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A longitudinal study of non-motor symptom burden in Parkinson's disease after a transition to expert care

Kumar M. Prakash [a, c, d, e, *], Nivedita V. Nadkarni [b, e], Weng-Kit Lye [b, e], Ming-Hui Yong [a, c], Lai-Mun Chew [a, c, d], Eng-King Tan [a, c, d, e]

[a] Department of Neurology, Singapore
[b] Centre for Quantitative Medicine, Singapore
[c] Singapore General Hospital, Singapore
[d] National Neuroscience Institute, Singapore
[e] Duke-NUS Graduate Medical School, Singapore

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ABSTRACT

Background: Non-motor symptoms (NMS) are common among patients with Parkinson's disease (PD) however little is known about their progression in terms of severity or burden after referral to expert care.
Objective: This study was aimed to establish the progression of NMS burden in PD patients after referral to tertiary healthcare centre and factors affecting it.
Methods: Newly referred PD patients were prospectively enrolled and follow-up for up to 18 months. Non-motor symptoms scale (NMSS) was used to evaluate the burden of non-motor symptoms.
Results: There was a significant median reduction of total NMS burden over the follow-up period. Similarly all NMS domains except domains 2 (sleep/fatigue), 3 (mood/cognition), 6 (gastrointestinal) and 7 (urinary) showed significant median reduction of scores. In the univariate regression analysis, Hoehn & Yahr staging, disease duration, visit, Schwab & England Activities of Daily Living score and UPDRS motor scores were individually predictive of change in total NMS burden. However, in the multivariable regression analysis only the latter three were significantly predictive of change in the total NMS burden.
Conclusion: There was a significant reduction of total NMS burden over the study period. The severity of motor and activity of daily living impairments as well as subsequent visit were the best predictors of NMS change.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and causes significant motor and non-motor problems [1–4]. Some of these problems may progress over time and significantly affect the quality of life, caregiver burden, health resource use and rates of institutionalization among PD patients [5–8].

Progression of motor symptoms and factors affecting it has been well studied and known. For example, age at onset, gender, baseline motor score, concomitant dementia as well as physical subtype of PD (tremor dominant versus akinetic-rigid type) has been known to significantly affect the progression of motor symptoms severity [9–12]. However there is limited knowledge about the progression of non-motor symptoms (NMS) burden and factors affecting it. Previous studies have elucidated on the change of NMS occurrence [3,13–15] over time however, to the best of our knowledge, there has not been any studies looking at the change of NMS burden that takes account of the frequency and severity of various NMS.

In addition, it is well known that drug therapy (particularly dopaminergic therapy) may significantly improve the motor symptoms especially in the early stages of disease [16,17]. However there is limited knowledge about similar findings with respect to the NMS burden in PD. In the last decade, there has been increasing awareness about the non-recognition NMS among healthcare professionals, patients and caregivers [18–20]. However little is known on the impact of improved recognition and therapy on the NMS burden.

* Corresponding author. Department of Neurology, Academia Level 4, Singapore General Hospital, 20 College Road, 169856, Singapore.
E-mail address: gnrpk@sgh.com.sg (K.M. Prakash).

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The primary aim of this observational study was to establish the progression of NMS burden in PD patients that are referred to a tertiary healthcare centre. In addition, we aimed to elucidate on the factors associated with the progression of these symptoms.

2. Methods

2.1. Patient eligibility criteria and recruitment

A total of 199 idiopathic PD patients, diagnosed according to the UK PD Brain Bank criteria [21], were prospectively recruited with consent from the movement disorders clinics in Singapore General Hospital (SGH), a tertiary healthcare centre. Patients with significant cognitive impairment as defined by Elderly Cognitive Assessment Questionnaire (ECAQ) [22] score of 5 points or less were excluded. Those with severe debilitating conditions (e.g. renal failure requiring dialysis, severe heart failure, liver failure or other terminal illness) were also excluded.

2.2. Study outcomes and other assessments

Demographic data was obtained from all recruited patients. Non-motor symptoms were assessed using the Non-Motor Symptoms Scale (NMSS) [23,24]. This validated scale evaluates 30 NMS which are grouped into 9 domains (cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucination, attention/memory, gastrointestinal, urinary, sexual function and miscellaneous). Each item in the NMSS rates a NMS according to its severity (scored from 0 to 3) and frequency (scored from 1 to 4) over the past month. The frequency is multiplied with the severity ratings to give a final score of the burden of the NMS. The sum of all NMS burden within a domain gives a domain score and the sum of all domain score gives the total NMS burden in a patient. The NMS burden is the primary outcome of interest to understand the progression of PD in the context of non-motor symptoms.

PD patients also were assessed for motor disabilities using the Part III (motor) Unified Parkinson's Disease Rating Scale (UPDRSm) [25] and the modified Hoehn and Yahr (H&Y) staging scale [26]. The ability to perform daily activities in terms of speed and independence was assessed using the Schwab and England Activities of Daily Living (S&E) score. The levodopa equivalent daily dose (LDD) was calculated according to standardized formulae: ([levodopa (mg)] + [Controlled release levodopa (mg) × 0.75] + [levodopa doses taken together with entacapone (mg) × 1.33] + [pramipexole (mg) × 100] + [ropinirole (mg) × 20] + [piribedil (mg) × 1] + [bromocriptine (mg) × 10]) [27].

The assessments were carried out face to face on the same day of specialist clinic visit at baseline and follow-up visits. The interval period between baseline and follow-up visits ranged from 12 to 18 months. All subjects were provided with symptomatic therapy (with either pharmacological or non-pharmacological therapy or in most cases both) if deemed necessary by the treating specialist. The pharmacological agents included dopaminergic agents such as levodopa (regular, controlled release as well as entacapone combination preparation) and dopamine agonists (e.g. bromocriptine, peribedil, pramipexole and ropinirole), analgesics (orally taken and locally applied), stool softeners, mood-stabilisers and others. And the non-pharmacological treatment included physiotherapy, occupational therapy, dietary change, speech therapy, cognitive behaviour therapy, counselling and education. Some patients with more significant non motor problems were also referred to other specialties (e.g. psychiatry, gastroenterology, urology and cardiologist) for further evaluation and co-management.

The baseline characteristics are as tabulated in Table 1.

2.3. Statistical analysis

Continuous data were summarized as mean (standard deviation) or median (inter quartile range) for symmetrically distributed and skewed data, respectively. Categorical data were summarized by frequency (%). Pearson's correlation coefficient was calculated to assess the correlations between the primary outcome variable (i.e. the total NMS burden) and total UPDRSm, LDD as well as the H&Y staging at baseline and follow-up visits. The Wilcoxon signed rank test was performed to test whether the median difference of the total NMS burden and the individual NMS domain scores between the two visits were significant. This was used because the distribution of the NMS scores both overall and by domain was skewed and therefore it is more meaningful to compare the median difference by visit rather than the mean difference. A linear mixed effects model was fit to assess the change in total NMS burden scores from baseline to follow-up visits with visit within subject as a random effect and other covariates as fixed effects. Large sample theory (the central limit theorem) ensures that deviation from the assumption of normality does not affect the robustness of parameter estimates. The mixed-effects model allows all non-missing data to be used in the analysis without imputation. However, to ensure unbiased estimates of the difference in means, it is required that the distribution of the data missingness conditional on the variables in the model and the observed data does not depend on the values of the missing data, so that the data is missing-at-random (MAR). This is a common and a reasonable assumption [28]. Univariate models were run for all covariates and those covariates for which the p-value was less than 0.15 were entered into a multivariable model and stepwise selection was performed for model building. Covariates that were clinically relevant were also entered in the model even if statistical significance was not achieved. A p-value of $\leq$0.05 was defined as significant. All analyses were performed in SAS version 9.3 and R version 3.0.0.

The study was approved by the Singhealth Centralized Institutional Review Board.

3. Results

A total of 147 patients completed the study. Forty-three were lost to follow-up (as they had either passed away or left to seek alternative therapy or their primary care providers for continuation of care) and four patients withdrew before completion of the assessments. The baseline demographics and assessments of the study finishers and non-finishers are shown in Table 1. A majority of them were males, of Chinese ethnicity, retirees and had attained no more than secondary level of education. More than three quarters of the patients had disease onset after the age of 50 years and were in early stages of PD (H&Y staging < 3).

At baseline, the three most prevalent NMS domains were domain 2 (sleep/fatigue; 74%), domain 7 (urinary; 67%) and domain 3 (mood/cognition; 63%). The least prevalent was domain 8 (sexual function; 14%). The median difference of the total NMS burden at

Table 1
Baseline characteristics of the PD patients.

Characteristic	Mean (SD) or median (IQR) or frequency (%)		
	Overall (N = 194)	Finisher (N = 147)	Non-finisher (N = 47)
Age	64.31 (10.16)	63.78 (9.76)	65.98 (11.29)
Gender (Male)	124 (63.9%)	90 (61.22%)	34 (72.3%)
Race			
(Chinese)	174 (89.7%)	134 (91.2%)	40 (85.1%)
(Malay)	9 (4.6%)	6 (4.1%)	3 (6.4%)
(Indian)	9 (4.6%)	5 (3.4%)	4 (8.5%)
(Others)	2 (1.1%)	2 (1.4%)	–
Education (Diploma or higher)	27 (15.7%)	22 (16.3%)	5 (13.5%)
Occupation (Retiree)	121 (62.4%)	88 (59.9%)	33 (70.2%)
Disease duration	5.76 (4.84)	5.79 (4.76)	5.68 (5.16)
Young onset (50 years and below)	20 (10.3%)	16 (10.9%)	4 (8.5%)
LDD	359.68 (306.69)	368.53 (304.33)	332.02 (315.66)
Total NMS burden	25.0 (13.0, 50.0)	26.0 (14.0, 50.0)	21.0 (10.0, 53.0)
Total UPDRSm	26.0 (12.0, 37.0)	25.5 (10.0, 36.0)	27.0 (14.0, 37.0)
Hoehn & Yahr stage (below 3)	152 (80.4%)	117 (82.4%)	35 (74.5%)
Schwab & England ADL score	90 (80, 90)	90 (80, 90)	90 (70, 90)

SD: Standard Deviation, IQR: Inter Quartile Range, LDD: Levodopa equivalent Daily Dose, NMS: Non-Motor Symptoms, UPDRSm: Unified Parkinson's Disease Rating Scale part III (motor), ADL: Activities of Daily Living.

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