Original Article

Prevalence of Non-motor Symptoms in Parkinson's Disease and Its Impact on Quality of Life in Tertiary Care Center in India

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Abstract

Context: Parkinson's disease (PD) is a neurodegenerative disease characterized by traditional motor features. Non-motor symptoms (NMS) are also seen in PD, which inevitably emerge through the disease progression and are often under-recognized and untargeted. **Aims:** We studied the prevalence of NMS in PD and their impact on health-related quality of life (HRQoL). **Materials and Methods:** A cross-sectional observational study from January 2017 to July 2017 of PD patients (n = 100) was done. NMS and HRQoL are measured using NMS scoring scale; PD questionnaire-39 and Hoehn and Yahr scale, respectively. Motor symptoms were assessed using scales for outcome in Parkinson's disease (SCoPA) - motor scoring scale. **Statistical Analysis:** Descriptive statistics calculated for NMS' prevalence. Continuous variables were assessed by two-tailed t-test and discrete and categorical variables by chi-square test. Multiple linear regression analysis was done among scoring scales to identify the influence on 39-item Parkinson's disease questionnaire (PDQ-39) scoring scale. All statistical data collected are analyzed with SSPS software version- 20 for windows. **Results:** In 100 study population, 66 were males and 34 females. The mean age was 68.35 years and median onset of duration of PD was 3.49 with 64.6% on treatment. Fatigue, pain, and lightheadedness were more prevalent NMS with 78%, 75%, and 69%, respectively. With regression analysis, strongest predictor was NMSS score (P = 0.000), with each unit increase, it is associated with nearly 0.65 increase in PDQ-39 score. **Conclusion:** Though motor symptoms define the disease, NMS have a larger impact on HRQoL in PD and on caregiver's life. Understanding the pattern and effect of NMS is needed for targeted treatment strategies.

Keywords: Hoehn and Yahr scale, non-motor symptoms, non-motor symptoms scoring scale, Parkinson's disease, PD questionnaire-39 items, scales of outcome.

Introduction

Parkinson's disease (PD) is a neurodegenerative disease characterized by classic motor symptoms, namely rigidity, resting tremor, bradykinesia, and postural instability. It is ranked as the second most common degenerative disease worldwide after Alzheimer's disease.[1] Clinically, it has heterogenous motor and non-motor manifestations, which have significant impact on both patient and caregiver. Non-motor symptoms (NMS) of PD are a concealed entity which is often unattended. They are considered as prodromal symptoms which start in the subclinical phase of PD or may inevitably emerge through the progression of the disease in association with motor symptoms.[2] NMS observed in PD are briefed out in Table 1.[3] Among the NMS, anosmia, rapid eye movement sleep behavior disorders, and mood disorders occur as premotor symptoms. Others include significant weight loss or gain, fatigue, depression, fear, anxiety, and impulsive behaviors, which affect at any stage of the disease. Cognitive impairment, apathy, and dysautonomia are considered to occur in late onset of the disease. PD is a synucleinopathy with a hallmark feature of deposition of Lewy bodies in neurons, presynaptic terminals, and glia. These deposits not only accumulate in basal ganglia but also extensively in other areas such as an olfactory bulb, retina, sympathetic and parasympathetic ganglia, skin, and salivary glands causing impairment of dopaminergic and non-dopaminergic neurons, contributing to the occurrence of NMS.[4] Prevalence of PD in Asian countries is about 15–119 per 100,000 and incidence ranges from 10 to 20 per 100,000. Here, we assessed the prevalence of NMS in PD and their impact on the morbid illness of the disease. Studies regarding the pattern of NMS, time of occurrence, and its impact on affected individuals need limelight to assess their contribution to the morbidity of the disease.[5,6] This study was considered as first one from Tamil Nadu and very few studies have been reported from India.

Subjects and Methods

The study is based on a prospective collection of data of patients (n = 100) diagnosed as PD defined according to

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Table 1: Non-motor symptoms in Parkinson's disease

Sensory abnormalities	Impairment of olfaction
	Vision disturbances (reduced contrast sensitivity, impaired color discrimination, convergence insufficiency, and dry eye syndrome)
	Abnormal pain sensitivity
Neuropsychiatry and cognitive manifestations	Depression
	Anxiety and panic attacks
	Apathy, anhedonia, and executive dysfunction
	Fear
	Dementia
	Psychosis, delusions, and hallucinations
	Dopamine dysregulation syndrome
	Impulse control disorders like punding
	Fatigue
Autonomic disturbances	Gastrointestinal: Constipation, dysphagia and gastroparesis, drooling of saliva, impaired gastric emptying
	Cardiovascular: Orthostatic hypotension (also include post prandial and nocturnal hypotension)
	Urinary disturbances: urgency, frequency, nocturia (detrusor overactivity)
	Reproductive system: Sexual dysfunction (erectile dysfunction, premature ejaculation, difficulty in reaching orgasm)
	Thermoregulation: paroxysmal drenching sweats, heat or cold intolerance
Sleep	Rapid eye movement sleep behavior disorder
	Restless leg syndrome
	Insomnia
	Excessive daytime sleepiness
	Sleep-disordered breathing

UPDRS criteria,[7] attending as OPD/as inpatient meeting the inclusion and exclusion criteria are taken into the study.

Inclusion criteria included the following: age >18 years and who were able to provide signed informed consent. Exclusion criteria included: Parkinson plus diseases; structural nervous system lesions causing similar symptoms; concomitant severe systemic illness, such as cardiac failure, hepatic failure, renal failure, severe arthritis, and other related disorders causing hindrance to clinical assessment; interfering with assessment or inability to provide informed consent – blindness, heard of hearing, severe speech impairment, and severe dementia.

We obtained ethical clearance from the institution PSG Institute of Medical Sciences & Research, recognized by The Strategic Initiative for Developing Capacity in Ethical Review (SIDCER). We took written informed consent from study population and prepared a proforma for data collection. Demographic data, such as name, age, sex, education, risk factors, duration of disease, and treatment for disease taken, were collected according to the proforma. We did mini-mental status examination and also assessed under language, orientation, registration, attention, and recall. Score <21 were excluded from the study. The motor assessment was done using scales for outcome in Parkinson's disease (SCoPA) – motor scoring scale, which includes three significant domains (motor examination, activities of daily living, and motor complications) with 21 subtypes in total.[6] NMS were assessed using NMS scale, which has 9 domains with a total of 30 items.[8] They include cardiovascular including falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, and miscellaneous. Each of them was scored with severity (0–3) and frequency (0–4) and multiplied. All domains are summed up to obtain the final score. Usually, NMS scoring scale will assess the burden of NMS within the past 3 months. Among different standard generic scales used in PD, we used 39-item Parkinson's disease questionnaire (PDQ-39) for assessing quality of life.[9] It included eight domains (mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort) related to both motor symptoms and NMS. We assessed with five responses – never, occasionally, sometimes, often, and always for each (which were scored 0, 25, 50, 75, and 100, respectively). The higher the score, poorer the quality of life. We analyzed the correlation between non-motor scoring scale and PDQ-39 by regression analysis and their impact on each dimension of PDQ-39. Hoehn and Yahr staging was done in patients to know the disease disability on patient health.[10]

Statistical analysis

We calculated the mean and standard deviation (SD) for quantitative demographic data and qualitative data were shown in percentage. Descriptive statistics are used to analyze NMS prevalence. Continuous variables were assessed by two-tailed *t*-test. Discrete and categorical variables were compared by Chi-square test. *P* value was significant when it was <0.05. Multiple linear regression analysis was done among scoring scales to identify the influence on PDQ 39 scoring scale depicting the quality of life in patients with PD**.** All statistical data collected are analyzed with SSPS software version-20 for windows.

Results

In the study population of 100 patients, 66 were males and 34 were females. The mean age of entire study was 68.35 years with a mean age in males was 68.58 years and in females was 67.91 years. Mean onset of the duration of illness in years was 3.49 with a SD of 3.94 with 64.60% of them were on treatment. The predominant age group among the study population was 61–70 years (n = 38), then followed by 71–80 years (n = 26) constituting more than 50% of the study population. Only two patients were found to be <50 years of age and 13 patients aged >80 years. There were 21 patients in the age range of 51–60 years.

Hoehn and Yahr staging showed the predominant population in Stage 2 to Stage 3 (n = 42) with a mean score of 2.95 (SD = 0.94). Mean motor scoring assessed by SCoPa scaling was 26.9 with SD of 14.12. Mean PDQ39 score was 1423.50 (SD = 761.27) with a range of 0–3,275. NMS was

Table 2: Descriptive statistics of the applied rating scales

	Minimum	Maximum	Mean	Std. Deviation
NMSS score	2.00	194.00	72.8100	44.16262
Cardiovascular	0.00	16.00	4.0200	3.97462
Sleep	0.00	38.00	10.8500	8.98301
Mood	0.00	57.00	21.7500	18.24766
Perceptual	0.00	65.00	2.0600	8.48507
Attention	0.00	33.00	5.9596	7.50091
Gastrointestinal	0.00	26.00	6.4400	6.43117
Urinary	0.00	36.00	10.6700	11.31911
Sexual	0.00	9.00	0.2700	1.38429
Miscellaneous	0.00	36.00	10.8500	8.11455
SCoPA - motor total score	1.00	59.00	26.9500	14.1211
Motor	0.00	36.00	18.5800	8.57667
Activities of daily living	0.00	20.00	7.5300	5.52580
Motor complications	0.00	6.00	0.8400	1.60000
PDQ-39 - total score	0.00	3275.00	1423.5000	761.26904
Hoehn and Yahr scaling score	1.00	5.00	2.9450	0.94253

NMSS=non-motor symptom scale; SCoPA=scales for outcome in Parkinson's disease; PDQ-39=39-item Parkinson's disease questionnaire; Std=standard

Table 3: Percentage of patients reporting each non-motor symptom as measured by NMSS and its correlation with PDQ-39

NMSS Domain	Group	Mean	*n*	Std. Deviation	*P**
Cardiovascular	No symptoms	1025.9	27	762.5073	0.001
	With symptoms	1570.5	73	711.12614	
Sleep	No symptoms	882.81	16	652.60496	0.002
	With symptoms	1526.5	84	739.72226	
Mood	No symptoms	654.41	17	421.05107	0.000
	With symptoms	1581	83	719.26443	
Perceptual	No symptoms	1330.7	83	744.83307	0.006
	With symptoms	1876.5	17	692.79047	
Attention	No symptoms	982.89	38	661.95108	0.000
	With symptoms	1693.5	62	692.6123	
Gastrointestinal	No symptoms	954.17	24	675.12747	0.000
	With symptoms	1571.7	76	729.69562	
Urinary	No symptoms	1502.9	26	859.22427	0.539
	With symptoms	1395.6	74	728.06224	
Sexual	No symptoms	1417.5	97	769.33552	0.658
	With symptoms	1616.7	3	467.92984	
Miscellaneous	No symptoms	1092.5	10	726.39234	0.148
	With symptoms	1460.3	90	760.00716	

NMSS=non-motor symptoms scale; PDQ-39=39-item Parkinson's disease questionnaire; Std – standard, *P significant<0.01

assessed using NMS scale. All patients had at least one NMS with a mean total score of 72.81 (SD = 44.16) and range of 2–194 [Table 2].

Cardiovascular, mood, miscellaneous, and urinary domains were more prevalent with a mean of 72.81, 21.75, 10.85, and 10.67, respectively. The rest domains included sleep (10.85), gastrointestinal (6.43), attention (5.95), perceptual (2.06), and sexual (1.34) in decreasing order of their means. Among subcategories, fatigue, pain, lightheadedness, and impaired

Table 4: Multiple linear regression model for PDQ-39

	Adjusted R^2	Standardized Beta	*t*	Significance
*PDQ-39 model	0.654			
(Constant)		−6.915	−0.044	0.965
SCoPA - motor		0.431	3.991	0.000
NMSS - total		0.291	3.717	0.000
Hoehn and Yahr staging		0.184	1.768	0.080

PDQ-39=39-item Parkinson's disease questionnaire; SCoPA=scales for outcome in Parkinson's disease; NMSS=non-motor symptoms scale

taste or smell were more prevalent NMS with 78%, 75%, 69%, and 67% prevalence rates, respectively, whereas double vision, altered interests in sex, problems having sex, and delusions were least prevalent with 1%, 1%, 3%, and 9%, respectively.

The mean PDQ-39 score was 1423.5 with SD of 761.26. Spearman's rank correlation showed almost all the subdomains of NMS except for perceptual, urinary, and sexual domains had shown a stronger correlation with PDQ-39 score than Hoehn and Yahr stage [Table 3]. NMS has a stronger association with PDQ-39 than SCoPA and Hoehn and Yahr score. Cardiovascular, mood, attention, and gastrointestinal domains have shown significant impact on motor symptoms with P value <0.01. Urinary, sexual, and perceptual have the least effect on SCoPA motor score.

Total NMS in everyone has noted the impact on PDQ-39 scores with P value of 0.01 along with motor symptoms. Health-related quality of life was predicted by multiple regression analysis. The pattern of the regression model for PDQ-39 showed Hoehn and Yahr stage, NMS, and SCoPA were independent variables. The model accounted for 65.4% (PDQ39) of the variance. With regression analysis, strongest predictor was NMSS score (P = 0.000), with each

unit increase, it was associated with nearly 0.29 increase in PDQ-39 score [Table 4 and Figure 1]. Given the regression models and the correlation coefficient between NMS and PDQ-39 domains, there is a significant influence of NMSS and SCoPA scoring scales on PDQ 39. Hoehn and Yahr scoring has not much influence on morbidity of the study population. As the NMSS score is the increased quality of life becomes worse.

Discussion

NMS of PD are a spectrum which is often unnoticed in PD individuals.[2] It occurs mostly due to lack of awareness among healthy individuals or most of the patients usually keep them unrevealed thinking them as unrelated. About 20% of PD patients have NMS as presenting symptoms.[11] NMS have become the major disability and cause for frequent hospital admissions. It was said that among the NMS, earliest to be detected are a loss of smell, impaired rapid eye movement (REM) sleep behavior, mood disorders, and orthostatic hypotension. It is compared with a few other studies done worldwide [Table 5]. A first multicenter international cross-sectional study on NMS in PD done by Chaudhari *et al*. involving about 411 patients across the world. Nocturia, fatigue, and dribbling saliva were the most common complaints with a higher correlation between NMS and PDQ-39. This study is the first one done to analyze NMS in Southern India to the best of our knowledge.

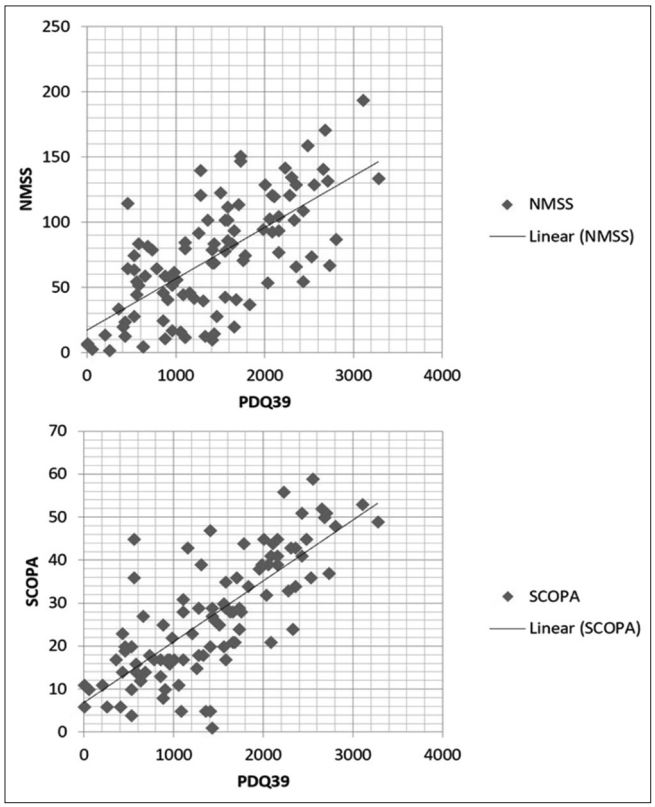

Figure 1: Scattered plots of correlations between health-related quality of life and clinical rating rates

In our study, fatigue being the most prevalent one of NMS, which was like one study done in Iran by Mehri Salari *et al*., whereas in a Taiwan study done by Weng-Ming Liu *et al*. and in an Indian study done by Ravan *et al*. where urinary symptoms were predominantly followed by constipation as most prevalent NMS.[18] A cross-sectional study of NMS done by Aaron de Souza *et al*. showed that anxiety, urinary urgency, and constipation were common NMS noted and an increased occurrence of NMS proportionate with age was seen. In this study, REM sleep behavior disorder was present in only 23% and did not show a significant effect on the study population. Urinary symptoms also did not show a significant effect on PDQ-39 scoring scales. All studies commonly showed on multivariate regression analysis; NMS have considerable correlation with PDQ-39 scores with *P* value being significant like that observed in our study with *P* value of (0.000). In contrast to the study of Martinez-Martin *et al*. and Aaron de Souza *et al*., we did not show the age and duration of disease onset as independent variables.[12]

The PD patients have been universally reported of NMS symptoms and their significant distress to quality life. The presence of NMS in a PD patient determines the quality of life and stands as the most significant challenge to treating

Table 5: Prevalence of non-motor symptoms in Parkinson's disease in major worldwide studies

Study	Mean age (years)	Mean duration (years) [standard deviation]	Study population	% Population having NMS	Prevalent non-motor symptoms	Duration of study
Present study	68.35	3.49 [3.98]	100	100	Fatigue, pain, light headedness	6 months (2017)
A.de Souza *et al*. (India)[12]	62.5	4	171	91.8	Anxiety, urgency, constipation	6 months (2012)
Weng-Ming Liu *et al*. (Taiwan)[13]	66.1	6.11 [4.13]	210	98	Nocturia, constipation, urgency	11 months (2014)
Martinez-Martin P *et al*. (Spain)[6]	64.48	8.07 [5.75]	411	100	Nocturia, fatigue, dribbling of saliva	-
Mehri Salari *et al*. (Iran)[14]	62	6.1 [5.0]	81	100	Fatigue, constipation, anxiety	1 year (2014)
Bugalho P *et al*. (Portugal)[5]	77.3	7.6 [6.3]	125	100	Insomnia, depression, urgency	1 year (2014-2015)
K.M.Prakash *et al*. (Singapore)[15]	64.37	5.8 [4.86]	227	100	Sleep, fatigue, mood, apathy	1 year (2013-2014)
Tie-mei Zhang *et al*. (China)[16]	61	3.9 [4.6]	1119	70.8	Smell disturbances, depression, sleep	4 years 7 months (2011-2015)
Tibar H *et al*. (Morroco)[17]	60.77	6 [3.5]	117	100	Urinary, sleep, gastrointestinal	-

physicians. They are suboptimal in presentation and often left untreated and missed. Identifying the specific patterns of NMS occurrence concerning time of motor symptoms has been pivotal in understanding the evolution and its contribution to disease morbidity of PD individuals. Routine assessment of NMS by using simple questionnaires like NMS Quest and their impact on life by using PDQ-8, PDQ-39, and Hoehn and Yahr scoring can give us a quick snapshot of NMS burden of each patient during last month. Drawbacks in this study are small sample size restricted to a specific geographical region. More collaborative studies are to be considered to understand NMS in more detail and their impact on the affected individual.

Conclusion

NMS forms an integral part of PD from premotor stage to end stage. They have more significant impact and compromise the quality of life, which urges the need to recognize and uncover at the earliest possible. We need to accomplish a multidisciplinary team and a holistic approach for identification of NMS in PD. Evidence-based need for treatment of NMS in PD is still an unmet need and needs to be enlightened while considering treatment strategies.

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Conflicts of interest

There are no conflicts of interest.

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