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Sex differences in progression to mild cognitive impairment and dementia in Parkinson's disease

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ABSTRACT

Introduction: Identification of factors associated with progression of cognitive symptoms in Parkinson's disease (PD) is important for treatment planning, clinical care, and design of future clinical trials. The current study sought to identify whether prediction of cognitive progression is aided by examining baseline cognitive features, and whether this differs according to stage of cognitive disease.

Methods: Participants with PD in the Pacific Udall Center Clinical Consortium who had longitudinal data available and were nondemented at baseline were included in the study (n = 418). Logistic and Cox regression models were utilized to examine the relationship between cognitive, demographic, and clinical variables with risk and time to progression from no cognitive impairment to mild cognitive impairment (PD-MCI) or dementia (PDD), and from PD-MCI to PDD.

Results: Processing speed (OR = 1.05, p = 0.009) and working memory (OR = 1.01, p = 0.03) were associated with conversion to PDD among those with PD-MCI at baseline, over and above demographic variables. Conversely, the primary predictive factor in the transition from no cognitive impairment to PD-MCI or PDD was male sex (OR = 4.47, p = 0.004), and males progressed more rapidly than females (p = 0.01). Further, among females with shorter disease duration, progression was slower than for their male counterparts, and poor baseline performance on semantic verbal fluency was associated with shorter time to cognitive impairment in females but not in males.

Conclusions: This study provides evidence for sex differences in the progression to cognitive impairment in PD, while specific cognitive features become more important indicators of progression with impending conversion to PDD.

Parkinson's disease (PD) is strongly associated with the development of cognitive impairment, widely recognized as one of the most frequent nonmotor symptoms of the disease [1]. Among newly diagnosed individuals, the prevalence of mild cognitive

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impairment (PD-MCI) approaches 30%, and dementia (PDD) is increasingly recognized as an eventual and almost inevitable consequence of PD [2]. The development of cognitive symptoms during the course of PD is associated with decreased quality of life and loss of independence [3,4]. Identification of specific features that predict progression of cognitive symptoms could have meaningful implications for treatment planning and clinical management for patients with PD, and may provide guidance for future clinical trial design.

Progression of cognitive symptoms in PD is recognized to vary widely, with some patients remaining relatively stable for many years, while others progress more rapidly to dementia [5]. In terms of specific cognitive features, PDD is often associated most strongly with cognitive functions that are largely mediated by dopamine-independent posterior-cortical brain regions [6]. Fronto-striatal deficits, on the other hand, which primarily impact executive abilities and attention, are considered nearly universal in PD but may be less closely associated with the dementia syndrome [6,7]. This is not consistent, however, as progression to both PD-MCI and PDD is associated with decline in executive skills and attention in some studies [8,9]. Given the small sample sizes of prior studies and the known heterogeneity of cognitive dysfunction in PD, however, it is difficult to generalize these results.

The current study compares baseline cognitive, demographic, and clinical characteristics of participants who remain cognitively stable and those who progress over the course of follow up in a large, well-characterized prevalent PD cohort. We seek to identify whether prediction of cognitive symptom progression is aided by examining baseline cognitive test performance, and whether this differs according to stage of cognitive disease.

1. Methods

1.1. Subjects

Participants were drawn from the Pacific Udall Center Clinical Consortium, a collaboration between multiple institutions that enroll prevalent idiopathic PD cohorts with a goal of harmonizing detailed clinical and neuropsychological evaluation, as previously described [10]. This study includes three sites with currently available longitudinal data: University of Washington/Veterans Affairs Puget Sound Health Care System and Oregon Health Sciences University/Veterans Affairs Portland Health Care System, together comprising the Pacific Udall Center, and the Udall Center at Johns Hopkins University.

All participants met the United Kingdom Parkinson's Disease Society Brain Bank (UKBB) clinical diagnostic criteria for PD, had cognitive diagnostic information available, and had at least one follow up visit ($n = 567$). Sixty-nine participants were diagnosed with dementia at baseline and one participant had “unknown” cognitive status due to potential confounding information that precluded a final cognitive diagnosis. Of the remaining 497 participants, 19 participants reverted from PD-MCI to no cognitive impairment (consistent with prior literature [11]) and 60 participants were missing data, for a total of 418 participants available for analyses. The institutional review board of each participating institution approved the study, and all participants provided written informed consent.

1.2. Cognitive diagnosis and variables

Participants were assigned motor and cognitive diagnoses at a clinical diagnostic consensus conference. Cognitive diagnoses were made using published diagnostic criteria for PDD [12] and PD-MCI [13]. Extensive neuropsychological and clinical assessments were available for determination of cognitive diagnosis and permitted assignment of diagnosis using PD-MCI Level II criteria [10].

A set of core cognitive variables that have been administered since the inception of the cohort and are given across all sites were included the current analyses. These include: 1) Montreal Cognitive Assessment; 2) Hopkins Verbal Learning Test-Revised, a list learning test that assesses immediate verbal learning, delayed recall, and recognition memory; 3) Letter-Number Sequencing and Trail Making Test (Part B minus Part A), which measure auditory and visuospatial working memory, respectively; 4) Digit Symbol, a measure of processing speed/working memory; 5) Judgment of Line Orientation, a measure of visuospatial ability, and 6) semantic and phonemic verbal fluency. All participants were rated in the ON state if they were taking PD medications.

1.3. Secondary variables

History of cardiovascular risk and hypertension (from the Hachinski Ischemic Index), head injury, and past alcohol and tobacco use were collected at baseline. Genomic DNA was prepared using standard procedures as described previously [14,15]. Genes previously associated with cognitive function in the PD Cognitive Genetics Consortium were included in the current analyses and included 1) loss of function mutations in the glucocerebrosidase (*GBA*) gene as well as the E326K single nucleotide polymorphism in the *GBA* gene, and 2) presence of an apolipoprotein E $\varepsilon 4$ (*APOE* $\varepsilon 4$) allele.

1.4. Statistical analyses

Group differences in baseline clinical, demographic, and cognitive characteristics were assessed using t-tests, Kruskall-Wallis tests, or chi-square tests. To determine the association between baseline cognitive test scores and subsequent conversion from one diagnostic group to the next, separate logistic regression models were run for conversion from no cognitive impairment to cognitive impairment (PD-MCI or PDD) and from PD-MCI to PDD. Model 1 included age, sex, education, disease duration, site, and length of follow-up; Model 2 added the cognitive variables. Receiver operating characteristic (ROC) curves were calculated for all models; comparisons between Model 1 and Model 2 areas under the curve (AUC) were made using the DeLong, DeLong, and Clarke-Pearson algorithm [16]. Hosmer-Lemeshow goodness of fit tests were calculated for each model. Separate Cox regression analyses were performed to assess time to conversion from no cognitive impairment to PD-MCI or PDD and from PD-MCI to PDD, including all cognitive variables and controlling for age, sex, education, disease duration, and site. Kaplan-Meier estimates were calculated for time to cognitive impairment for males and females, with log-rank tests performed to determine whether there was a significant difference between the curves. Kaplan−Meier curves were also generated separately for males and females for variables that interacted significantly with sex in the Cox regression analyses, using a median split for the variables of interest. Secondary analyses included genetic status and additional clinical variables, as well as more detailed examination of baseline differences between male and female participants. All analyses were performed using Stata 14.2.

2. Results

At baseline, cognitively impaired groups (PD-MCI and PDD) were older, more likely to be male, more likely to be an armed forces Veteran, and had more severe motor symptoms. Those with dementia had longer disease duration and were significantly more likely to carry a *GBA* variant. Group differences between cognitive

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