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Identifying clinical measures that most accurately reflect the progression of disability in Parkinson disease

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ABSTRACT

Introduction: The temporal relationship between disease and disability progression in Parkinson disease (PD) is not well understood. Our objective was to describe the natural, multidimensional trajectory of disability in persons with PD over a two-year period.

Methods: We conducted a multi-center, prospective cohort study involving four institutions. Data were collected at baseline and at 6-month intervals over 2 years using standardized clinical tests representing three World Health Organization defined disability domains: impairment, activity limitation, and participation restriction. Unadjusted mixed effects growth models characterized trajectories of disability in the three disability domains. The data set was analyzed using restricted maximum likelihood (REML) estimation. Standardized estimates of change were also computed using Cohen's d for each measure.

Results: Of the 266 enrolled participants, we analysed data from individuals who participated in at least 3 assessments (n = 207, 79%). Rates of disability progression over the 2-year period differed across domains. Moderate effects were detected for motor impairment (d = .28) and walking-related activity limitation (gait-related balance (d = .31); gait speed (d = .30)). Marginal effects were noted for upper extremity-related activity limitation (d = .11) and health-related quality of life participation restriction (d = .08).

Conclusions: The natural trajectory of walking-related activity limitation was the most potent indicator of evolving disability, suggesting that routine assessment of walking and periodic rehabilitation is likely to be warranted for many persons with PD. Natural trajectories of disability provide important comparison data for future intervention studies.

1. Introduction

Parkinson Disease (PD) is one of the most disabling chronic health conditions affecting older adults worldwide [1]. Despite advances in medical and surgical interventions, persons with PD experience a relentless progression of neurological signs and symptoms, physical mobility and poorer quality of life over several years [2].

Although decline in PD is anticipated, wide variation exists in the level of disability corresponding to a specific level of disease severity [3]. Furthermore, the temporal relationship between disease and disability progression is not well understood. Current understanding of evolving disability in PD is based on a small number of studies, with cross-sectional designs and/or limited and insufficient measures of disability [4–7]. Disease progression rates calculated from cross-sectional data in a recent study in PD were 1.5–2 times higher than those calculated from longitudinal data. Cross-sectional methods overestimate actual rate of progression [8].

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From 1980 to 2001, the World Health Organization (WHO) narrowly conceptualized disability as a single entity, manifested as diminished performance of everyday tasks that ultimately emerged as a result of signs and symptoms of a disease [9]. In 2001, the WHO endorsed what remains a contemporary, globally adopted disablement model: the International Classification of Functioning, Disability and Health (ICF). Unlike its predecessor, the ICF conceptualizes disability across three domains as *impairments* in body functions and structures, *activity limitations* (i.e., limitations in performance or capacity at the level of the whole person), and *participation restrictions* (i.e., restrictions in the ability to participate in life situations) [10]. The ICF model provides a framework for examining the complex relationships between disease progression and concurrently evolving, multidimensional facets of disability.

Our purpose was to expand current understanding of disease and disability progression in PD using the ICF model. To this end, we conducted a 2-year prospective cohort study to examine temporal relationships between disease progression and naturally evolving impairments, activity limitations, and participation restrictions. We hypothesized that distinct differences in the progression of disability would be observed across ICF domains.

2. Methods

2.1. Study population

Study participants were recruited from 2009 to 2012 through the Departments of Neurology at the University of Utah, the Parkinson's Disease and Movement Disorder Center at Boston University Medical Center, the Movement Disorders Center at Washington University in St Louis School of Medicine and the University of Alabama at Birmingham. Participants were community dwelling, $\geq$ 40 years of age, diagnosed with idiopathic PD by a neurologist (using UK Brain Bank Criteria), in Hoehn and Yahr (H&Y) stages 1–4, and scored $\geq$ 24/30 on the Mini-mental State Examination. Exclusion criteria were a diagnosis of atypical Parkinsonism, surgical management of PD, and non-English speaking. All four Institutional Review Boards approved the study, and all participants provided informed consent.

2.2. Study design and procedures

A prospective, longitudinal cohort study design was conducted across four institutions [11]. Data were collected at baseline and at 6-month intervals for two years. Demographic information, PD medications, fall history, medical and surgical history were collected via personal interview using standardized data collection forms. Levodopa equivalent daily dose (LEDD) was calculated for each participant.

Standardized clinical tests, which assessed disability using ICF constructs, were chosen due to their strong psychometric properties and clinical utility. All participants were tested during an "on" medication state. To ensure consistency, we provided research personnel at each site with a standard operating procedures manual and instructional video for administering and scoring the tests. We subsequently determined intra- and inter-rater reliability for each test based on evaluator scores from 2 video case examples viewed on two occasions one week apart. The ICC (1,4) values for the performance based measures utilized in this study ranged from .75 to .89.

2.3. Measure of impairment

Section III of the Movement Disorder Society sponsored Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was administered to assess motor impairment [12]. Individual items are scored on an ordinal scale of severity from low to high. Summed scores represent an underlying continuous concept, and therefore, are treated as a continuous variable [12]. Excellent factor validity, test-retest reliability (ICC = .93), high internal consistency and responsiveness have been demonstrated [12,13].

2.4. Measures of activity limitation

The 10-m walk (TMW) test measures self-selected gait speed and has been shown to be psychometrically robust in older adults and persons with PD [13]. Excellent test-retest reliability (ICC = .96) has been reported in PD [14]. The average speed of two trials was the dependent variable.

The Functional Gait Assessment (FGA) assesses walking with challenges to postural stability [14]. The FGA is a 10-item standardized test (e.g., walking with head turns, altering gait speed, backwards, narrowed base of support, negotiating obstacles) with each item scored on a 4-point ordinal scale (0–3). Total scores range from 0 to 30, with higher scores indicating better performance. Strong validity and test-retest reliability (ICC = .93) have been established [15].

The Nine Hole Peg Test (9-HPT) is a standardized, quantitative test of upper extremity function. Participants were asked to place and remove nine pegs from a pegboard, one at a time, as quickly as possible. The total time to complete the task was recorded. The mean of two trials for the dominant hand was used the dependent variable. The 9-HPT has high inter-rater and test-retest reliability (ICC = .88 for dominant hand; ICC = .91 for non-dominant hand) in PD and adequate sensitivity to detect impairments of hand function [16].

2.5. Measure of participation restriction

The Parkinson's Disease Questionnaire-39 (PDQ-39) contains 39 self-report items consisting of 8 domains and measures the degree of healthy, competent, and satisfying participation in daily life. The PDQ-39 has been shown to correlate negatively with participation in activities [17]. Scores are summed and represent an underlying continuous concept with higher scores representing worse quality of life [18]. Excellent internal consistency, test-retest reliability (ICC = .80–94 across 7 domains; ICC = .68 in the social support domain) and strong construct validity have been established [19].

2.6. Statistical analysis

Data were initially recorded on standardized study forms and subsequently entered into a Research Electronic Data Capture (REDCap) database hosted at the University of Utah. A research assistant verified accuracy of data entry by comparing electronic data with original hard copy data. Researchers at each site corrected discrepancies. Statistical analysis was conducted using SPSS Version 20.0 (IBM Corp. NY) and all comparisons at an alpha level of .05 were considered significant.

Descriptive statistics for the sample and baseline prognostic variables were examined for normal distribution, outliers, and missing values. Unadjusted mixed effects growth models characterized trajectories of disability in the three ICF domains. The data set was analyzed using restricted maximum likelihood (REML) estimation, using all data to compute parameter estimates. Intercepts and slopes for individual participants were modeled as random effects. The final model for each outcome was determined by comparing model fit between models with differing covariance structures (the relationship between repeated measures) and between models with and without a nonlinear term (i.e., quadratic