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Short communication

Baseline predictors of worsening apathy in Parkinson's disease: A prospective longitudinal study

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ABSTRACT

Introduction: Apathy is one of the most common behavioural disorders in Parkinson's disease (PD) and contributes significantly to a reduced quality of life in PD patients.
Methods: We conducted a prospective longitudinal study of 89 mild PD patients over 18 months, measuring apathy symptoms at 6-monthly intervals using the Starkstein Apathy Scale, as well as measures of motor and non-motor symptoms, cognitive function, and functional disability at baseline. Mixed-effects models were used to characterise the individual trajectories of apathy symptom severity, and linear regression with stepwise elimination procedure was used to select significant baseline predictors.
Results: Clinically significant levels of apathy were present in 42.7% of our sample at baseline, with symptom severity remaining relatively stable on average over the course of 18 months. Male gender, lower educational attainment, higher depression symptom severity, more severe functional disability, and the presence of dyskinesias at study entry predicted increasing apathy over the subsequent 18 months.
Conclusions: Patients with these factors are at risk for progression of apathy, which may be prevented by treating depression and functional disability. Further studies are needed to address both the specific neurobiological pathways and psychosocial factors underpinning apathy in PD.

1. Introduction

Apathy is a syndrome characterized by a primary lack of motivation, as manifested by diminished goal-directed behavior and cognitive activity as well as reduced spontaneous or evoked affect [1]. Among patients with Parkinson's disease (PD), a recent meta-analysis estimated the prevalence of apathy to be 39.8% [2]. Despite its high prevalence, apathy has been under-detected in PD patients, but has a significant impact on quality of life and is a major contributor to decreased functional autonomy and increased caregiver burden [2]. It is therefore important to understand how apathy progresses over the course of the disease and which factors contribute to its development.

Apathy has been traditionally considered an aspect of depression. Although both apathy and depression are frequently associated in PD patients [2] and may have overlapping symptoms (such as lack of interest), several studies have confirmed that apathy and depression can dissociate in PD and appear to be distinct constructs [3–5]. Apathetic PD patients often have more severe parkinsonism and require higher daily levodopa doses [2], implying that apathy and motor symptoms may arise from similar pathological mechanisms. Apathy has also been found to predict cognitive decline over time in PD patients without depression or dementia, and is specifically associated with deficits in executive function [2].

As the majority of prior studies have employed a cross-sectional design, this report extends previous work by evaluating the course of apathy in PD and investigating the factors that predict individual trajectories of apathy. To this end, we conducted a prospective study of apathy in non-demented, mild PD patients over 18 months, using a battery of well-validated psychiatric scales as well as measures of motor symptoms, non-motor symptoms, demographic

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and pharmacological information.

2. Methods

2.1. Subjects and setting

This is a prospective longitudinal study of subjects consecutively recruited from outpatient movement disorders clinics at a tertiary neurology centre between August 2011 and March 2012. Subjects with a diagnosis of idiopathic PD meeting the National Institute of Neurological Disorders and Stroke (NINDS) criteria, with mild PD (Hoehn and Yahr stage of <3) and without severe cognitive impairment (Mini Mental State Examination score > 16) were recruited. All patients subsequently also underwent full psychometric assessment to exclude those who fulfilled Movement Disorder Society criteria for PD dementia. The study was approved by the Centralized Institutional Review Board of the Singapore Health Services and voluntary informed consent was obtained from all subjects.

2.2. Assessments

At baseline and at 6-monthly intervals for a period of 18 months, apathy was assessed using the Starkstein Apathy Scale (SAS; 14 items with a four-level scale). The SAS is well-validated in the PD population and recommended for use by the Movement Disorders Society to screen for symptoms of apathy. At baseline, depression, anxiety, excessive daytime sleepiness, and functional disability were also assessed using the Geriatric Depression Scale (GDS), the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS 'A'), the Epworth Sleepiness Scale (ESS), and the modified Barthel Index respectively. Motor symptom severity was evaluated by movement disorder specialists using the UPDRS-III and modified Hoehn and Yahr (H&Y) staging. The presence of dyskinesias and motor fluctuations was determined using items 32 and 39 of the UPDRS-IV. Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) by trained neuropsychologists. All patients were assessed throughout while taking their normal medication and in the levodopa "ON" state. Baseline demographic (age, gender, education, age at PD diagnosis, disease duration) and pharmacological (antiparkinsonian and psychiatric medication) information were recorded. Doses of dopaminergic medication were converted to levodopa equivalent doses using a previously developed formula [6]. Use of antidepressants and/or anxiolytics was coded as a binary variable (yes/no).

2.3. Statistical analysis

The distributions of baseline clinical characteristics were examined using appropriate descriptive statistics. We examined the prevalence of clinically relevant symptoms of apathy at baseline, defined by ≥ 14 on the SAS. We also examined the population-averaged and individual trajectories of apathy symptom severity over 18 months.

Growth modeling is divided into two phases with several steps within each phase. In the first phase, we performed a linear mixed-effects analysis to identify and model the nature of change in apathy symptom severity over the study period. Fixed effects included time in the study (baseline, 6-, 12- and 18-month visit) and the quadratic term for time. Random effects included an intercept for subjects, as well as a by-subject random slope for the effect of time.

The following models were constructed:

1. A random intercept and fixed slope model
2. A random intercept and random slope model
3. A random intercept and random slope model including time as an additional quadratic term.

Likelihood ratio tests were performed to determine which model best characterised the nature of change in apathy symptom severity during the study period.

In the second phase, we identified baseline factors that explained individual differences in individual trajectories of apathy symptom severity. As these trajectories were best described as a linear slope, each patient's slope was calculated as a sum of the best linear unbiased prediction of the fixed and random effects of slope. The following factors measured at baseline were included in a linear regression model with individual apathy slope as the dependent variable:

(i) demographic measures (age at baseline visit, gender, educational attainment, age at PD diagnosis, disease duration),
(ii) motor symptom measures (UPDRS-III score, Hoehn and Yahr stage, presence of dyskinesias and clinical fluctuations),
(iii) non-motor symptom measures (depression, anxiety, daytime sleepiness, cognitive function, functional disability), and
(iv) pharmacological factors (daily levodopa equivalent dose, use of psychiatric medications).

This maximal model was reduced to a minimal adequate model (Model A) by stepwise backwards elimination of the variable with the highest p value from the model, until all variables were significant at p value < .05. A second model (Model B) was constructed by forcing variables found to be clinically important in the literature (baseline disease duration, baseline H&Y stage, and baseline MoCA scores) into the minimal adequate model.

All statistical analyses were performed in R version 3.1.2 and lme4 package. All analyses were two-sided and results were considered statistically significant if p value < .05.

3. Results

Ninety-two patients participated in this study. Of these, 89 completed at least 3 out of 4 visits and were included in the analyses. These patients were aged 46–81 years, primarily male (73%) and had mild PD, with a H&Y stage of 2.5 or less and low UPDRS-III scores (Table 1). At baseline, clinically significant levels of apathy (defined by SAS $\geq$ 14) were present in 42.7% of our sample. Although apathy symptom severity did not change significantly over time on average ($p = 0.75$), individual trajectories of apathy were highly variable.

In the first phase of growth modeling, model 2 (with time as a fixed effect and by-subject random slope for the effect of time) performed better than model 1 on the likelihood ratio test, indicating that there was significant inter-individual variability in apathy trajectories. Model 3 (including time as an additional quadratic term) performed poorly compared to model 2 on the likelihood ratio test, indicating that a straight line was a better fit than a curve in characterising individual trajectories of apathy symptom severity.

In the second phase, two models were constructed in order to identify baseline factors that predicted individual apathy trajectories (Table 2). Model A derived using stepwise elimination from the highest p value performed better than model B, with a lower AIC and similar adjusted R-squared value. In model A, male gender, lower educational attainment, higher depression symptom severity, more severe functional disability and the presence of