Cognitive & Behavioral Assessment

Neuropsychological comparison of incident MCI and prevalent MCI

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Abstract

Introduction: Little empirical work has been done to examine differences between mild cognitive impairment (MCI) diagnosed in research settings with longitudinal data (incident MCI) and MCI diagnosed in clinical settings (prevalent MCI). Because Alzheimer's disease progresses over a clinicopathological continuum, we examined the cognitive differences between these two different sources of MCI patients.

Methods: We compared 52 consecutively identified patients with prevalent amnestic MCI with 53 incident amnestic MCI participants from the Arizona APOE study. Neuropsychological data from common tests were compared encompassing four cognitive domains and one global indicator.

Results: Prevalent MCI cases performed significantly worse than incident MCI cases on global as well as domain-specific measures.

Discussion: By the time patients seek evaluation for memory loss, they have more severe single domain, amnestic MCI than research subjects with incident MCI. Studies of MCI should distinguish incident and prevalent not just single- and multiple-domain MCI.

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1. Introduction

Mild cognitive impairment (MCI) is often an intermediate stage along the continuum of normal brain aging to dementia [1–3]. MCI is classified into amnestic MCI (a-MCI) and nonamnestic MCI (na-MCI) groups based on the presence or absence of amnestic memory impairment, respectively [2]. Amnestic, single-domain MCI is often considered the earliest clinically symptomatic stage of the most common form of dementia, Alzheimer's disease (AD) [4]. Reported annual rates of progression of MCI to dementia are 10%–15% [5,6]; however, rates may differ between published studies due to differences in design and measurements [2,3,6].

The original Mayo Clinic criteria for a-MCI are as follows: (1) a memory complaint; (2) amnestic-type memory impairment for age on psychometric testing; (3) normal general cognitive function; (4) intact activities of daily living; and (5) not demented [1]. The core clinical criteria for individuals with MCI have since been updated along with the clinical criteria for AD to account for our ability to detect the pathophysiological process of AD (the development of Aβ plaques and neurofibrillary tangles), and changes in conceptualization regarding the clinical spectrum of AD [7]. The new core clinical criteria for MCI outlined are designed to be used in all clinical settings and use the term

"mild cognitive impairment (MCI) due to AD" to refer to the symptomatic predementia phase of AD [8]. The diagnostic criteria remain similar to the original with the addition of this increased focus on the association with AD. In addition, clinical research criteria have been outlined to incorporate biomarkers (such as CSF measures of lower $A\beta_{42}$, PET evidence of $A\beta$ deposition using a variety of ligands, and CSF measures of increased total tau or phosphorylated tau, p-tau) [8].

This study seeks to investigate the differences in patterns and severity of cognitive dysfunction in MCI by comparing two populations: those diagnosed with a-MCI after actively seeking medical attention for memory complaints (prevalent MCI cases) and those diagnosed with a-MCI in a longitudinal research setting (incident MCI cases). Based on prevalence-incidence (Neyman) bias [9,10], we hypothesized that prevalent MCI cases would show greater dysfunction on neuropsychological testing than incident MCI cases.

2. Methods

2.1. Study participants, design, and setting

The current incident single-domain a-MCI sample was derived from the Arizona APOE cohort study that is conducted at Mayo Clinic, Scottsdale, Arizona [11]. Briefly, cognitively normal individuals over the age of 21 years in Maricopa County were recruited from January 1, 1994 to December 31, 2017 through local media advertisements. Demographic, family, and medical data were obtained for each participant. All individuals gave written and informed consent, and the study was approved by the institutional review board. Each participant underwent screening tests including neurological examination, the Folstein Mini-Mental State Examination [12], the Hamilton Depression Rating Scale [12], the Functional Activities Questionnaire, the Instrumental Activities of Daily Living, and the Structured Psychiatric Interview from the DSM-3 [13] to confirm their normal neuropsychological state at the time of study entry. Neuropsychological tests were repeated every 1–2 years.

Incident MCI cases were defined as participants of the Arizona APOE cohort study who met published criteria for a-MCI [2] at follow-up and were cognitively normal at the time of their entry into the study. Incident MCI diagnoses span some years thus span both the original criteria for MCI by Petersen and colleagues as well as the revision by Albert et al. (2011) [8]. Incident MCI cases were identified as single-domain a-MCI cases after being enrolled in the study with a normal aging diagnosis. MCI diagnosis was a consensus diagnosis of DECL and RJC based on self and (when available) informant report and objective neuropsychological data. From the time of study inception to the time of this study, 53 participants progressed from normal cognition to single-domain, a-MCI. These research partici-

pants had been followed up at an average of 9.5 (standard deviation = 4.4) years at the time of the incident MCI diagnosis with the MCI diagnosis made on average at the fifth assessment (standard deviation = 2).

Prevalent MCI cases were defined as patients diagnosed with single-domain a-MCI after actively seeking medical attention for memory complaints. To increase the consistency of the test battery, patients were selected from consecutive cases from DECL neuropsychological evaluation practice. Patients were seen consecutively from 1/2008 to 5/2009. There were a total of 52 prevalent MCI cases identified in that time frame. These patients all received a consistent cognitive battery and were diagnosed with single-domain a-MCI.

2.2. Neuropsychological tests

Neuropsychological testing assessing four cognitive domains was available: (1) memory (Auditory Verbal Learning Test–Total Learning; Auditory Verbal Learning Test–Short-Term Memory; Auditory Verbal Learning Test–Long-Term Memory; Auditory Verbal Learning Test–Recognition Correct; Auditory Verbal Learning Test–Recognition False Positives); (2) executive function including speeded attention and cognitive flexibility (Trail Making Test-A; Trail Making Test-B); (3) language (Animals; Boston Naming Test; Controlled Oral Word Association); (4) visuospatial (Rey-Osterrieth Complex Figure Copy Test) [12] as well as one global estimate measure (Dementia Rating Scale). The Arizona APOE cohort was begun before the adoption of the uniform data set (UDS) by the National Alzheimer's Coordinating Center. When the UDS was adopted, these subjects began completing the UDS which began data collection for the TMT and Animals tasks [14,15]. Thus, 13 incident MCI cases diagnosed before the adoption of the UDS are missing the TMT and Animals as these were not a part of our original research neuropsychological battery.

2.3. Statistical methods

We compared the demographics and neuropsychological test scores between participants with prevalent MCI and incident MCI. Continuous demographic data (age and education) were compared using unpaired t-tests. Categorical demographic data (sex) were compared using chi-square tests. Owing to the significant age difference between the two groups, all neuropsychological test scores were evaluated using ANCOVA with age as the covariate. All P values were two tailed, and P values < 0.05 were considered significant. Cohen's d effect sizes were also calculated.

3. Results

The two groups did not differ in terms of education or sex; however, they did differ significantly in age. The prevalent MCI group was significantly older than the incident MCI group (76.17 [5.62] vs. 73.09 [6.60]; $P = .01$; Table 1).

Table 1
Participant demographics

Variable	Total, N = 105	Prevalent MCI, n = 52	Incident MCI, n = 53	P values
Age; mean years [SD]	74.62 [6.30]	76.17 [5.62]	73.09 [6.60]	.01*
Education; mean years [SD]	15.36 [2.98]	14.92 [3.04]	15.79 [2.87]	.14
Sex; % female	52 [49%]	25 [48%]	27 [51%]	.77

Abbreviations: MCI, mild cognitive impairment; SD, standard deviation.
*Indicates statistical significance between prevalent and incident MCI cases.

Incident MCI cases had their APOE e4 genotype determined as part of the overall aim of the APOE cohort longitudinal project. APOE status was not disclosed to the patient or to the neuropsychologist. In the incident MCI group, 15 (28%) were noncarriers, 19 (36%) were heterozygotes, and 19 (36%) were homozygotes for the APOE e4 allele. Genotype was not determined for the prevalent MCI cases as genotyping is not currently recommended for clinical diagnostic evaluation [16].

After controlling for age differences, there were significant differences between the prevalent MCI raw test scores and the incident MCI raw test scores in three scores from our memory measure: Auditory Verbal Learning Test–Total Learning (28.38 [6.85] vs. 32.74 [7.60]; $P = .01$), Auditory Verbal Learning Test–Long-Term Memory (0.83 [1.40] vs. 2.04 [1.83]; $P < .01$), AVLT Recognition Correct (8.3 [3.2] vs. 9.9 [2.9]); one test of timed attention: Trail Making Test-A (44.04 [15.52] vs. 32.70 [10.75]; $P < .01$); the visuospatial test: Rey-Osterrieth Complex Figure Copy Test (25.85[5.79] vs. 32.48 [4.03]; $P < .01$); all of the language tests: Controlled Oral Word Association (31.65 [9.57] vs. 45.83 [12.88]; $P < .01$), Boston Naming Test (49.90 [6.43] vs. 53.53 [4.99]; $P = .02$), Animals (14.46 [4.68] vs. 18.78 [4.61]; $P < .01$); and the global indicator: Dementia Rating Scale (128.14 [7.30] vs. 136.27 [5.49]; $P < .01$; Table 2).

4. Discussion

We observed significant differences between prevalent and incident cases of single-domain a-MCI in cognitive function in all four cognitive domains and a global indicator. This included more severe memory impairment in prevalent MCI cases, but also lower scores in other areas of cognition even if those did not represent impairment or result in a diagnosis of multidomain impairment. These findings support the presence of a continuum of cognitive function within the concept of MCI, even when the sole impairment is memory. Therefore, by the time patients seek medical attention, they have more significant cognitive impairment and are closer to a clinical presentation consistent with dementia.

Predicting rates of progression from MCI to dementia depends on the patient's current disease severity. Thus, incident

Table 2
Neuropsychological test results in prevalent MCI and incident MCI patients

Test	Prevalent MCI, mean [SD]	Incident MCI, mean [SD]	P values	Cohen's d effect size
CFT Copy	25.85 [5.79]	32.48 [4.03]	<.01*	1.33
AVLT-TL	28.38 [6.85]	32.74 [7.60]	.01*	0.60
AVLT-STM	3.04 [2.28]	3.98 [2.47]	.13	0.40
AVLT-LTM	0.83 [1.40]	2.04 [1.83]	<0.01*	0.74
AVLT-Recog	8.3 [3.2]	9.9 [2.9]	.02*	0.53
AVLT-FP	2.2 [2.0]	1.7 [1.7]	.24	0.27
COWA	31.65 [9.57]	45.83 [12.88]	<.01*	1.25
BNT	49.90 [6.43]	53.53 [4.99]	.02*	0.63
DRS	128.14 [7.30]	136.27 [5.49]	<.01*	1.26
Animals	14.46 [4.68]	18.78 [4.61]	<.01*	0.93
TMT-A	44.04 [15.52]	32.70 [10.75]	<.01*	0.83
TMT-B	127.81 [59.70]	105.90 [51.44]	.14	0.39

Abbreviations: AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; CFT Copy, Complex Figure Copy; COWA, Controlled Oral Word Association; DRS, Dementia Rating Scale; FP, Recognition False Positives; LTM, Long-Term Memory; Recog, Recognition; SD, standard deviation; STM, Short-Term Memory; TL, Total Learning; TMT, Trail Making Test; MCI, mild cognitive impairment.
*Indicates statistical significance between prevalent and incident MCI test scores ($P < .05$).

cases, which represent a lower severity, would be expected to have a lower rate of "conversion" than prevalent cases, consistent with the theory of prevalence-incidence bias [9]. However, this construct has not been empirically investigated in the context of neurocognitive research involving subjects with MCI and may account, in part, for discrepancies between various studies in rates of conversion from MCI to dementia. In addition, in most research studies focused on identification of predictors of progression from MCI to dementia (such as FDG-PET or CSF biomarkers [17], neuropsychiatric symptoms and speed of cognitive impairment progression [18], and white matter hyperintensities [19]), the MCI cohorts were recruited from prevalent MCI cases. It is unclear if these predictors would have the same strength or timing if evaluated in cohorts of incident MCI.

Also relevant is predicting progression from normal aging to MCI. Earliest prediction is crucial for earlier treatment, which is especially important when a curative therapy is developed. A variety of indicators have been evaluated including physical indicators, imaging markers [20], cognitive markers [11,21], subjective complaints [22], and emotional symptoms [23,24]. This study demonstrates the value of longitudinal neuropsychological evaluation, especially in those who are asymptomatic but potentially at risk for development of cognitive decline. The use of longitudinal neuropsychological examinations allowed for earlier identification of clinical change and therefore earlier clinical diagnosis, an important preamble to treatment strategies that target the earliest disease stage of a neurocognitive disorder.

Strategies to detect prevalent MCI sooner could include more routine cognitive screen in older adults as well as more routine referral of adults with cognitive complaints

for neuropsychological evaluation. The Medicare Annual Wellness Visit requires a review of activities of daily living (ADLs) and instrumental ADLs as well as detecting cognitive impairment (primarily by self or other report) but does not recommend actual objective assessment of cognitive functioning [25]. However, in MCI, ADLs and instrumental ADLs are, by definition, not significantly impacted, and it can be difficult to distinguish MCI from normal cognitive changes when considering subjective reports. Thus, utilization of objective measures of cognitive function more routinely in older adults may help diagnose prevalent cases sooner. This may include a formal mental status examination by a primary physician or a lower bar for sending individuals with subjective complaints for neuropsychological evaluation. Earlier objective evaluation may identify prevalent MCI cases sooner by documenting very mild impairment sooner or, if the examination is normal, by establishing a baseline assessment that may allow for earlier detection in longitudinal assessment if cognitive concerns continue.

Strengths of this study include the elimination of biases by the use of a single neuropsychologist with a consistent battery in the prevalent MCI sample to diagnose the prevalent MCI cases and the sole inclusion of aMCI patients in both groups (e.g., exclusion of multidomain and nonamnestic variants from both samples).

One limitation of this study was that there were no scores for 13 incident MCI patients on the Animals, Trail Making Test-A, and Trail Making Test-B tests as these were not added to the standard battery used in the APOE cohort until adoption of the UDS [14,15]. A second limitation is that we lack biomarker support of AD in both samples but do have APOE genotype in the incident cases. Previous research has shown that ε4 is a strong predictor of clinical progression to AD in MCI [26] and the positive predictive value of *APOE* ε4 for AD in a neuropathologically confirmed series of dementia patients was 97% [27]. Third, the prevalent MCI cases were a convenient case series sample, not an a priori designed study with a consistent battery across samples which led to a limited number of overlapping neuropsychological tests used in the visuospatial and executive function domains. However, our prevalent MCI sample fulfilled our intention of comparison with a true clinical cohort. Finally, Mayo Clinic is a tertiary referral clinic. This may have led to referral bias, which has been shown to have significant effects on research studies [10]. Therefore, it is possible that those who were evaluated may not be representative of general clinical populations.

A future study should include an a priori design with a consistent battery across samples and incorporate more neuropsychological tests assessing the visuospatial and executive function domains.

5. Conclusion

MCI includes a continuum of severity. By the time patients ultimately diagnosed with amnestic single-domain MCI seek clinical evaluation for memory loss, they have more widespread cognitive change than research subjects with incident MCI diagnosed through comprehensive evaluation despite both groups meeting clinical criteria for amnestic single-domain MCI. This earlier diagnosis is important for estimating progression rates and for clinical trials with the goal of treating people as early as possible. Future studies should distinguish the source of MCI cases (incident or prevalence cohorts) and hence severity of MCI even within single domain a-MCI cohorts.

Acknowledgments

RESEARCH IN CONTEXT

1. Systematic review: Previous research predicting progression from normal aging to MCI or MCI to dementia has resulted in a range of estimates. This study aimed to explore the differences between mild cognitive impairment (MCI) diagnosed in a clinical setting and MCI diagnosed in research setting with longitudinal data.

2. Interpretation: Findings are placed in the context of the impact on setting in determining rates of progression in MCI.

3. Future directions: The results of this study demonstrate the importance of longitudinal neuropsychological examination in the detection of early clinical change, which could lead to earlier diagnosis and treatment.

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