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Depression and anxiety are co-morbid but dissociable in mild Parkinson's disease: A prospective longitudinal study of patterns and predictors

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ABSTRACT

Background: Depression and anxiety are common in Parkinson's disease (PD) and contribute significantly to a reduced quality of life in PD patients. Though they often co-exist, it is unclear whether depression and anxiety result from a shared pathological process. We studied the longitudinal course and determinants of depression and anxiety in PD in order to understand which factors contribute to the development of these symptoms.

Methods: We conducted a prospective longitudinal study of 89 mild PD patients over 18 months, measuring depressive and anxiety symptoms at 6 monthly intervals using the Geriatric Depression Scale and Hospital Anxiety and Depression Scale – 'Anxiety' subscale. Univariate and multivariate Generalised Estimating Equations were used to investigate the course of depression and anxiety and their association with demographic factors, motor measures, non-motor symptoms, and pharmacological factors.

Results: Depression and anxiety were co-morbid in 13.5% of the sample. Depressive symptoms remained relatively stable while anxiety symptoms improved over the course of 18 months. Severity of depressive symptoms was associated with female gender, motor fluctuations, apathy, and anxiety, while severity of anxiety was associated with older age, higher educational attainment, shorter disease duration, younger age of disease onset, and excessive daytime sleepiness.

Conclusions: Although depression and anxiety are frequently co-morbid in PD, they were dissociable from each other. They had distinct trajectories and different longitudinal relationships with demographic, motor, and non-motor factors that were unique to each disorder.

1. Introduction

Although Parkinson's disease (PD) is primarily a movement disorder, it is also accompanied by non-motor symptoms [1]. Of these, depression and anxiety are increasingly recognized as the most frequent psychiatric symptoms in PD, with prevalence estimates of 2.7–90% [2] and 5.3–40% [3] respectively. Both appear to be a direct consequence of PD pathology rather than a response to the disability caused by PD. However, higher levels of depression have also been found to predict more rapid disease progression [4]. Despite their high prevalence, these symptoms have been under-detected and consequently, under-treated. Though often overlooked, psychiatric symptoms have a significant impact on quality of life and are associated with negative health outcomes and increased mortality [5]. It is therefore important to understand how these symptoms progress and which factors contribute to the development of these symptoms.

Although depression and anxiety are co-morbid in PD in 14–26% of PD patients [6], it remains unclear whether they share common or differing underlying causes. While depression has been extensively researched in PD, anxiety disorders are relatively understudied [7] and very few studies have investigated both depression and anxiety [8]. A recent systematic review found that the factors associated with both depression and anxiety disorders in PD include PD onset and duration, disease stage, frequency and

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severity of motor symptoms, motor fluctuations, and autonomic symptoms [8]. Although depression and anxiety frequently co-occurred in the same patients, they were associated with different factors – PD patients with depressive symptoms had lower cognitive function and increased motor severity as measured by multiple indices, whereas those with anxiety symptoms were more likely to be younger and female [7]. However, the majority of these studies employed a cross-sectional design.

We therefore undertook this prospective longitudinal study to understand the prevalence and course of depression and anxiety symptoms; and to compare their longitudinal relationships with demographic, clinical (motor and non-motor), and pharmacological factors.

2. Methods

2.1. Participants and setting

This is a prospective longitudinal study of participants consecutively recruited from outpatient movement disorders clinics at a tertiary neurology centre between August 2011 and March 2012. Participants with a diagnosis of probable 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, PD subtype (tremor dominant, postural instability/gait difficulty or indeterminate) was determined from the Unified Parkinson's Disease Rating Scale (UPDRS) Part II and III, according to the method proposed by Jankovic and colleagues [9]. The presence of dyskinesias and motor fluctuations was determined using items 32 and 39 of the UPDRS Part IV (complications of therapy).

At baseline and at 6-monthly intervals for a period of 18 months, depression and anxiety were assessed using the Geriatric Depression Scale (GDS [10]; 15 items with a binary response) and the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS 'A' [11]; 7 items with a four-level scale) respectively. The GDS is well validated in the PD population and recommended for use by the Movement Disorders Society to screen for symptoms of depression [12]. The HADS was one of six rating scales classified as 'suggested' for assessment of anxiety in PD by a Movement Disorder Society task force [3]. Apathy, excessive daytime sleepiness, and functional disability were also assessed using the Starkstein Apathy Scale (SAS [13]), the Epworth Sleepiness Scale (ESS [14]), and the modified Barthel Index [15] respectively. Motor symptom severity was evaluated by movement disorder specialists using the UPDRS Part III and Part V (modified Hoehn and Yahr staging). 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.

2.3. Medication

Doses of dopaminergic medication were converted to levodopa equivalent doses using a previously developed formula [16]. Use of antidepressants and/or anxiolytics was coded as a binary variable (yes/no).

2.4. Statistical analysis

The distributions of demographic and baseline clinical characteristics were examined using appropriate descriptive statistics. We first examined the distribution of clinically relevant symptoms of depression and anxiety at baseline, defined by ≥4 on the GDS [17] and ≥8 on the HADS 'A' [11] respectively. To estimate the longitudinal change in symptom severity of depression and anxiety during the study period, univariate Generalised Estimating Equations (GEE) analyses were applied to regression analyses with repeated measures [18], including GDS and HADS 'A' scores as the dependent variable and number of visits as the independent variable in the models.

Univariate and multivariate GEE analyses were conducted to analyse the association of the following factors with the population-averaged GDS and HADS 'A' scores over the study period:

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

All statistical analyses were performed using IBM SPSS Statistics version 22 and geepack package in R version 3.1.2. All analyses were two-sided and results were considered statistically significant if $p < 0.05$.

3. Results

3.1. Participant characteristics at baseline

Ninety-two patients participated in this study. Of these, 89 patients completed at least 3 out of 4 visits and were included in the final analyses. The patients included were aged between 46.4 and 81.1 years, were primarily male (73%) and had mild PD, with a Hoehn and Yahr stage of 2.5 or less and low UPDRS-III scores ($M = 18.83$, $SD = 7.75$, Table 1). Clinically significant levels of depression (≥4 on the GDS [17]) and anxiety (≥8 on the HADS 'A' [11]) were present in 34.8% ($n = 31$) and 21.3% ($n = 19$) of our sample respectively. 13.5% of patients had clinically significant levels of both depression and anxiety, while 21.3% had isolated depression and 7.9% had isolated anxiety. Despite this, only 6 patients (6.74%) were on psychiatric medications (antidepressants and/or anxiolytics).

3.2. Course of depression and anxiety

Results from univariate GEE analysis with visit number as the independent variable indicated that depression (as measured by GDS scores) was relatively stable ($p = 0.52$, Fig. 1a, Table 1). In contrast, the severity of anxiety symptoms, as measured by mean HADS 'A' score, decreased significantly over time ($p = 0.004$, Fig. 1b, Table 1). Results were similar when adjusted for use of psychiatric medications.