

Assessment of Non-Motor Symptoms of Parkinson's Disease and Their Impact on the Quality of Life: An Observational Study

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Abstract

Background: During the past decade the view of Parkinson's disease (PD) as a motor disorder has changed significantly and currently it is recognized as a multisystem disorder with diverse non-motor symptoms (NMS). **Aims:** The present study aimed to evaluate and characterize the NMS and study their impact on quality of life (QoL) in a PD patient cohort. **Material and Methods:** This was a cross-sectional study where 92 PD patients fulfilling the UK Parkinson's disease society brain bank criteria were enrolled from a movement disorder clinic. All patients were evaluated using unified Parkinson's disease rating scale, non-motor symptoms scale (NMSS) for the non-motor symptoms, and Parkinson's disease questionnaire-39 (PDQ-39) for the QoL. The impact of NMS on QoL was assessed statistically. **Results:** A total of 92 patients were enrolled with a mean age of 55.40 ± 7.37 years, mean age of onset of disease 51.62 ± 6.38 years, and mean disease duration of 3.78 ± 1.54 years. Type of disease was akinetic rigid variant in 29.3% (n = 27), tremor predominant type in 36.9% (n = 34), and mixed type in 33.6% (n = 31). Mean Hoehn and Yahr stage was 2.12 ± 0.54 . In the NMSS, most common symptom was sleep and fatigue (83%), followed by urinary tract symptoms (63%), mood and cognition (51%), cardiovascular symptoms and falls (43%), gastrointestinal tract symptoms (38%), and sexual function (33%). Univariate analyses showed that all NMS domains had a significant correlation with PDQ-39 with $P < 0.01$. **Conclusion:** Our study shows that NMS in PD are fairly common and significantly impact the QoL.

Keywords: NMSS, Non-motor symptoms, PDQ-39, Parkinson's disease, UPDRS

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease with evolving complex pathophysiology. Even after its been two centuries since the first description of PD, the disease concepts and treatment are still evolving.^[1] PD is defined mainly by motor symptoms bradykinesia, rigidity, rest tremors, loss of postural reflexes, flexed posture, and freezing. From being a motor disorder, the paradigm has now shifted to non-motor symptoms (NMS) with the involvement of the non-dopaminergic system. These NMS are often neglected, may antedate the diagnosis of PD by even a decade, and adversely affect the quality of life (QoL). The wide range of NMS includes sleep disturbances, urological dysfunction, autonomic manifestations, and cognition and mood changes. Other rare symptoms like social and sexual dysfunction also impact the patient's QoL.^[2] While most PD patients are troubled by these symptoms in the advanced stage, some NMS cause a significant burden in management even in the early part of the disease. Neuropsychiatric and behavioral features in the advanced stages cause a great amount of burden to the caregiver. Hence their timely recognition and management assume great importance to preserve the QoL of patients.

Although recently some studies have given importance to NMS in developing countries, the main focus is predominantly on motor symptoms with the current treatment guidelines concerned about motor symptoms due to limited knowledge

about NMS. In the present study, we aimed to evaluate the prevalence of NMS and its impact on health-related quality of life (HRQoL) aspect in patients with PD.

MATERIALS AND METHODS

Study design

The present study is a prospective, cross-sectional, hospital-based, single-center study at a tertiary care center in the northern part of India.

Study population

All consecutive patients of idiopathic Parkinson's disease (IPD) according to UK Parkinson's disease society brain bank criteria presented to the outpatient department and movement disorder

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clinic of a tertiary care University Hospital enrolled, from July 2017 to June 19. Patients with atypical forms of PD, secondary PD, other neurodegenerative diseases, and patients with significant cognitive impairment interfering with answering the questionnaire were excluded from the study depicted as a flowchart [Figure 1].

Data collection

The clinical and demographic details were recorded, and all patients underwent unified Parkinson's disease rating scale-1 [(UPDRS-1) (mentation, behavior, and mood)], UPDRS-2 (activities of daily living), UPDRS-3 (Motor symptoms), and UPDRS-4 (motor fluctuations and dyskinesias) consisting of 42 items over the severity of 0–4.^[3] Hoehn and Yahr scale was used to assess the stage and severity of PD patients.^[4] NMS were assessed using the non-motor symptom severity scale (NMSS), which consists of 30 items in 9 domains. They are as follows cardiovascular (2 items), sleep/fatigue (4 items), mood/apathy (6 items), perceptual problems and hallucination (3 items), attention/memory (3 items), gastrointestinal (GI) tract (3 items), urinary (3 items), sexual dysfunction (2 items), miscellaneous (4 items for pain, taste or smell, weight change, and excessive sweating). Each item in NMSS is scored as a multiple of severity (0–3) and frequency (0–4), we calculated the mean score of each domain for comparison.^[5] Patients were examined in the ON state.

The HRQoL of the patients was evaluated using the Parkinson's disease questionnaire-39 (PDQ-39) scale.^[6] PDQ-39 questionnaire has 39 items covering eight discrete dimensions: mobility (10 items), activities of daily living (6 items), emotional well-being (6 items), social stigma (4 items), social

support (3 items), cognition (4 items), communication (3 items), and bodily discomfort (3 items). The score for each item ranges from 0 to 4 as 0 is never, 1 is occasional, 2 is sometimes, 3 is often, and 4 is always. The mean was calculated for every 8 domains and compared. Ethical clearance for the study was obtained from the Institutional Ethical Committee (EC/269). Informed consent was obtained from every patient.

Statistical analysis

Clinical features and demographic data were analyzed using parametric and non-parametric tests. Statistical package for social sciences version 23.0 software was used for analysis. All quantitative data were expressed as mean \pm standard deviation (SD) or median with an interquartile range. Categorical data were expressed in numbers and percentages. The comparison between NMS prevalence and clinical phenotypes was done using logistic regression. The correlation between PDQ-39 and clinical variables was determined by univariate analysis, using the Spearman test for quantitative variables.

RESULTS

In the present study, we enrolled 92 patients with IPD after using strict inclusion and exclusion criteria. The mean age of patients was 55.40 ± 7.37 years and the mean disease duration was 3.78 ± 1.54 years. Males were 72% with male: female ratio of 2.9:1.1.

Right-sided disease onset was seen in 50% of patients, left-sided disease onset was seen in 46.7% of patients, and bilateral disease onset was seen in only 3.2% of patients. Out of 92 patients, 36.9% ($n = 34$) had tremor predominant PD, 29.3% had akinetic rigid variant, and 33.6% had a mixed variant of PD. UPDRS-1 with a mean score of 4.32 ± 2.06 , UPDRS-2 with the mean score of 12.58 ± 7.05 , UPDRS-3 with the mean score of 13.87 ± 7.89 , and UPDRS-4 the mean score was 4.88 ± 2.31 . Hoehn and Yahr mean score was 2.12 ± 0.54 .

NMS in PD patients

We divided NMS as per domains described in the NMSS scale and assessed for frequency and severity of symptoms in PD patients. All patients ($n = 92$) had at least one NMS during the assessment. Mean NMS scores with SD and percentages in our patients were summarized in Table 1.

Correlation between dimensions of NMSS with various disease characteristics

There was a significant correlation between total NMS scorings and age, stage of the disease, duration of the disease, and individual UPDRS scorings. We did not find a significant correlation between the age of the patients and NMSS [Table 2].

Correlation of Individual NMSS dimensions with UPDRS scores

We found a significant correlation between individual NMSS domains and UPDRS scores in the present study except for sexual function and UPDRS-2 scores [Table 3].

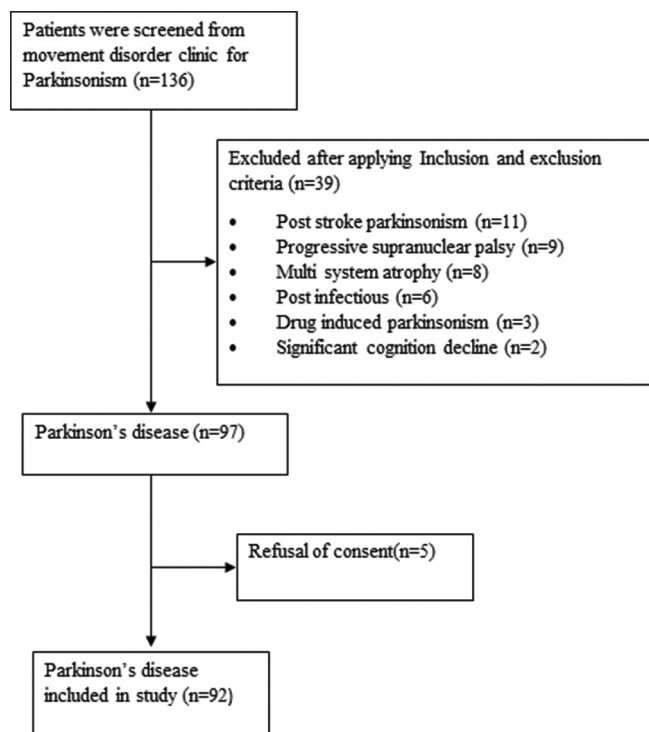


Figure 1: Flowchart showing patient selection for the study

Table 1: NMSS domains and mean scores of PD patients

NMSS domains	Minimum	Maximum	Mean±SD
Cardiovascular + falls	1	12	5.20±2.409
Sleep + fatigue	1	22	7.65±3.669
Mood/cognition	2	42	11.28±7.456
Perceptual problems/hallucination	1	16	6.60±2.762
Attention/memory	1	26	7.15±4.123
GI tract	1	18	6.30±3.131
Urinary	1	24	6.67±3.612
Sexual function	1	24	6.72±3.916
Miscellaneous	2	17	7.00±2.882
NMSS total	11	207	64.57±33.960

NMSS=Non-Motor Symptoms Scale; PD=Parkinson's Disease;
GI=Gastrointestinal

Table 2: Correlation values dimensions of NMSS with various disease characteristics

Parameters	Total NMSS score
Age	<i>P</i> : 0.57 Spearman's Rho: 0.092
Stage of disease	<i>P</i> : <0.001 Spearman's Rho: 0.720**
Duration of disease	<i>P</i> : <0.001 Spearman's Rho: 0.592**
UPDRS-1	<i>P</i> : <0.001 Spearman's Rho: 0.652**
UPDRS-2	<i>P</i> : <0.001 Spearman's Rho: 0.568**
UPDRS-3	<i>P</i> : <0.001 Spearman's Rho: 0.570**
UPDRS-4	<i>P</i> : <0.001 Spearman's Rho: 0.576**

*Correlation is significant at the 0.05 level (2 tailed). **Correlation is significant at the 0.01 level (2 tailed). NMSS=Non-Motor Symptoms Scale; UPDRS=Parkinson's Disease Rating Scale

HRQoL: PDQ-39

PDQ-39 was applied to all the patients in the study. Its domains were divided into four subgroups including Parkinson's symptoms (mobility, activities of daily living, and communication), systemic symptoms (bodily discomfort, cognition), social functions (social support), and emotional functions (emotional well-being, stigma). The mean total PDQ-39 score was 36.88 ± 19.36 . Individual mean scores for each subgroup are mentioned in Table 4.

Correlation between PDQ-39 and disease characteristic

In the present study, we found a significant correlation between PDQ-39 scores with the stage of the disease, duration of the disease, and total UPDRS scores. Individual UPDRS scores were correlated with PDQ-39 scores but showed a poor correlation in UPDRS-2 and UPDRS-3 [Table 5].

Correlation between NMSS and PDQ-39 scores

There was a significant correlation between individual domains of NMSS with all the domains of PDQ-39 in

our study. Total scores and NMSS were compared with total PDQ-39 scores, which also showed a significant correlation ($p < 0.001$) [Table 6].

DISCUSSION

In the present study, we observed a 100% prevalence of NMS since all the patients enrolled had one or other NMS. Previous studies on NMS have reported a high prevalence but only a few mentioned 100% prevalence.^[7-9] A Moroccan cohort of 132 PD patients also reported the presence of NMS symptoms in all included patients.^[7] QoL study in Egyptian patients with PD identified NMS in all participants ($n = 97$) with fatigue, mood disturbances, and memory as the most important NMS.^[8] In developing countries, the situation is worse since patients only visit once motor symptoms occur. A study from Iran enrolled 87 PD patients and reported onset of PD with NMS in 20% and prevalence of NMS was 100%.^[9] Indian studies mentioned NMS prevalence varying between 52 and 100% in PD patients; most reported NMS are pain, fatigue, and light-headedness. In the current study, the prevalence was in line with other studies from India which also mentioned the high prevalence of NMS (Pappala *et al.*^[10] 93.75%, Ravan *et al.*^[11] 100%, de Souza *et al.*^[12] 91.8%, and Krishnan *et al.* 100%).^[13]

Demographic data of our cohort showed 67 male patients and 25 female patients with a male: female ratio of 2.68:1 and the age of onset of disease was 51.62 years. We had a slightly higher male preponderance 72.8% and the incidence of disease was in a lower age group compared to global data.^[14,15] Tremor predominant type ($n = 34$) was more common, followed by mixed type ($n = 31$) and akinetic rigid variant ($n = 27$) was the least common type. Previously a study by Tibar *et al.*^[7] on NMS mentioned mixed type to be more common (40.2%) and tremor-dominant second most common form of PD (39.3%) and akinetic rigid form to be least common (20.5%). The side of onset in our group of PD patients was right-sided $n = 46$, left-sided $n = 43$, and bilateral disease onset was noted in $n = 3$ patients.

Screening for NMS showed that urinary symptoms, sleep, and fatigue were the most common NMS, and hallucination, perception, and sexual functions were the least affected in our cohort. Nocturia and urinary urgency are the most troublesome NMS symptoms reported in the literature.^[16] Sleep onset problems and excessive daytime sleepiness and urinary symptoms affect the QoL in PD patients. Excessive daytime sleepiness is reported in 21–76% of PD patients in the previous study.^[17]

Urinary complaints are more common in atypical PD (multiple system atrophy) owing to autonomic dysfunction and involvement of the Onuf's nucleus. In patients with IPD, urinary dysfunction is reported in 60–70% of patients.^[18] Urinary urgency, urge incontinence, and frequency were the most common urinary symptoms. Urodynamic studies showed detrusor hyperactivity in two-thirds of individuals. In our patients, we found that 63.2% reported either urgency/nocturia

Table 3: Correlation of Individual NMSS dimensions with UPDRS scores

NMSS domains	UPDRS-1	UPDRS-2	UPDRS-3	UPDRS-4
Cardiovascular and falls				
<i>P</i>	<0.001	<0.001	<0.001	<0.001
Spearman's Rho	0.671**	0.561**	0.550**	0.515**
Sleep and fatigue				
<i>P</i>	<0.001	<0.001	<0.001	<0.001
Spearman's Rho	0.649**	0.554**	0.551**	0.551**
Mood/cognition				
<i>P</i>	<0.001	<0.001	0.002	<0.001
Spearman's Rho	0.589**	0.467**	0.472**	0.590**
Perceptual problems/hallucination				
<i>P</i>	<0.001	<0.001	<0.001	<0.001
Spearman's Rho	0.508**	0.568**	0.549**	0.437**
Attention/memory				
<i>P</i>	<0.001	<0.001	<0.001	<0.001
Spearman's Rho	0.555**	0.564**	0.555**	0.440**
GI tract				
<i>P</i>	<0.001	<0.001	<0.001	<0.001
Spearman's Rho	0.557**	0.551**	0.579**	0.441**
Urinary				
<i>P</i>	<0.001	0.03	0.028	0.04
Spearman's Rho	0.535**	0.344*	0.347*	0.501**
Sexual function				
<i>P</i>	0.005	0.101	0.053	0.017
Spearman's Rho	0.434**	0.263	0.308	0.447**
Miscellaneous				
<i>P</i>	0.003	0.005	0.006	0.001
Spearman's Rho	0.452**	0.438**	0.429**	0.526**

*Correlation is significant at the 0.05 level (2 tailed). **Correlation is significant at the 0.01 level (2 tailed). NMSS=Non-Motor Symptoms Scale; UPDRS=Parkinson's Disease Rating Scale; GI=Gastrointestinal

Table 4: PDQ-39 dimensions in PD patients

Parameters	Minimum	Maximum	Mean±SD
Parkinson's symptoms	6	50	11.08±6.952
Systemic symptoms	3	20	7.40±3.373
Social functions	3	22	8.35±3.549
Emotional functions	4	36	10.05±5.262
Total PDQ-39 score	16	128	36.88±19.136

PD=Parkinson's Disease; PDQ-39=Parkinson's Disease Questionnaire-39

or increased frequency. Many of these patients reach the urology clinic for these symptoms and are often treated for urinary tract infection or prostatic hyperplasia. A study of PD patients in a urology clinic reported nocturia in 77%, urgency in 36%, and frequency in 32%. Urodynamic studies showed neurogenic detrusor overactivity in 67.3%, detrusor under activity in 12.2%, and 20.4% had normal detrusor function.^[19]

Swallowing difficulty, excessive salivation, and constipation are the most common GI NMS in PD and rarely PD can have complications like megacolon, obstruction, intestinal perforation, and gastroparesis. In a previous study around 60–80%, PD patients have GI symptoms and they are the commonest cause of emergency admissions secondary to aspiration and malnutrition.^[20] Constipation is the earliest among these and it can present even before motor symptoms.

Early in the course of the disease, there is a loss of neurons in the myenteric and submucosal plexus leading to slow gastric transit. In our study, 38.5% of PD patients had GI manifestations; constipation and excessive salivation were the most predominant among these symptoms. GI symptoms often hamper the treatment of the disease by decreased absorption of antiparkinsonian drugs and can lead to delayed ON or no ONs.

Sleep and fatigue were present in 82.8% of patients in the present study, implicating its importance as the NMS in PD patients. Sleep problem consists of delayed onset of sleep, frequent awakenings, nocturnal dystonia, restless leg symptoms, rapid eye movement behavioral disorder, and excessive daytime sleepiness. Sleep problems have a significant negative impact on the QoL in PD. Previous studies mentioned sleep-related problems are fairly common and they account for 27–80%. Most PD patients complain about excessive sleepiness and insomnia.^[21] Reviewing treatment history is important as antiparkinson drugs are also one of the causes of sleep problems and simply adjusting the dose or changing the timing of medication can alleviate the sleep problem.

Sexual function is a significant determinant of QoL in chronic disease; it also affects the quality and general satisfaction of the partner. Most men with PD have erectile dysfunction and

Table 5: Correlation between PDQ-39 and disease characteristic

	Parkinson's symptoms	Systemic symptoms	Social functions	Emotional functions	Total PDQ-39
Age					
<i>P</i>	0.332	0.163	0.308	0.415	0.165
Spearman's Rho	0.157	0.225	0.165	0.132	0.165
Stage of disease					
<i>P</i>	0.013	0.009	0.022	0.014	0.024
Spearman's Rho	0.388*	0.408**	0.361*	0.384*	0.355*
Duration of disease					
<i>P</i>	0.032	0.019	0.020	0.034	0.036
Spearman's Rho	0.339*	0.370	0.366*	0.332*	0.33.*
UPDRS-1					
<i>P</i>	0.411	0.013	0.024	0.415	0.000
Spearman's Rho	0.134	0.388*	0.355*	0.132	0.728**
UPDRS-2					
<i>P</i>	0.305	0.199	0.351	0.794	0.360
Spearman's Rho	0.166	0.207	0.151	0.043	0.149
UPDRS-3					
<i>P</i>	0.411	0.266	0.328	0.781	0.386
Spearman's Rho	0.134	0.180	0.159	0.045	0.141
UPDRS-4					
<i>P</i>	0.072	0.038	0.073	0.290	0.078
Spearman's Rho	0.287	0.330*	0.286	0.172	0.282
UPDRS-total					
<i>P</i>	0.000	0.000	0.000	0.000	0.000
Spearman's Rho	0.685**	0.688**	0.658**	0.650**	0.698**

*Correlation is significant at the 0.05 level (2 tailed). ** Correlation is significant at the 0.01 level (2 tailed). PDQ-39=Parkinson's Disease Questionnaire-39; UPDRS=Parkinson's Disease Rating Scale

premature ejaculation. In the current study, 32.2% of patients had sexual dysfunction on questioning and these symptoms are usually underreported due to cultural and social inhibitions. In Indian studies, around 25% of patients reported sexual problems in PD. At the same time, western studies on PD reported a prevalence of sexual dysfunction ranging from 37 to 65%.^[22]

Autonomic symptoms are reported in 14–80% of PD patients and are best evaluated by the scales for outcomes in Parkinson's disease-autonomic dysfunction scale.^[23] Orthostatic hypotension, syncope, excessive sweating, and urinary symptoms are predominant autonomic symptoms and they correlate with the progression of the disease and are often aggravated by dopaminergic therapy. The prevalence of orthostatic hypotension, defined by a fall of blood pressure of 20 mm Hg in systolic and 10 mm Hg in diastolic blood pressure, is about 20–58% of PD patients.^[24]

Neuropsychiatric symptoms and cognitive problems become more prevalent as the disease progresses. Many PD patients have mild cognitive impairment and slowness of thinking, 20% of these develop significant dementia over the years. In the present study, half of the patients (51.2%) reported mood changes and difficulty in concentration. Hallucination and perceptual problems were the least reported problems (11.2%). Hallucination and delusion are reported in 40% of PD patients and these features are one of the major determinants of hospital admissions.^[25] Identifying and treating neuropsychiatric

symptoms is important as they cause a significant burden on the patient and caregiver.

While treating PD, it is important to look beyond motor and NMS, as the QoL in PD patients is a major determinant of happiness and general satisfaction. We assessed HRQoL in PD patients with the PDQ-39 questionnaire. In our cohort, mobility, ADL, and emotional aspects of PDQ-39 were most affected, and the social domain was least involved. QoL in PD patients is affected early in the disease process and worsens over time. Mobility is the major determinant of a patient's QoL as it decides a patient's level of participation in daily activities and social interaction.

The present cohort correlation analysis between NMS and PDQ-39 showed a significant correlation between NMS and HRQoL. All the individual domains of the non-motor scale were significantly affecting the QoL in PD patients. Mobility, ADL, and social function had the most negative impact on PDQ-39 and the emotional aspect was less affected by NMS. A previous study with a large sample size showed neuropsychiatric symptoms like apathy, depression, and sleep disturbances are the major determinants of QoL.^[26] In our study, we found that all NMS can negatively impact the patient's QoL. Multivariate analysis in most of the studies reported autonomic symptoms, GI, and sleep is the major determinants of QoL in PD patients. We correlated PDQ-39 scores with age, stage of the disease, and UPDRS scores, and QoL was significantly affected by disease stage and UPDRS scores. There was no

Table 6: Correlation between NMSS and PDQ-39 scores

	Parkinson's symptoms	Systemic symptoms	Social functions	Emotional functions
Cardiovascular/falls				
<i>P</i>	<0.001	<0.001	<0.001	0.005
Spearman's Rho	0.634**	0.651**	0.622**	0.437**
Sleep and fatigue				
<i>P</i>	<0.001	<0.001	<0.001	0.006
Spearman's Rho	0.594**	0.655**	0.635**	0.425**
Mood/cognition				
<i>P</i>	0.002	<0.001	0.002	0.008
Spearman's Rho	0.479**	0.542**	0.505**	0.415**
Perceptual problems/hallucination				
<i>P</i>	0.002	<0.001	<0.001	0.006
Spearman's Rho	0.470**	0.518**	0.501**	0.429**
Attention/memory				
<i>P</i>	<0.001	<0.001	<0.001	0.017
Spearman's Rho	0.495**	0.551**	0.538**	0.376*
GI tract				
<i>P</i>	<0.001	<0.001	<0.001	<0.001
Spearman's Rho	0.607**	0.646**	0.668**	0.496**
Urinary				
<i>P</i>	<0.001	<0.001	<0.001	<0.001
Spearman's Rho	0.613**	0.637**	0.644**	0.539**
Sexual function				
<i>P</i>	<0.000	<0.001	<0.001	<0.001
Spearman's Rho	0.549**	0.627**	0.663**	0.515**
Miscellaneous				
<i>P</i>	0.015	0.004	0.005	0.026
Spearman's Rho	0.383*	0.450**	0.434**	0.352*

*Correlation is significant at the 0.05 level (2 tailed). **Correlation is significant at the 0.01 level (2 tailed). NMSS=Non-Motor Symptoms Scale; PDQ-39=Parkinson's Disease Questionnaire-39; GI=Gastrointestinal

correlation between age and PDQ-39 scores. A previous study also reported worsening of QoL as the disease stage progresses and UPDRS scores correlate well with the stage of the disease in PD.^[27] One of the major limitations of the present study is its cross-sectional nature; hence, the progression of NMS over time could not be assessed.

CONCLUSION

The NMS significantly influenced the QoL of every domain. Most of the patients had a long duration of existing NMS symptoms before recognition of the primary disease itself. In our study, all (100%) patients had one or other NMS over a while. Despite such a high prevalence of NMS, they remain largely under-recognized and undertreated. There is an unmet need for the early and correct diagnosis of NMS before and after the onset of motor symptoms of PD and appropriate treatment of the same to improve QoL.

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Informed consent

The authors affirm that informed consent was taken from all the participants in the study. Informed consent was obtained from

all individual participants for whom identifying information is included in this article. All patients signed informed consent regarding publishing their data. Both Dr Anand Kumar and Dr Sooraj Patil have contributed equally.

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Conflicts of interest

Both Dr. Anand Kumar and Dr. Sooraj Patil will have the first authorship. Rest there are no conflicts of interest between the authors to declare.

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