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Mild cognitive impairment in Parkinson's disease versus Alzheimer's disease

Lilah M. Besser [a, *], Irene Litvan [b], Sarah E. Monsell [a], Charles Mock [a], Sandra Weintraub [c], Xiao-Hua Zhou [a], Walter Kukull [a]

[a] National Alzheimer's Coordinating Center, University of Washington, 4311 11th Ave NE, Suite 300, Seattle, WA, 98105, USA
[b] University of California San Diego, Department of Neurosciences, National Parkinson Foundation Movement Disorder Center of Excellence, 8950 Villa La Jolla Drive, Suite C112, La Jolla, CA, 92037, USA
[c] Cognitive Neurology and Alzheimer's Disease Center, and Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, 320 E Superior, Searle 11-467, Chicago, IL, 60611, USA

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ABSTRACT

Introduction: No known studies have compared longitudinal characteristics between individuals with incident mild cognitive impairment due to Parkinson's disease (PD-MCI) versus Alzheimer's Disease (AD-MCI).

Methods: We used longitudinal data from the National Alzheimer's Coordinating Center's Uniform Data Set to compare 41 PD-MCI and 191 AD-MCI participants according to their demographics, presence of ≥1 APOE e4 allele, and baseline and change over time in clinical characteristics, neuropsychological test scores, and Clinical Dementia Rating sum of boxes (CDR-SB). Multivariable linear regression models with generalized estimating equations were used to account for clustered data and to test for baseline and longitudinal differences in neuropsychological test scores.

Results: PD-MCI and AD-MCI participants differed by many demographic and clinical characteristics. Significantly fewer PD-MCI participants developed dementia over one year. Compared to AD-MCI participants, PD-MCI participants performed better at baseline and over time on a global measure of cognition (Mini Mental State Exam), memory measures (immediate and delayed Logical Memory), and a language measure (Boston Naming Test), and additionally performed better over time on an attention measure (Digit Span Forward), a language measure (Vegetable List), a processing speed measure (Digit Symbol), and an overall measure of memory and functional impairment (CDR-SB).

Conclusion: Our study provides further evidence that PD-MCI is clinically distinct from AD-MCI and requires different tools for diagnosis and monitoring clinical progression. More importantly, this study suggests that PD-MCI takes longer to convert into dementia than AD-MCI, findings that require replication by other studies.

1. Introduction

Approximately 27% of non-demented individuals with Parkinson's disease have mild cognitive impairment (PD-MCI), and up to 60% with PD-MCI convert to PD dementia within four years [1–5]. While some studies have found that PD-MCI participants often have non-amnestic, single domain MCI with deficits in attention, visuospatial function, and executive functioning, other studies have found amnestic presentations of PD-MCI [5]. Although PD-MCI appears to be heterogenous [1–10], previous studies also suggest that the clinical and neuropsychological features are distinct from MCI due to other etiologies, such as Alzheimer's disease (AD-MCI).

In 2012, the Movement Disorders Society (MDS) published PD-MCI diagnostic criteria [11] that were designed primarily to capture and diagnose PD-MCI as a transition state between normal cognition and dementia among participants with PD. Although the MDS developed the new criteria based on an understanding of the typical differences between PD-MCI and MCI due to other

* Corresponding author.
E-mail addresses: lmbesser@uw.edu (L.M. Besser), ilitvan@ucsd.edu (I. Litvan), smonsell@uw.edu (S.E. Monsell), cmock@u.washington.edu (C. Mock), sweintraub@northwestern.edu (S. Weintraub), azhou@u.washington.edu (X.-H. Zhou), Kukull@uw.edu (W. Kukull).

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etiologies, to our knowledge no studies have compared the longitudinal differences in clinical characteristics and neuropsychological test scores between participants with PD-MCI and AD-MCI. Therefore, our primary aim was to characterize longitudinal changes in participants with incident PD-MCI compared to AD-MCI, the more common MCI etiology.

2. Methods

2.1. Participants

We used longitudinal data collected between September 2005 and March 2015 from the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) to study participants at 31 past and present U.S. Alzheimer's Disease Centers (ADC). ADCs have collected demographic, clinical, diagnostic, neuropsychological, and neuropathology data on UDS participants with normal cognition, mild cognitive impairment (MCI), and dementia approximately annually since 2005. UDS participants come from clinic samples, public recruitment efforts, participant referrals, other ongoing studies, and occasionally population-based samples. Because recruitment methods vary, UDS participants are best described as a clinical case series. Additional details about the UDS sample are found elsewhere [12,13].

2.2. Inclusion and exclusion criteria for main sample

We defined MCI in both groups according to the Petersen criteria [14] (the UDS neuropsychological tests limited our ability to define PD-MCI according to the new MDS criteria [11]). The PD-MCI participants had a primary diagnosis of PD (i.e., met the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria for PD) and MCI for $\geq$1 visit. The AD-MCI participants had primary probable AD as the suspected etiology at the incident MCI diagnosis and at their last UDS visit, and no contributing etiologic diagnosis at any UDS visit. ADCs are required to provide a suspected etiologic diagnosis for participants diagnosed with MCI. We restricted our analyses to incident MCI cases to help reduce clinical or neuropsychological score differences in the groups due simply to differences in time elapsed since diagnosis. We required all participants to have normal cognition or some impairment (impaired not MCI) but not MCI at their initial UDS visit. Impaired not MCI was diagnosed by clinicians as some cognitive impairment not meeting the Petersen criteria for MCI. The first follow-up visit with an incident MCI diagnosis was the starting point for inclusion in this study and is termed the baseline visit. Only participants with at least one UDS visit completed after their baseline MCI visit were included in our analyses.

Among the 31,872 participants in the UDS as of March 2015, 216 met our PD-MCI criteria and 1065 met our AD-MCI criteria. We excluded those without an incident MCI diagnosis during UDS follow-up and without at least one visit following the baseline visit, resulting in the final sample of 41 PD-MCI and 191 AD-MCI participants.

2.3. Standard protocol approvals, registrations, and patient consents

Research using the NACC database was approved by the University of Washington Institutional Review Board. Informed consent was obtained at the individual ADCs. The NACC data were de-identified.

2.4. Demographic, clinical, and neuropsychological variables

At each UDS visit, information was collected on demographics, self-reported health history, clinical symptoms, and medication use, and participants were evaluated using the standardized UDS neuropsychological test battery and clinical exam. The Unified Parkinson's Disease Rating Scale [UPDRS] was used to measure motor disturbances [15].

The UDS neuropsychological battery [16] contains the Mini-Mental State Examination (MMSE), measuring global cognitive function; Digit Span Forward and Digit Span Backward (Wechsler Memory Scale-Revised [WMS-R]), measuring attention; Digit Symbol (Wechsler Adult Intelligence Scale-Revised [WAIS-R]) and Trail Making Test Part A, measuring processing speed; Trail Making Test Part B, measuring executive function; Immediate and Delayed Logical Memory (WMS-R), measuring episodic memory; and Animal list generation, Vegetable list generation, and the Boston Naming Test (BNT), measuring language. Visuospatial function was measured using the MMSE pentagon score (1 = correct, 0 = incorrect).

Participants (and their co-participants) reported any prescription medication use within two weeks preceding the UDS visit. We created variables to indicate use of: 1) anticholinergics, 2) amantadine, 3) dopaminergics, 4) memantine, 5) cholinesterase inhibitors, and 6) RBD medications (drug list, Supplemental Table 1). We used existing NACC variables to assess use of antipsychotics and antidepressants (NACC's derived variables documentation [17]). The Clinical Dementia Rating (CDR) was conducted at each visit. The CDR sum of boxes (CDR-SB) is a summary measure of scores for memory, orientation, judgment, community affairs, home and hobbies, and personal care, and ranges from 0 (no impairment) to 18 (greatest impairment). During the neurological exam, clinicians determine whether one or more of the following domains are affected: memory, language, attention, executive function, and visuospatial function. Dementia was diagnosed by meeting the standard criteria for dementia of the Alzheimer's type or for other non-Alzheimer's dementing disorders. Diagnoses were made by a single qualified clinician or through consensus by a team of clinicians.

2.5. Neuropathology data sample

The standardized Neuropathology Form and Coding Guidebook were used to collect neuropathological examination data [18,19]. Our analysis focused on neuropathology was restricted to participants with MCI, a clinical diagnosis primary PD, and no contributing AD diagnosis at their last visit before death. AD-MCI participants had MCI, an etiologic diagnosis of primary probable AD, and no contributing diagnoses at the last visit before death. Most of the participants in the main sample (n = 235) (described above) were not in the neuropathology sample (n = 38), and only 11 of the 38 participants with neuropathology data were in the main sample.

Neuropathological diagnoses were not used when defining the two groups because we aimed to describe the underlying neuropathology among those with clinical PD-MCI compared with clinical AD-MCI. The two groups were compared according to the neuritic plaque density (none, sparse, moderate, frequent), Braak stage for neurofibrillary degeneration (Stages 0, I/II, III/IV, V/VI), Lewy body (LB) pathology (no pathology, brainstem predominant, limbic, neocortical, or other/unspecified region) and presence of cerebrovascular disease (large artery infarct or lacune, microinfarct [cortical infarcts observed only through a microscope], cerebral hemorrhage or microbleed).

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