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Pre-MCI and MCI:

Neuropsychological, Clinical, and Imaging Features and Progression Rates

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Abstract

Objective—To compare clinical, imaging, and neuropsychological characteristics and longitudinal course of subjects with premild cognitive impairment (Pre-MCI), who exhibit features of MCI on clinical examination but lack impairment on neuropsychological examination, to subjects with no cognitive impairment (NCI), nonamnestic MCI (naMCI), amnestic MCI (aMCI), and mild dementia.

Methods—For 369 subjects, clinical dementia rating sum of boxes (CDR-SB), ApoE genotyping, cardiovascular risk factors, parkinsonism (UPDRS) scores, structural brain MRIs, and neuropsychological testing were obtained at baseline, whereas 275 of these subjects received an annual follow-up for 2–3 years.

Results—At baseline, Pre-MCI subjects showed impairment on tests of executive function and language, higher apathy scores, and lower left hippocampal volumes (HPCV) in comparison to NCI subjects. Pre-MCI subjects showed less impairment on at least one memory measure, CDR-SB and UPDRS scores, in comparison to naMCI, aMCI and mild dementia subjects. Follow-up over 2–3 years showed 28.6% of Pre-MCI subjects, but less than 5% of NCI subjects progressed to MCI or dementia. Progression rates to dementia were equivalent between naMCI (22.2%) and aMCI (34.5%) groups, but greater than for the Pre-MCI group (2.4%). Progression to dementia was best predicted by the CDR-SB, a list learning and executive function test.

Conclusion—This study demonstrates that clinically defined Pre-MCI has cognitive, functional, motor, behavioral and imaging features that are intermediate between NCI and MCI states at baseline. Pre-MCI subjects showed accelerated rates of progression to MCI as compared to NCI subjects, but slower rates of progression to dementia than MCI subjects.

Keywords

Algorithmic diagnosis; Alzheimer disease; amnestic MCI; clinical diagnosis; dementia; hippocampal volume; longitudinal analysis; MCI; mild cognitive impairment; MRI; neuropsychological tests; pre-MCI

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Current clinical criteria for a diagnosis of Alzheimer disease (AD) require the presence of dementia, even though clinicopathologic studies show that approximately one-third of individuals with pathologic evidence of AD at autopsy (Braak Stage V or VI) are not demented during life.[1,2] Although a significant correlation exists between the severity of AD brain pathology and the degree of cognitive impairment, the clinical syndrome generally lags well behind the pathologic changes of AD.[3] Indeed, the severity of AD pathology in the vast majority of patients who carry a diagnosis of amnestic mild cognitive impairment (aMCI) is indistinguishable from that of clinically diagnosed AD patients.[3] Our current reliance on the presence of dementia or even MCI as a criterion for AD diagnosis may need to be reconsidered if it is shown that negative outcomes of disease-modifying therapies for AD are a consequence of targeting relatively advanced stages of the disease. It has been suggested that anti-Aβ therapies may be more effective if implemented even prior to onset of AD symptoms.[4]

New criteria that have been suggested for making an earlier diagnosis of AD in the amnestic MCI (aMCI) stage[5] include the use of biomarkers to increase diagnostic validity. However, between aMCI and no cognitive impairment (NCI) a definable Pre-MCI state may exist. Among subjects who are classified as Pre-MCI, based only on informant reports, it has been reported that 90% have AD pathology at autopsy.[6] Subjects in this intermediate state between NCI and MCI present with symptomatic cognitive and subtle functional impairment on history, although cognitive deficits are not confirmed on formal neuropsychological testing.

The goals of this study were: (a) to define and compare the clinical, neuropsychological, functional, motor, imaging and genetic features of NCI, Pre-MCI and MCI states; (b) assess longitudinal progression of these predementia states and evaluate functional, neuropsychological, motor and imaging endophenotypes as predictors of progression to dementia.

METHODS

Subject Recruitment

We evaluated 369 subjects, 52–91 years of age, man and woman, including English and Spanish speakers, who were participants in the Florida Alzheimer Disease Research Center Clinical Core (FADRC-CC) in Miami Beach and Tampa, Florida. The study was approved by the institutional review board at Mount Sinai Medical Center, Miami Beach, the University of Miami and the University of South Florida, Tampa. All subjects or a legal representative provided informed consent.

Evaluations

The following were completed on all subjects at baseline and annually on follow-up evaluations: (1) full clinical history, obtained from a reliable informant; (2) neurologic evaluation; (3) psychiatric evaluation, including administration of the Geriatric Depression scale (GDS;[7]) and the Neuropsychiatric Inventory;[8] (4) Clinical Disease Rating scale (CDR-SB;[9]); (5) Mini-Mental State Exam (MMSE[10]); (6) a neuropsychological test battery, as outlined in NACC protocol, as well as additional tests, which included the Three Trial Fuld Object Memory Evaluation (FOME[11]), and the Hopkins Verbal Learning Test (HVLT[12]); (7) Unified Parkinson Disease Rating Scale (UPDRS, motor section[13]) has been documented as a sensitive tool for quantifying motor dysfunction and parkinsonism in patients with various forms of MCI and dementia.

Cardiovascular Risk (CVR) Score was calculated as the sum of 10 independent risk factors[14] selected from the NACC/UDS assessment protocol (Form A5: Subject Health History;[15]).

Diagnostic Procedures

Subjects, with or without memory complaints, were evaluated independently by the physician and the neuropsychologist and each clinician arrived at a clinical diagnosis of Normal Cognition (NCI), MCI or Dementia without knowledge of the other clinician's evaluations findings or diagnosis, as follows:

a. Physician's Cognitive Diagnosis (PhyDx): The physician's cognitive diagnosis of NCI, MCI or Dementia was based on the subject's entire clinical history and functional status, which was derived from the history itself, CDR rating, functional activity questionnaire, MMSE score and subscores, taking into account the subjects' educational and cultural background, sensory (especially visual and hearing) and motor deficits, language and speech disorders, medical and psychiatric conditions and the perceived reliability of the informant. For a diagnosis of MCI the physician took into consideration evident deficits in orientation, immediate or delayed recall, language (naming, comprehension, or fluency), performing calculations or copying figures, as described by a knowledgeable informant or as present on the examination. Additionally, on the examination of the patient the physician also noted the presence of subtle cognitive and personality deficits, such as repetitiveness, impaired logical reasoning, difficulty understanding or following implicit and even explicit instructions, executive dysfunction, perseverative behaviors, and mental rigidity.[6]

b. Neuropsychological Diagnosis (NPDx): All neuropsychological tests were administered in the subjects' native language (English or Spanish) and compared to age and education adjusted normative data, as described previously.[17,18] Memory measures were: the 3-trial Fuld Object Memory Evaluation[11] and Delayed Visual Reproduction of the Wechsler Memory Scale-R.[19] Nonmemory tests included: category fluency,[20] letter fluency (language;[21]), Block Design-WAIS-III (visuospatial;[22]), Trails B (Executive;[21]), and Similarities-WAIS-R (Executive;[23]). Neuropsychological classification[17,18] were made as follows: (a) a test score of 1.5 SD or greater below expected normative values on any single test for MCI syndromes; and (b) 2.0 SD or greater below expected normative values in one memory and one nonmemory test for dementia (corresponding to NINCDS-ADRDA criteria;[24] Nomenclature used for NPDx was No Cognitive Impairment (NCI), Nonamnestic MCI (naMCI; single or multidomain), amnestic MCI (aMCI; single or multidomain) and Dementia.

c. Algorithmic Consensus Cognitive Diagnoses (AlgDx): Thresholds for diagnosing predementia states can be arbitrary,[6,7,14] leading to considerable diagnostic variability among clinicians and research teams. An algorithmic approach to consensus diagnosis[16] combined the PhyDx with the NPDx, for baseline and longitudinal evaluations, as follows: (a) a PhyDx and a NPDx of normal (NCI) received an AlgDx of NCI; (b) a PhyDx diagnosis of MCI and a NPDx of aMCI or naMCI meeting all of Petersen's[25] formal criteria for MCI, received an AlgDx of aMCI or naMCI, respectively; (c) a PhyDx of dementia and a NPDx of Dementia or MCI (amnestic or nonamnestic) received an AlgDx of Dementia. (d) as is shown in Table 1, PhyDx of MCI, but a NPDx of normal received a consensus cognitive diagnosis of Pre-MCI. These criteria for a diagnosis of Pre-MCI provide a formal definition of an intermediate state between NCI and MCI, described as "Impaired, not MCI" under the National Alzheimer Coordinating Center (NACC) Uniform

Data Set (UDS) (http://www.alz.washington.edu/NONMEMBER/UDS/DOCS/VER2/tfpguide.pdf), Form D1, page 28 (section 4e).

d. MRI Scans were acquired using a proprietary 3-D volumetric protocol on a Siemens Symphony, 1.5 Tesla machine (Iselin, NJ). Volumetric analysis of brain MRIs utilized modified International Brain Atlases using Statistical Parametric Mapping (IBASPM;[26]).

e. ApoE genotype was determined using standard methods.[27] ApoEε4 frequencies were subsequently calculated for each diagnostic group.

Statistical Analysis Correcting for Age and Education

Group comparisons of means were analyzed using a series of one-way analyses of variance (ANOVA), Scheffé' post-hoc procedure was used to examine differences between means. Special consideration was necessary for analyses of MRI scores, which are not normally distributed and are strongly influenced by age, a prominent risk factor for AD. Rather than adjusting for the effects of age, we used a median split by age of the NCI subjects and performed all analyses using the older group of NCI subjects, who are age-equivalent to the non-NCI subject groups as controls. To compare NCI subjects and the other groups, for each MRI measure we determined thresholds for the most "impaired" tertile of scores, that is, the lowest tertile for hippocampal volumetric measures. We then compared percentages of subjects in each diagnostic group falling within the most impaired tertile for that measure, using χ^2 analysis. Comparison of transition rates from one diagnostic group to another was assessed using χ^2 analysis. Any 2 × 2 χ^2 group contrasts were subjected to Yate's correction for discontinuity. Predictors of progression to specific endpoints were evaluated using Cox regression.

RESULTS

Demographic Variables

Among the 369 subjects there were group differences (Table 2) with regards to age ($F_{[4, 364]}$= 9.90; p<0.001), educational attainment ($F_{[4, 4350]}$= 6.95; p<0.001) and gender [χ^2(df = 4 = 16.26; p≤0.004]. There were no statistically significant group differences with regards to primary language [χ^2(df = 4) = 8.32; p = 0.08]. Post-hoc tests of means indicated that (a) NCI subjects were younger than all Pre-MCI and dementia groups; (b) naMCI subjects had a preponderance of male subjects and NCI subjects had a preponderance of women; (c) educational attainment was lower among naMCI subjects than all other diagnostic groups. Because of these differences, we conducted ANOVAs in other subsequent analyses correcting for age and education. Since this did not effect the obtained results, only uncorrected analyses are presented below.

Clinical and APOE Genotype Comparisons

There were group differences (Table 3) for MMSE ($F_{[4, 360]}$= 81.34; p<0.001), CDR-SB ($F_{[4, 364]}$= 205.43; p<0.001), apathy [χ^2(df = 4,364) = 17.73; p<0.001], GDS ($F_{[4, 364]}$= 4.33; p<0.01) and UPDRS scores ($F_{[5, 363]}$= 15.93; p<0.001) as well as the percentage of subjects having one or more ApoE4 allele [χ^2(df = 4) = 21.66; p<0.001], but not for CVR scores ($F_{[4, 359]}$= 2.30; p = ns). Post-hoc tests showed: (a) MMSE scores were highest among NCI and Pre-MCI groups, intermediate among naMCI and aMCI groups and lowest among the dementia group; (b) CDR-SB scores were lowest among NCI and Pre-MCI groups, intermediate among naMCI and aMCI groups and highest among the dementia group; (c) Pre-MCI, naMCI, aMCI and dementia groups had higher apathy scores than the NCI group; (d) GDS scores were higher among the naMCI group than the other study groups; (e)

UPDRS scores were lowest among the NCI and Pre-MCI groups, intermediate among the aMCI group and highest among the dementia and naMCI groups; (f) a higher percentage of dementia subjects had one or more APOE e4 alleles relative to the NCI group.

Neuropsychological Comparisons

Subjects with aMCI and dementia performed lower relative to NCI subjects on all neuropsychological measures, with the exception of Trails B, for which only the dementia group had higher time of completion scores than the NCI group (Table 4). Pre-MCI subjects scored lower than NCI subjects on Category Fluency and Digit Symbol score, but after adjusting for the effects of age, only Category Fluency scores were lower among Pre-MCI relative to NCI groups. Scores for naMCI subjects were lower than for NCI subjects on the Total SIT Interference score, delayed paragraph recall, delayed recall of the HVLT, Category Fluency and Digit Symbol even after adjusting for age.

MRI Volumetric Comparisons

No significant differences were found between younger (mean age± SD = 68.5± 2.2 year) and older NCI groups (mean age± SD = 78.4± 3.4 year) on hippocampal measures. There were significant differences in left hippocampal volumes (Table 3) for percentages of subjects in the lowest tertile of scores (for all subjects), between older NCI subjects (14.3%) versus Pre-MCI (35.4%), naMCI (40.0%), aMCI (37.5%) and dementia (72.1%) subjects. Not shown in Table 4 are the findings for the right hemisphere, where the only differences noted were in the percentage of subjects in the lowest tertile of scores between older NCI subjects (20.4%) and aMCI (41.3%) the dementia (59.0%) groups.

Longitudinal Follow-up

Longitudinal data were used for the last available follow-up among 275 subjects who had achieved their second or third annual follow-up from their baseline evaluation (average length of follow-up = 31.1 ± 6.6 months). There was no difference in time of follow-up between diagnostic groups ($F_{[4, 254]}$= .65; p = ns). As indicated in Table 5, there were statistically significant differences with regards to rate of decline over time [χ^2(DF = 20) = 214.40 p<0.001]. Over 78% of NCI subjects retained that classification whereas 10.0% were classified as Pre-MCI, 2.5% as aMCI and 8% as naMCI or dementia. In contrast, 14.5% of Pre-MCI subjects had progressed to aMCI, 11.9% to naMCI and 2.4% to dementia. Post-hoc tests indicated that a greater number of Pre-MCI subjects (28.6%) than NCI subjects progressed to an MCI or demented state [4.1%] [χ^2(DF = 1) = 20.24; p<0.001]. Among aMCI subjects, 34.5% progressed to dementia, 43.6% remained aMCI and 10.9% reverted to a normal or Pre-MCI state. Among naMCI subjects 22.2% progressed to dementia, 33.3% remained in a naMCI state, 27.8% reverted to Pre-MCI or unclassified and 11.1% to NCI. Post-hoc tests indicated that a greater number of aMCI subjects χ^2(DF = 2) = [χ^2(DF = 2) = 54.95; p<0.001] and naMCI subjects [χ^2(DF = 2) = 25.74; p<0.001] progressed to a demented state compared to Pre-MCI-NP and NCI subjects. Among those diagnosed to have dementia initially, only one case (2.5%) changed diagnosis (to aMCI).

Predictors of Decline to a Clinical Endpoint

Pre-MCI and MCI subjects who progressed to dementia at the first to third annual follow-up evaluations were found at their baseline visit to be older ($F_{[1, 180]}$= 8.58; p = 0.004), with higher CDR-SB scores ($F_{[1, 187]}$= 25.26; p <0.001), lower left sided hippocampal volumes ($F_{[1, 122]}$= 5.08; p = 0.026), lower Hopkins Verbal Learning Test-Delayed Recall scores ($F_{[1, 183]}$= 33.51; p= 0.02), lower Semantic Interference Test score ($F_{[1, 181]}$= 27.52; p <0.001), lower 3-Trial OME scores ($F_{[1, 177]}$= 46.85; p <0.001), lower delayed paragraph recall scores ($F_{[1, 182]}$= 17.41; p<0.001), higher UPDRS scores ($F_{[1, 182]}$= 14.46; p<0.001),

lower Category Fluency scores ($F_{[1, 184]}$= 4.22; p = 0.04) and higher Trails B scores ($F_{[1, 164]}$= 7.05; p = 0.009). When these variables were entered into a step-wise Cox regression, the only significant predictors of rate of progression to dementia were the 3-Trial Fuld-OME score (B =−0.121; SE = 0.038; Wald =10.16 p≤0.001); Trails B time (B = .003; SE = .001; Wald = 5.88 p≤0.016) and CDR-SB scores (B = .578; SE = .223; Wald = 6.71 p≤0.01).

DISCUSSION

The rationale for identifying a Pre-MCI diagnostic entity, that precedes the MCI stage of AD, is to enable investigation of discrete risk or etiological factors for AD, and interventions with disease-modifying treatments and secondary preventive measures at a stage of AD, when such interventions are most likely to be effective.[4] The label "Pre-MCI" has been used previously to describe subjects who are presumed to be in a very early stage of AD, when cognitive function is in the "normal" range, but an increased risk for progression to dementia is suggested either by subjective memory complaints,[28,29] or biomarkers suggest the presence of the disease, for example, regional brain atrophy on MRI scans; regional hypometabolism or elevated fibrillary amyloid levels in the neocortex on positron emission tomographic scans; abnormal activation patterns on functional MRI; elevated tau/aβ ratios in the CSF.[30–34] In contrast, in this study we developed specific clinical criteria, which relied on the subtle cognitive and personality changes which occur well before the development of the more obvious clinical syndrome of Alzheimer disease, *but with the absence of objective neuropsychological deficits, to define Pre-MCI. As depicted in* Table 1, Pre-MCI is diagnosed when an experienced physician categorizes a subject, *with or without subjective memory complaints, as "MCI", because of the presence of subtle cognitive and functional impairments*[6] *that are evident on the history or examination, but neuropsychological testing shows the subject to be normal or not meeting formal criteria for MCI. Pre-MCI should be considered a true precursor to MCI because unlike either amnestic or nonamnestic MCI, there is the absence of identifiable deficits on an extensive battery of neuropsychological tests, including three tests of memory (logical memory from the Wechsler Memory Scale, the FOME and the HVLT).*

Although, the inclusion of a Pre-MCI state introduces an artificial milestone into the continuum between NCI and MCI, such milestones serve many practical purposes, such as communicating the stage of a disease process to others and providing entry or exclusion criteria and, possibly, end points in clinical trials. Currently, Pre-MCI, as we have defined it, must be regarded as a research entity, requiring confirmation by other research groups, before it can achieve the status of a clinical condition. The most important factor that will determine whether an identical or similar definition for Pre-MCI is replicated by other groups is the rate of progression, which we have found to be intermediate between NCI and MCI. A reversal to NCI is inevitably more likely to occur as the diagnoses of cognitive states are made at earlier and earlier stages of a presumed disease process. Such reversal of diagnosis may represent misdiagnosis at the initial evaluation or may represent some of the natural fluctuation that occurs in any disease condition, especially when assessments are made at an early stage of the disease. Although there is a role for CSF or other biomarkers to assist in the diagnosis of the etiology of a Pre-MCI syndrome, the biomarkers do not help to determine the presence or absence of a Pre-MCI. Analogous to MCI or dementia, Pre-MCI, as we have defined it, is essentially a stand-alone clinical/cognitive syndrome, with no implications as to the etiology of Pre-MCI. In this study hippocampal atrophy was included as a biomarker, merely to add weight to the significance of the Pre-MCI syndrome we have described and to suggest the presence an underlying neurodegenerative disease.

Subjects with Pre-MCI, as defined in this study, do not have identifiable deficits after detailed neuropsychological evaluation with multiple memory and nonmemory tests. The lack of objective cognitive deficits therefore distinguishes subjects with Pre-MCI from those who are identified merely by a score of 0.5 on the CDR scale (a minority of whom may meet our definition of Pre-MCI), as well as subjects who meet Peterson's MCI criteria. Nevertheless, there may be a great deal of overlap among these groups on pathologic examination, as evidenced by autopsy studies which have shown that at least one-third of elderly subjects who were thought to be cognitively normal at the time of death, carried the pathology of Alzheimer disease in the medial temporal lobes.[1,35] Multiple factors, such as cognitive and brain reserve, quality of education, comorbid medical and psychiatric conditions, may dictate whether a particular subject with AD pathology manifests objective neuropsychological deficits. However, from a clinical standpoint, in spite of being categorized as cognitively normal, Pre-MCI subjects as a group had significantly lower scores than NCI subjects on tests that required speed of processing (category fluency and digit symbol) (Table 4). Pre-MCI subjects also had greater levels of apathy, abnormally elevated scores on a test of motor performance (UPDRS) and greater frequency of hippocampal volumes in the lowest tertile (Table 3). On most neuropsychological, functional, behavioral, motor and imaging measures, Pre-MCI subjects had scores that were generally intermediate between those of NCI and MCI subjects (Tables 3 and 4). Pre-MCI subjects progressed to some form of MCI at an annual rate which was significantly greater that for NCI subjects and the rate of reversal from Pre-MCI to NCI, whereas numerically higher, was not statistically higher than for naMCI and aMCI states (Table 5). Factors that are known to influence progression of MCI states to dementia, were also found to influence progression of Pre-MCI states to MCI and dementia, including the number of memory tests[36] and cognitive domains showing impairment,[37] and the presence and severity of hippocampal atrophy on MRI scans.[38,39] These clinical, neuropsychological, and imaging features, as well as the rates of progression to MCI states or dementia, suggest that a significantly higher proportion of Pre-MCI subjects have early degenerative pathology in the brain than do NCI subjects. Those subjects that do not progress, or revert to NCI on follow-up, likely have conditions such as anxiety, depression, low educational level, or premorbid and developmental conditions which are misdiagnosed as Pre-MCI. When all predictors of progression were accounted for, performance on a memory test (the three-trial Fuld OME), an executive function test (Trails B) and a functional measure (CDR-SB) were the only significant remaining predictors, which is consistent with previous experience in predementia states.[18,40,41]

Homogeneity of methods in reconciling the physician's diagnosis and the neuropsychologist's diagnosis, which tends to be very discrepant in early predementia states,[16] is important for achieving reproducible diagnoses in cross-sectional and longitudinal, because it ensures higher reliability in the diagnosis of conditions such as MCI and, particularly, pre-MCI states. In this study, it is likely that the use of an algorithmic consensus diagnosis[16] for baseline and longitudinal evaluations, rather than the traditional consensus diagnosis, reduced the variance in the rates of progression to more impaired states and the rates of reversal to less impaired states, enabling a more reliable estimates and more effective comparison of the rates of change between diagnostic groups. Among subjects with a diagnosis of dementia, 97.5% retained that classification on follow-up (one of 40 subjects was classified as aMCI) and 13.4% of those with a diagnosis of aMCI progressed to dementia over an average 31 month period, whereas reversal to NCI was only 2.8% annually. The annual rate of progression of aMCI to dementia in the current study is well above the average of about 9% in clinic studies and 4.9% in community studies (range: 1%–28%).[42–47] The rate of reversal of aMCI to NCI in our study is also well below the 10%–40% range previously reported.[45,46,48] Among subjects classified as naMCI at baseline, annual rate of progression to dementia was 8.6% and the annual rate of reversal to NCI was

4.3% (15.1% annually, when Pre-MCI states were included), which is historically low,[49] but consistent with our previous findings in a community-based cohort wherein we also used an algorithmic diagnosis scheme.[36] Previous studies have shown biologic overlap among aMCI and naMCI subjects, with respect to patterns of metabolic deficits and activation on MRI studies,[50,51] as well as the progression rates toward dementia or reversal toward NCI.[40]

The findings than naMCI subjects had decreased memory scores, decreased hippocampal volume, greater apathy, higher depression scores, and UPDRS scores relative to NCI subjects, suggests the possibility that many naMCI cases likely represent incipient AD. In fact, Storandt et al[6] demonstrated that nearly 40% of cognitively impaired subjects who went on to develop pathologically proven AD did not have amnestic deficits on initial evaluation. It is possible that higher levels of cognitive reserve in the memory domain may have enabled these subjects to obtain scores in the normal range on memory measures; although these subjects are clearly at risk for progressive memory impairment over time. Abnormal accumulation of fibrillar amyloid in the brain (especially in the medial frontal, parietal, precuneus regions, and the striatum), measured by amyloid labeling agents and positron emission tomographic scans, is also found in about one-third of cognitively normal subjects.[52] In the current study 14.3% of NCI subjects and 40% of naMCI subjects (as well as 37.5% of aMCI subjects) had hippocampal volumes that fell in the lowest tertile for all subjects in the study. Using the lowest tertile of hippocampal volumes as a comparative index of the presence of neurodegenerative pathology in the medial temporal lobes among subject groups, and a 33% rate of AD pathology previously reported among NCI cohorts, we estimate that it is likely that a sizable majority of our MCI and dementia subjects in the present cohort have underlying AD brain pathology.

Although a relatively large number of subjects were evaluated at baseline, a weakness in this study was the proportionately small number of subject who underwent extended follow-up evaluations, especially in the naMCI group, thereby limiting the interpretation of the results for this group. Furthermore, while baseline CDR-SB scores and scores on certain neuropsychological measures (the 3-Trial OME and Trails B) predicted decline to dementia among subjects with Pre-MCI and MCI, these results were largely based on subjects who had established MCI and relativley short period of follow-up. Nevertheless, we have defined a Pre-MCI state, which is intermediate in most respects between NCI and MCI states, and which may serve as a baseline diagnosis in clinical trials evaluating secondary prevention and treatment of AD, and for studying the effect of biologic factors in the incipient phases of AD. The subtleties of impairment in predementia states mandate the use of well-defined clinical and neuropsychological criteria, which is especially true for Pre-MCI, to enhance the specificty of the diagnosis without substantially compromising its sensitivity.

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TABLE 1

Algorithmic Diagnosis of Predementia States Neuropsychological Diagnosis

	Neuropsychological Diagnosis			
Clinician's Diagnosis	**Normal**	**Nonamnestic MCI**	**Amnestic MCI**	**Dementia**
Normal	Normal	Unclassified	Unclassified	aMCI
MCI	PreMCI	naMCI	aMCI	aMCI
Dementia	PreMCI	naMCI	Dementia	Dementia

Clinical Diagnoses (red); Neuropsychological Diagnoses (blue); Algorithmic Diagnoses (green)

TABLE 2

Demographic Characteristics

Diagnosis	NCI (N = 148)	Pre-MCI (N = 55)	naMCI (N = 25)	aMCI (N = 80)	Dementia (n = 61)	*F*
Age	71.7[a] (SD =5.5)	75.6[b] (SD = 7.0)	75.4[ab] (SD = 6.4)	75.1[ab] (SD = 6.1)	76.6[b] (SD = 6.2)	9.90[e]
Education	14.5[a] (SD = 3.3)	13.7[a] (SD = 4.0)	10.6[b] (SD = 3.4	13.4[a] (SD = 3.1	13.5[a] (SD = 3.4)	6.95[e]
% Female	66.9%	41.8%	40.0%	48.8%	5084%	$\chi^2 = 16.26$[d]
% English-speaking	75.3%	72.7%	48.0%	67.5%	72.1%	$\chi^2 = 8.32$

NCI: no cognitive impairment; MCI: mild cognitive impairment; Non-Amn MCI: Nonamnestic MCI; Am-MCI: Amnestic MCI.

[c] $p<0.05$.

[d] $p\leq0.01$.

[e] $p\leq0.001$. Means with different alphabetic superscripts differ by post-hoc tests of means conducted using the Scheffé' procedure.

TABLE 3

Clinical Characteristics of Different Diagnostic Groups

Diagnosis	NCI	PreMCI	naMCI	aMCI	Dementia	*F*
MMSE	29.00[a] (SD = 1.2)	27.82[ab] (SD = 2.0)	26.08[bc] (SD = 2.4)	26.72[b] (SD = 2.4)	23.57[d] (SD = 2.9)	81.46[g]
CDR-SB	0.25[a] (SD = .4)	1.03[a] (SD = .9)	1.92[b] (SD = 1.5)	1.68[b] (SD = 1.2)	4.84[c] (SD = 1.8)	205.43[g]
Apathy	4.8%	20.0%[h]	38.0% [h]	25.6% [h]	50.8% [h]	59.45[g]
GDS	1.66[a] (SD = 2.3)	2.38[ab] (SD = 3.1)	3.40[b] (SD = 2.7)	2.51[ab] (SD = 2.4)	2.69[ab] (SD = 2.4)	4.33[f]
Cardiovascular Risk Score	2.38 (SD = 1.5)	2.89 (SD = 1.7)	2.68 (SD = 1.7)	2.93 (SD = 1.6)	2.97 (SD = 1.9)	2.30
UPDRS Scale	1.67[a] (SD = 3.3)	3.71[a] (SD = 4.6)	9.16[c] (SD = 8.9)	7.26[bc] (SD = 10.1)	8.44[cd] (SD = 10.0)	15.93[g]
HPC (Left) Volumes (Lowest Tertile)	14.3%	34.5% [h]	40.0% [h]	37.5% [h]	72.1% [h]	40.33[g]
% with an ApoE4 allele	24.0%	34.1%	15.4%	39.2%	60.9% [h]	21.66[g]

NCI: no cognitive impairment; Non-Amn MCI: Nonamnestic MCI; Am-MCI: Amnestic MCI.

[e] p<0.05.

[f] p≤0.01.

[g] p≤0.001.

Means with different alphabetic superscripts differ by post-hoc tests of means conducted using the Scheffé' procedure.

[h] Different from percentage for NCI.

TABLE 4

Neuropsychological Test Performance

Diagnosis	NCI	PreMCI	naMCI	aMCI	Dementia	*F*
Fuld 3-Trial OME	25.64[a] (SD = 2.1)	24.18[a] (SD = 2.0)	24.12[a] (SD = 2.3)	18.04[b] (SD = 4.13	10.62[c] (SD = 6.2)	214.36[g]
SIT Total Interference Score	13.22[a] (SD = 2.5)	11.18[ab] (SD = 3.1)	10.48[b] (SD = 3.3)	7.58[c] (SD = 3.1)	3.28[d] (SD = 2.8)	148.43[g]
Delayed Paragraph Recall	10.69[a] (SD = 3.9)	9.13[a] (SD = 3.6)	6.79[b] (SD = 3.7)	5.27[b] (SD = 4.1)	2.66[c] (SD = 3.5)	59.54[g]
HVLT-II Delay Recall	8.80[a] (SD = 2.4)	7.46[ab] (SD = 2.5)	6.17[b] (SD = 2.5)	4.16[c] (SD = 3.1)	1.91[d] (SD = 3.8)	88.64[g]
Category Fluency	48.00[a] (SD = 10.7)	40.41[b] (SD = 9.3)	36.28[b] (SD = 8.9)	35.48[b] (SD = 8.0)	25.33[c] (SD = 8.9)	67.32[g]
Digit Symbol	46.32[a] (SD = 9.6)	39.59[b] (SD = 10.8)	29.64[cd] (SD = 9.5)	34.61[bc] (SD = 10.8)	26.85[d] (SD = 10.8)	48.64[g]
Trails B	86.83[a] (SD = 34.0)	129.50[a] (SD = 102.43)	151.60[a] (SD = 48.5)	141.68[a] (SD = 62.7)	368.53[b] (SD = 281.9)	49.56[g]

NCI: No Cognitive Impairment; MCI: mild cognitive impairment; Non-Amn MCI: Non-Amnestic MCI; Am-MCI: Amnestic MCI.

[e] $p<0.05$;

[f] $p\leq0.01$;

[g] $p\leq0.001$. Means with different alphabetic superscripts differ by post-hoc tests of means conducted using the Scheffé' procedure.

TABLE 5

Change in Diagnosis over 2–3 Year Follow-up for 275 Subjects

Diagnostic Group	NCI	PreMCI	Unclassified	naMCI	aMCI	Dementia
NCI (N = 120)	94 (78.3%)	12 (10.0%)	9 (7.5%)	1 (0.8%)	3 (2.5%)	1 (0.8%)
PreMCI- (N = 42)	18 (42.9%)	10 (23.8%)	2 (4.8%)	5 (11.9%)	6 (14.3%)	1 (2.4%)
aMCI (N = 55)	4 (7.3%)	2 (3.6%)	2 (3.6%)	4 (7.3%)	24 (43.6%)	19 (34.5%)
naMCI (N = 18)	2 (11.1%)	2 (11.1%)	3 (16.7%)	6 (33.3%)	1 (5.6%)	4 (22.2%)
Dementia (N = 40)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	39 (97.5%)

NCI: No Cognitive Impairment; aMCI: Amnestic Mild Cognitive Impairment;

aMCI: Non-Amnestic MCI; aMCI = Amnestic MCI.

χ^2 (DF = 20) = 315.40; p<0.001.