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Latent classes of mild cognitive impairment are associated with clinical outcomes and neuropathology: Analysis of data from the National Alzheimer's Coordinating Center

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ABSTRACT

Given the importance of identifying prodromes of dementia with specific etiologies, we assessed whether seven latent classes of mild cognitive impairment (MCI), defined empirically based on cognitive, functional, and neuropsychiatric information at initial visit, are associated with distinct clinical outcomes and neuropathological features. We separated 6034 participants with a baseline diagnosis of MCI into seven latent classes using previously defined criteria. We found that these latent classes of MCI differed significantly in their clinical outcomes, survival time, and neuropathology. Two amnestic multi-domain subgroups, as well as two other subgroups with functional impairments and neuropsychiatric disturbances, were at higher risk of not only a 'pure' form of Alzheimer's disease (AD) pathology, but also a 'mixed' pathology consisting of both AD and vascular features. Moreover, the seven latent classes had different risks of Lewy bodies, hippocampal sclerosis, and frontotemporal lobar degeneration (FTLD). This study indicates that data-driven subgroups of MCI are clinicopathologically informative and, with refinement, could lead to targeted interventions focused on each etiology.

1. Introduction

Advances in AD drug development have led to late-stage clinical trials of potentially disease-modifying therapies. Unfortunately, to date, none of these trials has achieved their primary outcome measures (Cummings et al., 2017; Doody et al., 2014; Salloway et al., 2014). In parallel, biomarker studies in both sporadic and autosomal-dominant genetic forms of AD have yielded compelling evidence that dementia due to AD represents the product of a pathological process spanning two decades (Bateman et al., 2012; Jack et al., 2013). The primary target of current therapeutic development, the Aβ peptide that accumulates in senile plaques, is among the earliest lesions in the brains of individuals who develop AD. Since there is ample evidence that anti-amyloid therapeutics achieve target engagement and clearance of Aβ (Nicoll et al., 2003; Sevigny et al., 2016), a plausible explanation for the failure in these clinical trials is that Aβ must be eliminated earlier in the course of disease to produce clinical benefit.

MCI represents an important syndromic entity that encompasses early stages of decline associated with neurodegenerative diseases including AD (Abner et al., 2017; Morris et al., 2001; Petersen et al., 2001; Sperling et al., 2011). While specific criteria and definitions of MCI vary, they generally include significant decline in one or more cognitive domains with relative preservation of functional activities of daily living. When MCI is seen in conjunction with biological markers, such as CSF levels of Aβ and the microtubule-associated protein Tau, that reliably predict the presence of AD pathology, it represents a prodromal stage of AD. Importantly, efforts to develop effective disease-modifying treatments for AD have increasingly focused on identifying and enrolling participants with MCI due to prodromal AD. As symptoms of MCI can be produced by a broad range of etiologies, biomarker

Abbreviations: Aβ, amyloid-beta; AD, Alzheimer's disease; ADC, Alzheimer's Disease Center; AMN, amnestic; CSF, cerebrospinal fluid; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; FX, functional impairments; GEE, generalized estimating equations; IADL, instrumental activity of daily living; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NACC, National Alzheimer's Coordinating Center; NP, neuropsychiatric features; pAD, probable or possible Alzheimer's disease; PET, positron-emission tomography; PPA, primary progressive aphasia; TDP-43, TAR DNA-binding protein 43; UDS, Uniform Data Set; VaD, vascular dementia

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confirmation of underlying AD pathology is essential in screening appropriate participants for AD clinical trials. While effective, current methods based on CSF or PET tracers are invasive and costly. The ability to discriminate among individuals with MCI to accurately predict underlying pathology or predict clinical course could have a dramatic impact on the design and execution of disease-modifying clinical trials for AD.

By expanding the phenotype to include not only cognitive performance but also neuropsychiatric and functional features, we previously identified remarkable heterogeneity among persons with MCI, consisting of seven latent classes (Hanfelt et al., 2011). Moreover, two of these latent classes were more likely to have an elevated Rosen-Hachinski score, a marker of probable cerebrovascular disease, suggesting that there might be important differences in etiology among the latent classes (Hanfelt et al., 2011).

The goal of the current study was to investigate the clinicopathological relevance of these data-driven subgroups of MCI, by investigating whether these subgroups differed with regard to both clinical outcomes and neuropathological features. We separated individuals with MCI into one of seven MCI classes based on clinical features at the time of initial MCI diagnosis. The clinical course of these individuals and neuropathological findings at autopsy were analyzed to determine if distinct MCI subgroups followed characteristic clinical trajectories or demonstrated specific associations with pathological features.

2. Materials and methods

2.1. Participants

We used data from 39 past and present ADCs collected between September 2005 and the June 2015 data freeze of the UDS. Inclusion criteria for the current study required that participants had: 1) a diagnosis of MCI at initial visit from the clinicians at each center and 2) non-missing information on age, years of education, and race. In addition, we required that participants had a MMSE score of 22 or greater at initial visit, in order to exclude a small number of MCI subjects with suspiciously low MMSE scores. We considered the additional requirement that participants had a Clinical Dementia Rating score of 0.5 at initial visit. However, we rejected this cutoff since this would place the emphasis on a memory impaired sample and thus miss other cognitive subtypes.

2.2. Measures

2.2.1. Phenotypes of MCI at initial visit

Cognitive test scores were based on the UDS Neuropsychological Battery version 2.0, a core battery of measures collected by the ADCs evaluating overall cognitive status (MMSE), executive functioning (Trail Making Test), language (Boston Naming Test, category fluency), attention (Digit Span and Digit Symbol), and episodic memory (Logical Memory, Story A) (Weintraub et al., 2009). Raw scores were converted to standardized scores (z scores) by using the demographic characteristics, specifically age, years of education, and race, of the UDS cognitively normal participants as the reference group (Hanfelt et al., 2011). Functional abilities were evaluated by having the informant complete the Functional Activities Questionnaire, which measures dependence performing IADLs over the previous four weeks (Pfeffer et al., 1982). Informants also received the Neuropsychiatric Inventory Questionnaire to provide a reliable assessment of problematic behavioral changes in the last month (Kaufer et al., 2000). Participants provided a self-report of depressive symptoms via the short form of the Geriatric Depression Scale (GDS; 15 items) (Sheikh and Yesavage, 1986).

2.2.2. Neuropathological features

Neuropathological characteristics were extracted from several versions of the NACC Neuropathology Data Set using the July 2014 data dictionary (last modification 12/5/2016). Reported pathological elements have evolved over time with modifications and additions. Evaluation of classical elements, such as CERAD and Braak scores, was available in nearly all cases (n = 410 and 406, respectively), while data on newer (e.g. TDP-43) or less common (e.g. neoplasm) features were more limited. In some instances, distinctions based on anatomic distribution (Brainstem vs. Limbic Lewy bodies) or pathological patterns (e.g., PSP vs. CBD vs. Pick FTLD-Tau subtypes) were grouped together to increase sample size. Combined sample size for Lewy Body included Absent (n = 291), Brainstem or Limbic (n = 57), and Neocortical (n = 47), and combined FTLD-Tau cases included Absent (n = 355) and Present (n = 55).

2.2.3. Analysis

Participants were assigned objectively into one of seven subgroups of MCI based on characteristics at their initial visit using previously established criteria from our paper on latent class analysis (Hanfelt et al., 2011). We derived the following Classes based on the interpretation of cognitive test scores at least 1.5 SDs below the cognitively normal group as evidence of impairment: 1) “minimally impaired”, a group indistinguishable from the cognitively normal group; 2) “amnestic only” (AMN Only), characterized by a subtle impairment in delayed memory only; 3) “amnestic with functional impairments and neuropsychiatric features” (AMN + FX + NP), characterized by impairments in both immediate and delayed memory, difficulties performing IADL, and neuropsychiatric disturbances; 4) “amnestic multi-domain” (AMN Multi), characterized by impairments across cognitive domains including episodic and semantic memory, language, and executive function; 5) “amnestic multi-domain with functional impairments and neuropsychiatric features” (AMN Multi + FX + NP), a subtype that differed from the AMN Multi group in having difficulties performing IADL and also in having neuropsychiatric disturbances, as well as impairments across a broader spectrum of cognitive domains, including attention and visuomotor skills; 6) “functional impairments and neuropsychiatric features” (FX + NP Only), a group experiencing functional and behavioral impairments but with no cognitive impairment detected in the neuropsychological examination; and 7) “executive function and language impairments” (Exec FX + Lang), a subgroup distinguished neuropsychologically by impairment in nonmemory domains.

In all regression analyses, we adjusted for sex and age at first visit. Logistic regression analysis was used to compare the MCI subgroups with regard to cardiovascular comorbidity at initial visit. GEE with time x subgroup interaction terms, where the effect of time was modelled nonlinearly, was used to compare the longitudinal trajectories of cognitive decline across the MCI subgroups (Liang and Zeger, 1986). Given the relatively short follow-up time, a quadratic model sufficed to depict any nonlinear rates of decline. We adjusted for selective attrition in the GEE analysis by including stabilized inverse probability of attrition weights based on sex, age, and MCI subgroup (Weuve et al., 2012). Overall survival times were compared using proportional-hazards regression. Time to conversion from MCI to dementia, as diagnosed by clinicians at each center, was compared using the standard competing risks method of Fine and Gray (1999). Since neuropathology developed over time and was observed only at autopsy, to compare neuropathological features among the MCI subtypes it was important that we incorporated into the analysis the time to death: otherwise, naively ignoring the time to death would have led, for example, to the spurious conclusion that the least-impaired subtype had the highest proportion of lacunes, owing to the tangential fact that the least-impaired subtype lived the longest. To avoid such spurious conclusions, we compared the MCI subtypes with regard to neuropathological features, taking into account both the types of the neuropathological features and the time point of the observation (i.e., death). More specifically, we studied sets of neuropathological findings, defined so that death with one type of