The weaknesses of this study lie in the selection biases inherent in the self-selected, community-based, primary research population and the strong referral bias inherent in the population of subjects seen in a tertiary care research clinic.

Despite these reservations, the present data add to our current understanding of MCI in distinct populations of subjects. A more thorough understanding of the impact and acceptance of the diagnosis of MCI in naïve populations, and of the evolution of cognitive decline in MCI is imperative if we hope to move the diagnosis of MCI out of the research setting and into clinical practice. Efforts to develop and implement primary screening measures for predementia cognitive decline are likewise critically dependent on such observations, future discoveries, the development and implementation of effective strategies for educating the general population, disclosure of the diagnosis of MCI, and provision of effective interventional strategies as they are developed.

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