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Sex Differences in the Clinical Progression of Parkinson's Disease

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ABSTRACT

Objective: To describe characteristics of Parkinson's disease by sex and determine if differences in disease progression exist.

Design: Longitudinal, observational study.

Setting: Twenty-one National Parkinson Foundation Centers of Excellence.

Participants: People ($N = 4,679$; 63% men and 37% women) with idiopathic Parkinson's disease.

Methods: Demographic and clinical data at enrollment and after 1 year were collected. We defined progression as a 1-year change in the following functional health outcome measures: (a) health-related quality of life (Parkinson's Disease Questionnaire–39), (b) Timed Up and Go test, (c) cognitive function, and (d) number of medications. We compared baseline characteristics between men and women. Then, linear regression models were built to assess the independent contribution of sex to progression.

Results: At baseline, women were significantly more likely to be older and have greater disease severity and more comorbidities than men despite similar duration of disease. This finding corresponded to worse function as assessed by the Parkinson's Disease Questionnaire–39 and Timed Up and Go test but not to number of medications and cognitive function. After 1 year, declines across all functional measures except delayed recall occurred. No significant changes in Parkinson's Disease Questionnaire–39, Timed Up and Go, number of medications, or verbal fluency between men and women occurred. Women had a more significant improvement in delayed recall than men.

Conclusion: Numerous small baseline differences occurred between men and women with PD, although differences in markers of progression were few. Findings suggest that clinical manifestations and prognosis appear similar by sex under the same treatment conditions.

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Researchers have described sex differences across a wide spectrum in Parkinson's disease (PD). These differences include risk, clinical presentation, and health outcomes. Although women have been reported to have a lower risk of PD, they have a greater mortality and earlier nursing home placement than men (Safarpour et al., 2015; Willis et al., 2012; Wooten, Currie, Bovbjerg, Lee, & Patrie, 2004). Some of these differences are hypothesized to be related to differences in sex hormone exposure and sex chromosome effects (Smith & Dahodwala, 2014). However, additional factors such as differences in access to specialty care, socioeconomic differences, and sex bias may also have a role (Saunders-Pullman, Wang, Stanley, & Bressman, 2011). Unfortunately, the degree to which each factor contributes to sex differences is unknown. Additionally, there has been little study of interventions to reduce sex disparities in PD.

Clinical motor and nonmotor features are one area in which sex differences have been described in PD. However, results have been conflicting, partly because of differences in sample characteristics and sizes and in measurement tools used. In a recent large cross-sectional study of participants enrolled in a randomized clinical treatment trial, no significant differences were seen in health-related quality of life or disease severity between men and women (Augustine et al., 2015). However, investigators did find that women performed better on tests of cognitive function than men. On the other hand, in another large cross-sectional study of more than 1,000 participants seen at a single site, researchers found that at baseline assessment women with PD had greater disease severity and disability than men (Baba, Putzke, Whaley, Wszolek, & Uitti, 2005). In previous clinic-based studies, researchers also described more frequent levodopa-induced dyskinesias and

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The biological and social determinants of sex differences in Parkinson's disease risk, progression, and outcomes are poorly understood.

greater nonmotor symptoms among women than men (Baba et al., 2005; Haaxma et al., 2007; Lyons, Hubble, Troster, Pahwa, & Koller, 1998; Picillo et al., 2013; Solla et al., 2012).

Several small longitudinal studies of PD progression compared clinical features by sex, with mixed results. In an older study of 47 men and 23 women followed up for 6 years, researchers did not find any differences in disability, dyskinesias, or dementia between groups (Diamond, Markham, Hoehn, McDowell, & Muenter, 1990). Similarly, in a community-based study of 237 participants, researchers did not find any differences in motor progression between men and women with PD (Louis et al., 1999). However, in a clinic-based study of men and women at various stages of PD and follow-up time, investigators reported that men had a more rapid decline in nonmotor complaints and disability (Jankovic & Kapadia, 2001). In a 5-year study of disease progression among 129 participants, investigators found that men with PD had more severe motor impairment than women, but this was not associated with worse quality of life (Velseboer et al., 2013).

Defining the exact role of sex in the course of PD has important implications. If sex is linked to disease progression, then it is possible that hormone-based therapies may have therapeutic benefits. It is important to study this question in an appropriately powered sample and under similar treatment conditions to reduce the effects of differential access to care on health outcomes. In an effort to better understand the characteristics of sex differences in the motor and nonmotor manifestations of PD, we sought to describe the demographic and clinical characteristics of PD by sex among a large population-based cohort of people seen at movement disorder clinics worldwide and determine if there are sex differences in the clinical progression of patient-centered outcome measures.

Methods

Study Design and Sample

The present study was a secondary analysis of data already drawn from the longitudinal, observational study of PD patients enrolled in the National Parkinson Foundation (NPF) Parkinson's Outcomes Project. The authors are all investigators involved in this project. The NPF Parkinson's Outcomes Project is intended to examine the quality of care provided at NPF Centers of Excellence for PD and to determine which factors improve health outcomes for their patients to increase accessibility to the best treatments for people with PD. Participants are followed up annually at 21 international NPF Centers of Excellence located in Canada, the Netherlands, Israel, and the United States. Participant enrollment began in 2009, and new participants continue to be enrolled every year; there is no anticipated end to this project. Only participants with a physician diagnosis of idiopathic PD and at least 1 year of follow-up data were included in the analysis. The 1-year follow-up criterion for this analysis was selected to minimize the effects of differential loss to follow-up by sex. The sample size of 4,679 participants allowed us to detect a one-point difference in mean quality of life scores between groups with a probability (power) .80. There was no remuneration for participation in this project. All measures selected for use in this study are widely used within PD research and are described in detail below. Approval from the institutional review board at each site was obtained before the start of participant recruitment. We obtained written informed consent from all participants.

Data Collection

Annual patient and caregiver data were collected during a regular clinical visit. Patient data include demographics, number of comorbidities, medications, disease duration, Hoehn and Yahr (H&Y) stage (Goetz et al., 2004), five-word recall and verbal fluency (Chou et al., 2010; Nasreddine et al., 2005), Timed Up and Go (TUG) test score (Morris, Morris, & Iansek, 2001), and Parkinson's Disease Questionnaire–39 (PDQ-39) score. The PDQ-39 is a disease-specific health-related quality of life scale (Peto, Jenkinson, & Fitzpatrick, 1998). Markers of disease progression were defined as 1-year change in PDQ-39 and subscales, TUG, number of medications, verbal fluency score, and five-word recall.

H&Y Stage Scale. The H&Y Stage Scale score ranges from 1 to 5 (1 = *Unilateral involvement only*; 2 = *Bilateral or midline involvement with normal balance*; 3 = *Mild to moderate bilateral disease with impaired postural reflexes*; 4 = *Severe disability, still able to walk or stand unassisted*; 5 = *Wheelchair bound or bedridden*).

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