ORIGINAL ARTICLE

The impact of non-motor symptoms on the quality of life of Parkinson's disease patients: a longitudinal study

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Background and purpose: Non-motor symptoms (NMSs) are common amongst patients with Parkinson's disease (PD); however, little is known about their influence on the health-related quality of life (QoL) over a defined follow-up period. The study was aimed to establish the impact of NMSs on the QoL of patients with PD over a 2-year follow-up period.

Method: A total of 227 newly referred PD patients were prospectively recruited between 2013 and 2014. The Non-Motor Symptoms Scale was used to evaluate NMSs burden whilst QoL was assessed with the Parkinson's Disease Questionnaire-39 items. Motor disabilities were assessed using the Part III (motor) Unified Parkinson's Disease Rating Scale (UPDRSm).

Results: The mean age was 64.37 (10.18) years; 59.9% were males and a majority (89.0%) were ethnic Chinese. Almost 65% were unemployed and 84.6% had attained no more than secondary level of education. In the univariate analysis, total NMSs burden, age, gender, subsequent visit, Hoehn and Yahr staging, disease duration and UPDRSm score were individually predictive of change in the Parkinson's Disease Questionnaire Summary Index score from baseline to follow-up visit. However, in the multivariate analysis, total NMSs burden significantly predicted the QoL scores whilst motor scores did not. Specifically, NMS domains 2 (sleep/fatigue), 3 (mood/apathy) and 5 (attention/memory) were most significantly predictive of QoL change.

Conclusion: Unlike motor disabilities, NMSs burden, in particular sleep, mood and attention, have a significant impact on the QoL of PD patients over a 2-year follow-up period.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease [1,2]. Over time, it causes progressive motor problems [3–5] that may significantly affect not only the health-related quality of life (QoL) of patients and their caregivers but also health resources and rates of institutionalization [6,7].

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Similarly there has been increasing evidence, particularly in the last decade, that the occurrence of various non-motor symptoms (NMSs) may also negatively affect the QoL of PD patients [8–17]. However, little is known about what impact the severity or burden of individual NMSs has on the overall QoL. In addition, to the best of our knowledge, there has not been any longitudinal study involving PD patients that describes the influence of NMSs burden on the QoL change over a defined follow-up period.

Also, to date, no longitudinal studies have evaluated how optimized PD therapy particularly of NMSs impacts QoL changes. This is highly relevant clinically as it will facilitate better anticipation and

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management of specific non-motor domains as the disease progresses.

To address these gaps in the current knowledge, a prospective longitudinal study was conducted over a 2-year follow-up period of patients with PD treated at our tertiary care centre with the following objectives: (i) to evaluate in detail the changes in motor symptoms, NMSs and QoL; and (ii) to identify the predictors of worsening QoL.

Methods

Patient eligibility, criteria and recruitment

This was a monocentre, observational, non-interventional, longitudinal study where a total of 227 idiopathic PD patients, diagnosed according to the UK PD Brain Bank criteria [18], were prospectively recruited with informed consent from the movement disorders clinics in Singapore General Hospital between 2013 and 2014. Patients with significant cognitive impairment as defined by an Elderly Cognitive Assessment Questionnaire [19] 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.

Study outcomes and other assessments

Demographic data were obtained from all recruited patients. NMSs were assessed using the Non-Motor Symptoms Scale (NMSS) [20,21]. This validated scale evaluates 30 NMSs that are grouped into nine domains (cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucination, attention/memory, gastrointestinal, urinary, sexual function and miscellaneous). Each item in the NMSS rates an 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 by the severity rating to give a final score representing the burden of the NMS. The sum of all NMSs burden within a domain gives a domain score and the sum of all domain scores gives the total NMSs burden in a patient. The total NMSs burden is the outcome of interest to track/quantify the progression of PD in the context of NMSs.

Quality of life was assessed by means of a Parkinson's disease-specific instrument, the Parkinson's Disease Questionnaire-39 (PDQ-39) [22]. It comprises 39 items grouped in eight domains: mobility (10 items), activities of daily living (six items), emotional well-being (six items), stigma (four items), social support (three items), cognition (four items), communication (three items) and bodily discomfort (three items). Responses were scored from a scale of 0 (never) to 4 (always). Each subscale's scores were transformed into a 0–100 scale by summing the items' raw scores, dividing by the maximum possible raw score and then multiplying by 100. A Summary Index (PDQ_SI) was obtained by calculating the mean of the eight domain scores. Higher scores reflected a poorer QoL.

Parkinson's disease patients were also assessed for motor disabilities during OFF state using the Part III (motor) Unified Parkinson's Disease Rating Scale (UPDRSm) [23] and the modified Hoehn and Yahr (H&Y) staging scale [24]. The ability to perform daily activities in terms of speed and independence was assessed using the Schwab and England Activities of Daily Living (ADL) score [25]. The levodopa equivalent daily dose (LEDD) was calculated according to standardized formulae: ([levodopa (mg)] + [controlled release levodopa (mg) $\times$ 0.75] + [levodopa doses taken together with entacapone (mg) $\times$ 1.33] + [pramipexole (mg) $\times$ 100] + [ropinirole (mg) $\times$ 20] + [piribedil (mg) $\times$ 1] + [bromocriptine (mg) $\times$ 10]) [26].

The above assessments were carried out face to face with subjects on the same days as their specialist clinic visit at baseline and subsequent follow-up visit up to 2 years (mean 22 $\pm$ 2 months). All subjects received symptomatic therapy (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 stabilizers and others. Rotigotine was not available in our centre during the study period. The non-pharmacological treatment included physiotherapy, occupational therapy, speech therapy, cognitive behaviour therapy, dietary 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.

Statistical analysis

Continuous data were summarized as mean (standard deviation) or median (interquartile range) for symmetrically distributed and skewed data, respectively. Categorical data were summarized by frequency (%). Patients were considered to have a domain-related NMS when they had at least one symptom within the NMS domain. Pearson's correlation coefficient was

calculated to assess the correlations between the primary outcome variable (i.e. the PDQ_SI score) and the total NMS score at baseline and follow-up visits. The Wilcoxon signed rank test was performed to test whether the median differences of the PDQ_SI score and the individual PDQ domain scores between the two visits were significant. This was used because the distribution of the PDQ scores (both Summary Index and by domain) was skewed and therefore it was more meaningful to compare the median difference by visit rather than the mean difference. To calculate the NMS domain prevalence, any domain score of greater than zero was considered as presence of the corresponding NMS. A linear mixed effects model was fitted to assess the change in PDQ_SI scores from baseline to follow-up visits with visit nested within subject as a random effect and other covariates as fixed effects. Univariate models were run for all covariates and those covariates for which the P value was less than 0.05 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 ≤ 0.05 was defined as significant. All analyses were performed in SAS version 9.3 and R version 3.0.0 (SAS Inc, Cary, NC, USA).

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

Results

A total of 43 patients did not complete the study (due to death, withdrawal or follow-up defaults). The baseline demographics were not significantly different between the study finishers and non-finishers. A majority of the patients were males, of Chinese ethnicity, unemployed and had attained no more than secondary level of education. Most were in early stages of disease and had onset after the age of 50 years. Twenty-six per cent had motor fluctuation and/or dyskinesia. Table 1 illustrates the baseline characteristics of the study patients. There was no significant difference at baseline between males and females, higher and lower educated as well as young- and older-onset patients for NMS, motor and QoL scores. However, when compared to employed patients, the unemployed ones had significantly higher median values of PDQ_SI (15.4 vs. 11.4, $P = 0.041$), NMSs burden (31.0 vs. 21.0, $P = 0.027$) and UPDRSm (30.0 vs. 22.5, $P = 0.012$).

The three most prevalent NMS domains at baseline were domain 2 (sleep/fatigue; 83%), domain 7 (urinary; 70%) and domain 9 (miscellaneous; 69%). The most prevalent at the final visit were domain 7 (88%), domain 2 (86%) and domain 3 (mood/apathy; 80%). On the other hand, domains 1 (cardiovascular), 4 (perceptual problems/hallucination) and 8 (sexual function) were the least prevalent domains at baseline and final visits.

Table 1 Baseline characteristics of the PD patients ($n = 227$)

Characteristics	Median (IQR) or mean (SD) or frequency (%)
Age	64.37 (10.18)
Gender (male)	136 (59.9 %)
Race (Chinese)	202 (89.0 %)
(Malay)	10 (4.4 %)
(Indian)	13 (5.7 %)
(Others)	2 (0.9 %)
Education (diploma or higher)	35 (15.6 %)
Occupation (none)	147 (64.8 %)
Disease duration (years)	5.80 (4.86)
Young onset (50 years and below)	24 (10.6 %)
LEDD	352.45 (305.36)
Total NMSs burden	25.0 (13.0, 51.0)
Total UPDRSm	27.0 (11.0, 36.0)
Hoehn and Yahr stage (below 3)	184 (81.1%)
Schwab and England ADL score	90 (80, 90)
PDQ_SI	12.3 (4.6, 27.6)

ADL, Activities of Daily Living; IQR, interquartile range; LEDD, levodopa equivalent daily dose; NMSs, non-motor symptoms; PDQ_SI, Parkinson's Disease Questionnaire Summary Index; UPDRSm, Unified Parkinson's Disease Rating Scale Part III (motor).

The PDQ_SI score correlated positively with the total NMSs burden at baseline ($r = 0.57$, $P < 0.001$) and final visits ($r = 0.71$, $P < 0.001$). Similarly, there was also a positive correlation between the PDQ_SI score and the UPDRSm score at baseline ($r = 0.32$, $P < 0.001$) and final visits ($r = 0.61$, $P < 0.001$). Over the follow-up period, there was a significant increment of motor scores (median difference 4.0, $P < 0.001$) as well as increment of LEDD (mean difference 70.52, $P < 0.001$). However, the total NMSs burden had a relatively modest but significant reduction (median difference 1.0, $P = 0.017$) (Table 2). With regard to QoL, there was a significant increment of PDQ_SI score over the follow-up period (median difference 3.2, $P = 0.004$). Domains 3 (emotional well-being), 6 (cognition) and 1 (mobility) had the highest median increment (8.3, $P < 0.001$; 6.3, $P < 0.001$; 2.5, $P = 0.007$, respectively) (Table 2).

In the univariate analysis, total NMSs burden, age, gender, subsequent visit, LEDD, H&Y staging, disease duration, ADL score and UPDRSm score were individually predictive of change in PDQ_SI score from baseline to final visit. For the multivariable model, the covariates included NMS scores, LEDD,

Table 2 Progression of motor and non-motor scores, Schwab and England Activities of Daily Living (ADL), quality of life (PDQ_SI) and levodopa equivalent daily dose (LEDD) of patients who completed the study

Clinical variable	Baseline mean (SD) or median (IQR)	Follow-up visit mean (SD) or median (IQR)	Magnitude of the change (follow-up − baseline) mean difference (SD) or median difference (IQR)	*P* value
Total NMSs burden	27.5 (13.5, 50.0)	26.0 (12.5, 46.0)	−1.0 (−13.5, 12.5)	0.017
Domain 1	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.068
Domain 2	6.0 (1.5, 12.5)	7.0 (2.5, 16.0)	1.5 (−3.0, 7.0)	0.004
Domain 3	3.0 (0.0, 9.0)	4.0 (1.0, 14.0)	1.0 (−3.0, 8.0)	0.016
Domain 4	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.009
Domain 5	2.0 (0.0, 4.0)	1.0 (0.0, 3.0)	0.0 (−3.0, 1.0)	0.027
Domain 6	0.0 (0.0, 4.0)	1.0 (0.0, 4.0)	0.0 (−2.0, 1.0)	0.697
Domain 7	3.0 (0.0, 8.0)	4.0 (2.0, 9.0)	1.0 (−3.0, 3.0)	0.304
Domain 8	0.0 (0.0, 2.0)	0.0 (0.0, 0.0)	0.0 (0.0, 2.0)	<0.001
Domain 9	3.0 (0.0, 8.0)	1.0 (0.0, 4.0)	−0.5 (−5.0, 1.0)	<0.001
Total UPDRSm	26.5 (9.8, 36.0)	34.0 (13.8, 41.5)	4.0 (−1.3, 10.0)	<0.001
LEDD	364.53 (305.01)	435.05 (288.20)	70.52 (214.67)	<0.001
Schwab and England ADL score	90 (80, 90)	80 (65, 90)	−10.0 (−20.0, 0.0)	<0.001
PDQ_SI	14.5 (5.5, 27.7)	15.4 (8.7, 30.6)	3.2 (−7.2, 14.6)	0.004
Domain 1	16.3 (2.5, 45.0)	16.3 (5.0, 70.0)	2.5 (−8.8, 22.5)	0.007
Domain 2	12.5 (0.0, 29.2)	10.4 (0.0, 47.9)	0.0 (−12.5, 27.1)	0.042
Domain 3	8.3 (0.0, 29.2)	20.8 (12.5, 41.7)	8.3 (−4.2, 20.8)	<0.001
Domain 4	0.0 (0.0, 18.8)	0.0 (0.0, 0.0)	0.0 (−12.5, 0.0)	0.252
Domain 5	0.0 (0.0, 8.3)	0.0 (0.0, 33.3)	0.0 (0.0, 8.3)	0.001
Domain 6	12.5 (0.0, 31.3)	25.0 (12.5, 43.8)	6.3 (0.0 ,28.1)	<0.001
Domain 7	8.3 (0.0, 33.3)	0.0 (0.0, 16.7)	0.0 (−16.7, 4.2)	0.072
Domain 8	16.7 (0.0, 33.3)	16.7 (0.0, 41.7)	0.0 (−16.7, 16.7)	0.260

IQR, Interquartile range; NMSs, non-motor symptoms; UPDRSm, Unified Parkinson's Disease Rating Scale Part III (motor).
Note: Wilcoxon rank sum test for variable presented as median (Q1, Q3); paired *t* test for variable presented as mean (SD).

disease duration, ADL score, occupation, education, subsequent visit, UPDRSm score and age. Although the H&Y staging was also individually predictive of PDQ_SI score change, it was not included in the multivariable modelling because of its collinearity with the UPDRSm score. After adjusting for the other covariates, the analysis showed that total NMSs burden, LEDD and the ADL scores significantly predicted the change in the PDQ_SI scores whilst UPDRSm did not (Table 3). Amongst the various domains of NMSs, domains 2 (sleep/fatigue) (estimate 0.30; $P = 0.008$), 3 (mood/apathy) (estimate 0.32; $P < 0.001$) and 5 (attention/memory) (estimate 0.63; $P < 0.001$) were most significantly predictive of QoL change.

Discussion

Previous NMS studies either have been cross-sectional studies or have provided longitudinal information limited only to the occurrence of various NMSs rather than the severity of NMSs over a defined follow-up period [5,27–31]. Antonini *et al*. [27] elucidated that sleep, gastrointestinal, attention/memory and skin disturbances became more prevalent during a 24-month follow-up whilst Vu *et al*. [28] reported that, in *de novo* PD patients, pain, sexual difficulties and weight change were significantly more frequent at a 2-year follow-up period. More recently, it was reported that there was a small but significant median reduction of total NMSs burden over an 18-month study period at our centre [32]. Cardiovascular, perceptual, attention/memory, sexual and miscellaneous domains had a significant reduction compared to baseline scores. In this study, it has been shown that despite having progressive motor impairment the non-motor problems provided a better prediction of the change of QoL of PD patients over a 2-year follow-up period. To our best knowledge, this is the first longitudinal study examining the impact of NMSs burden on QoL change.

The study results highlight a significant worsening of motor impairment compared to a slight reduction of total NMSs burden as well as modest change in the QoL over the follow-up period. The total UPDRSm scores increased by a median difference of 4.0 points (contributed predominantly by worsening scores of limb tremor, bradykinesia and rigidity) as opposed to the median reduction of total NMSs burden by 1.0 point over the follow-up period. In addition, whilst both motor symptoms and NMSs correlated positively

Table 3 Linear mixed model analysis: summary of potential clinical factors on PDQ_SI (dependent variable)

	Univariate analysis		Multivariable analysis	
Variable	Estimate	*P* value	Estimate	*P* value
Total NMSS	0.41	<0.001	0.27	<0.001
Domain 1	2.34	<0.001	0.10	0.782
Domain 2	1.24	<0.001	0.30	0.008
Domain 3	0.85	<0.001	0.32	<0.001
Domain 4	1.61	<0.001	0.31	0.144
Domain 5	1.81	<0.001	0.63	<0.001
Domain 6	1.51	<0.001	−0.13	0.524
Domain 7	0.59	0.002	0.002	0.986
Domain 8	2.55	0.003	0.72	0.235
Domain 9	1.17	<0.001	0.37	0.076
Schwab and England ADL Scale	−0.62	<0.001	−0.41	<0.001
LEDD	0.02	<0.001	0.006	0.006
UPDRSm	0.61	<0.001	0.07	0.195
Disease duration	1.12	<0.001	−0.05	0.696
Occupation (yes versus no)	−10.46	<0.001	−1.94	0.206
Gender (female versus male)	4.61	0.024	1.92	0.093
Education (lower versus higher)	5.36	0.051	−1.29	0.391
Age	0.26	0.014	−0.10	0.256
Visit (final versus baseline)	6.30	0.004	2.41	0.092
Hoehn and Yahr stage (<3 vs. ≥3)	−20.81	<0.001		

ADL, Activities of Daily Living; LEDD, levodopa equivalent daily dose; NMSS, Non-Motor Symptom Score; PDQ_SI, Parkinson's Disease Questionnaire Summary Index; UPDRSm, Unified Parkinson's Disease Rating Scale Part III (motor). The estimates are conditional on the random effect of subject with varying slopes for visit in the above model.

with QoL, the latter showed stronger correlation at baseline and final visits. These observations suggest that the overall NMSs burden has greater influence (compared to motor symptoms) on QoL changes over time.

Sleep/fatigue was not only amongst the most prevalent NMS domain but it was also the domain that most significantly predicted change in QoL over the follow-up period. However, urinary symptoms, despite being amongst the most prevalent domain, showed no significant influence on QoL change. On the other hand, mood/apathy as well as attention/memory symptoms, although less prevalent compared to the urinary domain, were significantly predictive of QoL change. These observations suggest that the higher prevalence of an individual NMS domain may not necessarily have a greater impact on the change in QoL. Apart from NMSs burden, LEDD and ADL (both of which changed significantly over 2 years) also independently predicted change in QoL over the follow-up period. The exact reasons for the findings are not entirely known but it is presumed that dopaminergic strategies and declining independence of ADL may have a direct impact on QoL changes.

It was found that cardiovascular and perceptual problems/hallucination domains were least prevalent or burdensome throughout the observation period. This is not surprising as our patients were mostly in the early stages of PD and these symptoms appear much later in the disease course. Similarly sexual symptoms also did not appear to have a significant impact on our study patients, in keeping with other studies involving Asian patients [9, 13, 14, 17]. It is not entirely clear if this is a true reflection or simply due to the fact that Asians are less forthcoming to discuss these symptoms.

In our study, unemployed PD patients had significantly worse motor and non-motor impairment as well as QoL compared to working patients. Most unemployed patients in Singapore are relatively older, retired and have a more sedentary lifestyle compared to the working group and perhaps these two factors may have an impact on the severity of symptoms that they experience which ultimately affect their QoL.

This study had several limitations. First, the NMSS scale relies on the subjective perception of symptom severity by subjects rather than objective diagnostic criteria. However, it allowed us to assess a wide range of symptoms in a reasonable amount of time and minimize responder fatigue. Secondly, the exclusion of PD patients with significant cognitive impairment (which is also associated with certain NMSs, such as apathy, hallucinations and depression) prevents us from making conclusions about this subpopulation of patients. Apart from that, our subsequent follow-up period was relatively wide (18–24 months) although the percentage who visited at the 18-month interval was small (2%). Finally, it is acknowledged that our study lacks normal controls to assess differences with PD patients. However, the main aim of our study was to prospectively evaluate the impact of NMSs burden on the QoL of patients with PD who were referred to our centre.

In conclusion, NMSs burden, in particular sleep/fatigue, mood/apathy and attention/memory, have significantly greater impact on the change in QoL of PD patients over a 2-year follow-up period. Therefore greater emphasis should be placed on better recognition, reporting and management of NMSs in addition to motor symptoms to improve the overall QoL of patients with PD.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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