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Current Concepts of Mild Cognitive Impairment and their Applicability to Persons At-Risk for Familial Alzheimer's Disease

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Abstract

The definition of mild cognitive impairment (MCI) as a precursor for Alzheimer's disease (AD) represented an important step forward in diagnosing the illness in its earliest stage. However, diagnoses based principally on cognitive performance have limitations in that there is variability between centers in which tests are employed and in how they are interpreted. Advances in our understanding of imaging and biochemical changes occurring early in the illness have improved our ability to diagnose AD in this early phase and diagnostic criteria for AD have been proposed recently based on such biomarkers. Persons inheriting autosomal dominant mutations causing familial AD (FAD) are essentially certain to develop the disease. In our studies of preclinical persons at-risk for inheriting FAD, we applied MCI diagnostic criteria to carriers of FAD mutations to ascertain the extent to which they identified persons in the earliest stages of the clinical illness. Our results indicate the relative prevalence of MCI subtypes varies considerably depending on the tests used to measure cognition. Furthermore, we found that cognitive complaints in such persons were less predictive of mutation status than were informants' reports of cognitive loss. The study of FAD provides an opportunity to test various criteria for early AD and these observations should be taken into consideration in future iterations of such diagnostic criteria.

Keywords

Mild cognitive impairment; alzheimer's disease; biomarkers; familial; presenilin-1; amyloid precursor protein; neuropsychology; presymptomatic

INTRODUCTION

Progress is being made in developing interventions that are truly effective in preventing or slowing the progression of Alzheimer's disease (AD). Should such treatments become available, it then becomes critical to identify persons who are in the earliest stages of the illness or are destined to develop it in the future. Towards this end, there have been substantial advancements in defining the cognitive [1,2], genetic [3], imaging [4,5] and biochemical [6, 7] features of the earliest stages of the illness. Many studies have shown that loss of delayed episodic memory typically occurs early in the disease [1,2]. In an attempt to study this early

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stage, the entity of mild cognitive impairment, or MCI, was defined. Persons meeting criteria for MCI are at an increased risk for worsening cognition and progressing to diagnosable AD [8]. Though the clinical entity of MCI and biological markers (“biomarkers”) for the subsequent development of AD have predictive value, none have perfect accuracy in identifying who will and who will not worsen and in what time frame.

In persons who have inherited autosomal dominant forms of AD (familial AD, or FAD) due to fully-penetrant alterations in the Amyloid Precursor Protein (*APP*), Presenilin-1 (*PSEN1*), or Presenilin-2 (*PSEN2*) genes, the future development of AD can be predicted with essentially 100% accuracy. This population therefore provides the opportunity to test the value of cognitive and biomarkers in predicting AD. Prior studies of persons at risk for FAD have demonstrated its utility in identifying clinical [9-11], biochemical [12,13], and imaging [14-17] changes occurring early in the disorder. In this paper we apply the Petersen criteria to a population of preclinical FAD mutation carriers studied with two different psychometric batteries to ascertain their utility in categorizing persons in the earliest stages of the illness. We then discuss the implications of our findings in the context of the evolving concept of MCI.

MCI AND THE PETERSEN CRITERIA

Dementia is defined by significant decline in memory and an additional domain of cognitive function to the extent that it interferes with one's occupational or social function [18]. Once it has been established that dementia is present, the most commonly used framework for the diagnosis of AD in research is the National Institute for Neurological, Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria [19]. Robust deficits in delayed episodic memory are particularly characteristic of dementia of the Alzheimer's type [1] and are frequently present early in the illness before other criteria for dementia are met [2]. In order to study this state in which relatively isolated episodic memory loss is present, formalized criteria for amnesic MCI were defined [20,21]. According to this definition, persons with “single-domain” amnesic MCI have a subjective memory complaint, an objectively demonstrable memory impairment (e.g. performance 1.5 standard deviations below that of age, gender, and education-matched peers) with other aspects of cognitive function being relatively intact, and largely preserved activities of daily living. By applying these criteria to various prospective studies, it has been estimated that 10-15% of such persons progress to diagnosable dementia per year [8], with the majority developing AD [22]. Not all persons with progressive cognitive decline present with predominant memory dysfunction and therefore other subtypes of MCI have been defined [21]. Amnesic vs. non-amnesic subtypes are differentiated by the presence or absence of a memory deficit and single vs. multiple domain subtypes by whether or not more than one domain of cognitive function is affected. The value of this classification system in predicting future diagnoses has been evaluated in prospective studies and has been found, at least preliminarily, to have some utility [23,24].

LIMITATIONS OF MCI CLASSIFICATION

Although the MCI state is clearly associated with a subsequent risk of developing dementia that is higher than that of similarly aged controls not meeting criteria for MCI, it is an imperfect predictor of who will develop dementia and which type of dementia will ensue. The rate at which MCI patients convert to dementia varies with different studies with at least one study showing that as many as 40% of MCI patients may revert to normal cognition [25]. The initial description of MCI includes the criterion that the patient in question subjectively experiences memory impairment. However, many patients in the earliest stages of AD have no such insight into their loss. Furthermore, when such subjective complaints are present, they may be more related to the presence of depression than to incipient AD [26]. Another shortcoming of the

current conceptualization of MCI is that it is defined by performance on neuropsychological tests at a single time point relative to normative data. Inter-individual differences, even in populations matched for age, gender, and education, are typically large. Therefore, longitudinal change *within* individuals, whether measured by psychometric testing or by the report of an informed surrogate, can provide a more sensitive indicator of incipient dementia. Storandt *et al.* [27] demonstrated that persons for whom informants identified a decline but who did not meet neuropsychological criteria for MCI nonetheless had a median time to develop diagnosable dementia of 7.8 years. Another limitation of the MCI classification scheme is that the specific cognitive criteria used in defining MCI varies among centers, neuropsychologists, and other clinicians. Not all persons agree on what constructs constitute a “cognitive domain,” what tests should be used to best assess performance within such domains, what degree of impairment constitutes abnormality, and what is the number of tests with impairment that is required to define loss in a domain. A final issue that arises has to do with the application of MCI as a clinical entity; specifically, we have observed a tendency for some physicians to use it as a diagnosis in persons with established dementia, apparently in order to avoid the dementia label and its associated stigma.

With the substantial advances that have been made in genetic, imaging, and biochemical characterization of preclinical dementia states, it should be possible to improve upon our ability to diagnose AD in its earliest stages beyond that provided by the concept of psychometrically defined MCI. A first attempt to formalize the use of these other modalities in the diagnosis of early AD was proposed by Dubois *et al.* [28]. In these criteria, the categories of MCI and possible AD are eliminated. The importance of an early deficit in episodic memory is retained, with such objective impairment constituting the core diagnostic feature. In order to qualify for probable AD according to these criteria, supporting biomarker evidence of either medial temporal lobe atrophy on magnetic resonance imaging (MRI), decreased beta-amyloid₄₂ and/or elevated total tau or phosphorylated tau in the cerebrospinal fluid (CSF), or the characteristic metabolic pattern detected with fluorodeoxy-glucose positron emission tomography (FDG-PET) must be present. Exclusionary criteria and pathological criteria for definite AD are similar to those of the NINCDS-ADRDA criteria.

FAMILIAL ALZHEIMER'S DISEASE

Familial AD due to *APP*, *PSEN1*, or *PSEN2* mutations is essentially fully penetrant. Though the age of disease onset within families can vary by decades, it is typically consistent within a few years [29]. Because of the reliability with which these mutations cause disease, in the proposed Dubois criteria the presence of such a mutation in a family member serves as supportive criteria for probable AD and a demonstrated genetic alteration in an affected person qualifies for definite AD. Though persons with FAD can have clinical features that are atypical for AD including young age of onset, early myoclonus [30], seizures [30], and spastic quadriparesis [31], and the neuropathology can differ from classic AD [32], FAD nonetheless provides a model for sporadic AD in which the future development of the disease can be predicted with essentially 100% certainty in completely asymptomatic persons. We sought to assess the Petersen criteria for the subtypes of MCI by applying them to persons at-risk for FAD by virtue of having first-degree relatives affected by the illness due to known FAD mutations.

MCI IN FAD

Methods

Two separate but partly overlapping populations of persons at-risk for FAD by virtue of having first-degree relatives with either *PSEN1* or *APP* mutations underwent neuropsychological testing using two different batteries by examiners blind to their genetic status. Genetic testing

was performed and the non-demented mutation carriers were classified according to the Petersen criteria depending on the presence or absence of a memory complaint and their neuropsychological test scores.

The first group (Group 1) consisted of Mexican persons tested in Mexico by author YR-A, all at-risk for *PSEN1* mutations. Potential subjects were asked whether or not they had difficulties with their memory or thinking. Those that indicated they did were additionally asked if they thought these problems interfered with their normal activities. Subjects answering “yes” to both these questions or for whom a clear history of functional decline was provided by an appropriate informant were classified as demented and were excluded. This left 51 non-demented subjects who underwent a neuropsychological test battery consisting of Spanish translations of instruments commonly used in English. The results of the comparisons between mutation carriers and non-carriers on individual tests have been reported previously [10]. From the raw scores, composite z-scores for four domains were calculated using the mean scores of non-mutation carriers. Specifically, Language [Boston Naming Test [33], Category (animals and fruit) and Letter (words beginning with “F” and “A”) Fluency], Visuospatial (Rey-Osterrieth Copy, Block Design [34], Visual Reproduction - Immediate, from the Wechsler Memory Scale – Revised, or WMS-R [35]), Verbal Memory (Delayed recall of a 10-word list [36], immediate recall of paired associates, Logical Memory - immediate recall from the WMS-R [35]), and Executive Function/Working Memory (Trails B time, Mental Control and Reverse Digit Span from the WMS-R [35]) composite scores were calculated. Mutation carriers that scored 1.5 standard deviations below non-carriers on these composite scores were defined as being impaired in that domain. Subjects were then classified as being single domain amnesic, multiple domain amnesic, single domain non-amnesic, or multiple domain non-amnesic MCI.

The second population (Group 2) consisted of 36 non-demented persons of Mexican descent who were tested at UCLA by author LDM. Eighteen of these subjects had previously undergone neuropsychological testing as part of Group 1 between 2 and 7 years earlier. They were at risk for either *PSEN1* (n = 28) or *APP* (n = 8) mutations. This group underwent the Clinical Dementia Rating (CDR) scale interview [37] with input from an unrelated informant and another Spanish-language neuropsychological battery. Subjects with CDR scores greater than 0.5 were excluded from further analyses. Z-scores of mutation carriers (n = 22) for cognitive domains were similarly calculated by comparing their scores to the means of non-carriers (n = 14). The domains consisted of Language (category fluency for animals, Object Naming from the Spanish-English Neuropsychological Assessment Scale, or SENAS [38]), Visuospatial (Rey-Osterrieth Figure Copy, Block Design from the WMS-R [35]), Verbal Memory (Word-List Learning Delayed Recall, Memory Verbal Prose Delayed Recall [39]) and Frontal/Executive Function (Stroop Interference Score [40], Color Trails Interference Score). Mutation carriers were classified according to MCI subtypes as above. Also, in Group 2, the rates of subject and informant reports of cognitive loss as determined in the CDR were compared between mutation carriers and non-carriers using Fisher's exact tests.

Results

In Group 1, 30 of the 51 subjects were mutation carriers. Fourteen of these 30 mutation carriers met criteria for one subtype of MCI (Table 1). Of these, 7 subjects met criteria for single domain non-amnesic MCI (all Executive Function/Working Memory) and 7 subjects met criteria for multiple domain MCI. Of these latter seven, all had involvement of Executive Function/Working Memory with 3 having additional impairment in Verbal Memory (2 also with Visuospatial deficits). The remaining 4 subjects had the additional involvement of Visuospatial function only. No subjects met criteria for single-domain amnesic MCI.

Among the memory measures available to calculate the Verbal Memory Subscore for Group 1, only one had a delayed recall component. Because of this under-representation of delayed memory measures, the composite Verbal Memory z-scores may have been artificially raised by subjects' relatively intact immediate memory. For this reason, we recalculated the Verbal Memory z-score using only the results from the Delayed Recall of the 10-word list. This resulted in an additional 3 subjects being classified as MCI with all of them being single domain amnesic MCI.

In Group 2, 36 subjects had CDR scores of either 0 ($n = 27$) or 0.5 ($n = 9$). Twenty-two of the 36 subjects were mutation carriers. Of these 22, 7 met criteria for MCI (Table 1). Three of these subjects met criteria for single domain amnesic, two for multiple domain amnesic MCI (one with Frontal/Executive and Visuospatial functions also affected with the remaining having only Visuospatial function additionally affected), and two for single domain non-amnesic (one with Language and one with Frontal/Executive function being affected) MCI.

In Group 2, 12 of 21 mutation carriers (data missing on one subject), or 57%, had subjective cognitive impairment that was no different from the rate in non-mutation carriers ($6/14 = 43\%$, Fisher's 2-sided exact test, $p = 0.50$). When informants' responses to the question regarding subjects' cognitive loss were compared, 1 out of 14 (7%) of non-carriers' informants reported such complaints compared to 9/22 (41%) of carriers' informants (Fisher's 2-sided exact test, $p = 0.054$). Among the seven carriers with MCI, five had subjective cognitive complaints and the informants of five of seven carriers thought the subjects had cognitive deficits.

DISCUSSION

We applied the Petersen criteria for MCI to a population that is destined to develop AD in the future. We employed two different neuropsychological test batteries and found diverse relative prevalences of MCI subtypes. In Group 1, using a composite score in which only 1 of 3 tests had a delayed recall component, no subjects met criteria for single domain amnesic MCI though 3 subjects met criteria for multiple domain amnesic MCI. When this single test was used as the verbal memory measure, 3 subjects met criteria for single domain amnesic MCI out of a total of 17 subjects with MCI. The results of MCI classification in Group 2 were more in-line with what is reported in sporadic AD with 5 of 7 subjects with MCI having memory impairment and 3 of these having single domain amnesic MCI. We feel that the sensitivity of MCI classification to differences in the methods used to quantitate cognition demonstrated in this example highlights a weakness of a classification scheme based largely on neuropsychological test scores.

An alternative explanation to our findings of disproportionate Executive Function/Working Memory Deficits in Group 1 is that persons with FAD experience deficits in this domain to a greater extent than occurs in preclinical sporadic AD. *PSEN1* pedigrees in which disproportionate frontal lobe dysfunction occurs have been reported [41], and we have found that Wisconsin Card Sorting Performance is impaired during the preclinical phase of the illness [42]. However, group studies in which scores on neuropsychological batteries are compared between mutation carriers and non-carriers do not consistently show disproportionate frontal lobe dysfunction [43]. When comparing the 30 mutation carriers in our study to 21 non-carriers, mean time to complete the Trails Making Test Part B was greatly prolonged in the non-demented mutation carriers [10] and this score contributed significantly to the Executive Function/Working Memory composite score. However, frontal lobe function measured using the interference scores on the Stroop and Color Trails tests was not consistently impaired in Group 2, again reinforcing the sensitivity of the MCI classification scheme to specific attributes of the tests and scoring systems employed.

In this population known to be at risk for genetic alterations causing FAD, 43% of non-mutation carriers in Group 2 thought they had cognitive deficits compared to 57% of carriers. Subjective cognitive loss therefore does not appear to be helpful in predicting who will and who will not go on to develop young-onset AD in these families. It is likely that this high rate of cognitive complaints is due in part to anxiety on the part of study participants with regard to their own genetic status and therefore may not apply to the general population presenting to memory clinics. However, it has been shown that subjective cognitive complaints in persons presenting to such tertiary centers are closely related to depression and anxiety and may or may not reflect incipient neurodegenerative disease [26]. In our population, informant report of cognitive decline was more helpful as it was present in 41% of carriers but only 7% of non-carriers. Many, but not all (5/7) persons with a subtype of MCI had cognitive complaints from either the subject or informant with complaints being present in both the informant and subject in four of the seven. This indicates that in addition to lacking specificity for those with early AD, the sensitivity of such complaints to early disease is less than optimal.

In the Dubois criteria, the requirement for an episodic memory deficit for the diagnosis of probable AD is retained. Though early memory dysfunction is typical of AD, such a deficit is not always the presenting feature. In addition to our data that suggest executive function can be affected early, many other exceptions occur [44] in that visuospatial deficits (posterior cortical atrophy or PCA [45]), language deficits (primary progressive aphasia, or PPA [46]), or even asymmetric motor deficits (akin to those of corticobasal degeneration [47]) can initially dominate the clinical picture. We anticipate that further refinement of our knowledge regarding biological markers more directly reflecting AD pathology than the cognitive features may obviate the requirement for an episodic memory deficit in the diagnosis of probable AD.

There are multiple limitations to our study that warrant mention. Eighteen subjects were common to Groups 1 and 2 so the two “sub-studies” described here are not completely independent. However, testing was performed at least two years apart and distinct neuropsychological measures were used to define MCI and its subtypes for the two groups. There are additional difficulties with regard to comparing the groups. Group 1 consisted entirely of Mexican nationals living in Mexico tested with an unvalidated battery consisting of English-language measures translated into Spanish. Group 2 was more mixed, consisting of both highly acculturated Mexican-Americans and Mexican nationals of variable educational levels. It is therefore possible that some of the discrepancies seen between groups in MCI subtypes are related to these differences.

A further weakness of our study is that in Group 1, objective evaluations from an unrelated informant were not systematically sought. Therefore, in some cases, our assessment of demented vs. non-demented status relied on subjects' own accounts. As such subjective reports in persons with incipient dementia are not always accurate, there is the possibility that some persons qualifying as mildly demented were included in Group 1.

Another important weakness of our study that we believe reflects weakness inherent in the psychometrically-defined MCI classification scheme is that there can be disagreement as to what tests most accurately reflect a cognitive construct or domain. In our study of Group 1, the tests that constituted the cognitive domains were chosen to be consistent with our previous publication [10] and may not have been optimal. For example, the inclusion of immediate recall of the Rey-O Figure (which clearly has a memory component) in the Visuospatial domain and tests of verbal fluency (which has an executive component) in the Language domain may have served to dilute differences between domains. However, lacking a “gold standard” of what constitutes a cognitive domain, we feel that no such constructs will be completely without detractors and therefore it is difficult to standardize the current criteria for MCI across clinicians and across centers.

The Dubois criteria represent an important step towards refining our ability to diagnose AD earlier in its course. As the markers proposed in the Dubois criteria are incompletely validated and many other potential modalities exist (e.g. putative amyloid and tau ligands like PIB [48] and FDDNP [49]), the authors expect that these criteria will be specified and modified in the future. Though there are some clinical, biochemical, and pathological differences between FAD and sporadic AD of later onset, the similarities are strong enough to support the utility of FAD mutation carriers as a model for presymptomatic AD. The continued study of persons at-risk for FAD will augment our ability to refine the diagnosis of AD in the earliest, presymptomatic stages.

Our data from this population demonstrate the sensitivity of current concepts of MCI to the neuropsychological battery employed and how scores are used to define it. In addition, our data confirm the observation that informant-based cognitive complaints are more predictive of the future development of AD than are such complaints provided by patients and that perhaps the importance of such subjective complaints should be de-emphasized in future criteria defining early AD.

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Table 1

Prevalence of Various MCI Subtypes Amongst Two Populations of Familial Alzheimer's Disease (FAD) Mutation Carriers

	Single Domain Amnestic MCI	Multiple Domain Amnestic MCI	Single Domain Non-Amnestic MCI	Multiple Domain Non-Amnestic MCI
Group 1 (30 FAD mutation carriers)	0	3 (10%)	7 (23%)	4 (13%)
Group 2 (22 FAD mutation carriers)	3 (14%)	2 (9%)	2 (9%)	0