

# Pattern of Non Motor Symptoms in Parkinson's Disease: A Prospective Observational Study from a Tertiary Care Centre, Bihar, India

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## ABSTRACT

**Introduction:** Non motor symptoms are highly prevalent in Parkinson's Disease (PD) but are often overshadowed by the dominance of motor symptoms.

**Aim:** To assess non motor symptoms in patients with Parkinson's disease.

**Materials and Methods:** In this prospective observational study, patients of PD fulfilling United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria were recruited, between August 2019 to July 2021, in the Neurology Department of Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India. The pattern of Non Motor Symptoms (NMS) in PD was studied using detailed questionnaire and association of NMS with age, gender and modified Hoehn and Yahr stage were assessed. Chi-square test and Student's t-test was calculated where required.

**Results:** Total 102 patients were included, with male constituting 73.5% patients. The mean age was 60.14±13.55 years. Constipation 74 (72.55%) was the most common NMS. Most of the patients belonged to mild stage (52.94%) followed by moderate (40.20%) and severe (6.86%) stages, according to modified Hoehn and Yahr classification. Rapid Eye Movement (REM) sleep behaviour disorder (n=15) and sexual dysfunction (n=28) were significantly more prevalent in male patients. Depression, REM sleep behaviour disorder, olfactory disturbance, visual disturbance, urinary urgency, sweating abnormality, constipation, vomiting and visual blurring were significantly common in patients with earlier disease stages while psychosis in patients with advanced stage.

**Conclusion:** This study showed the high prevalence of NMS in PD patient which is consistent with other studies, but there are differences in the frequency of individual symptoms which may relate to cultural and geographic differences.

**Keywords:** Constipation, Depression, Modified hoehn and yahr staging, Sleep behaviour disorder, Urinary urgency

## INTRODUCTION

Parkinson's Disease (PD) was first described by James Parkinson in 1817 as a disease characterised by involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with propensity to bend the trunk forward, and to pass from a walking to a running pace, the senses and intellect being uninjured [1]. Non Motor Symptoms (NMS) in PD constitute a major clinical challenge but are often overshadowed by the dominance of motor symptoms with the diagnostic criteria only based on motor features [2,3].

Non motor symptoms may predate the diagnosis of PD and reported in around one-fifth of the patients at the time of diagnosis [4]. There is marked variability in the frequency of NMS in the studies across the world with insomnia, urinary symptoms, memory impairment, constipation, fatigue and anxiety being the frequent NMS [5]. Most of the literature on the NMS of PD is from the western countries with few studies from India, and a single study from Eastern India [6-23]. This study is the comprehensive assessment of NMS of PD in a cohort of patients attending a tertiary care hospital of Bihar in Eastern India. A detailed study of NMS of PD would help to understand the burden of the illness and plan better care for such patients.

## MATERIALS AND METHODS

This prospective observational study was conducted in the Neurology Department at Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India, between August 2019 to July 2021. The study was approved by the Institutional Ethics Committee (1115/IEC/IGIMS/2019). Informed written consent was taken from patients.

**Inclusion and Exclusion criteria:** All patients of Idiopathic PD fulfilling United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria were included in the study [24]. Patients with history of recurrent strokes with step-wise progression of features, repeated head injury, definite encephalitis in the past, taking neuroleptic treatment at onset of symptoms, more than one affected relatives, exclusive unilateral features even after three years of onset, supranuclear gaze palsies, presence of cerebellar signs, early severe autonomic involvement, early severe dementia, presence of Babinski's sign, presence of cerebral tumour or communicating hydrocephalus, negative response to large doses of levodopa were excluded from the study.

Patients were evaluated and the following data were recorded

- Demographic data,
- Clinical manifestations
- Detailed clinical examination including various non motor and motor symptoms.

### Modified Hoehn and Yahr Staging

The questionnaire/scale used were modified Hoehn and Yahr staging and detailed questionnaire on NMS [25]. Modified Hoehn and Yahr stages were used to measure the severity of disease through stage 1-5. It was further classified into:

- Mild stage (1, 1.5, 2)
- Moderate stage (2.5, 3)
- Severe stage (4, 5)

The questionnaire for NMS were divided into subsets and used to assess whether or not NMS were present. Responses were marked in a yes or no answer.

## STATISTICAL ANALYSIS

The study data were entered and results were calculated from Statistical Package for the Social Science (SPSS) software version 17.0. Mean, Standard deviation, Standard error of mean were calculated in this study. The categorical variables were compared using the Chi-square test (or Fisher exact test) and continuous variables were compared using the independent t-test. A p-value <0.05 has been considered significant.

## RESULTS

Total 102 patients of PD were included in the study. The mean age of the patients were 60.14±13.55 years. Male to female ratio was 2.77:1. Most of the patients (58.82%) were above 60 years of age. Motor symptoms were present in all with bradykinesia (87.25%) being the most common. Majority of the patients were in Hoehn and Yahr stage 2 (30.39%) and least being in stage 5 (0.98%).

The most common NMS was constipation 74 (72.55%) followed by anxiety 66 (64.71%) and depression 63 (61.76%). Rapid Eye Movement (REM) sleep behaviour disorder were present in 16 (15.69%) patients, cognitive impairment in 12 (11.76%) and olfactory disturbance in 24 (23.53%) patients.

Most of the patients (42.16%) had 1-5 NMS. Only 5 (4.9%) patients did not have any NMS. Mean number of NMS in males was 6.69±4.52 and in females was 5.70±4.14. There was an increase in the prevalence of NMS with increasing age. The number of NMS increased with severity of the disease, from mild to severe modified Hoehn and Yahr stage (5 vs 8.42).

Significant difference was observed between male and female patients among some NMS with Rapid eye movement sleep Behaviour Disorder (RBD) (p-value=0.046) and sexual dysfunction (p-value=0.001) were significantly more prevalent in male patients, while sweating abnormality in form of excessive sweating (p-value=0.021) were significantly more in female patients [Table/Fig-1]. Significant difference was noted between modified Hoehn and Yahr stage of PD and few NMS i.e., depression (p-value=0.028), REM sleep behaviour disorder (p-value=0.033), olfactory disturbance (p-value=0.002), visual disturbance (p-value=0.000), urgency (p-value=0.004), sweating abnormality (p-value=0.030), constipation (p-value=0.006), vomiting (p-value=0.045), psychosis (p-value=0.001) and visual blurring (p-value=0.015).

There was a significant difference while comparing some NMS within different age groups. Restless leg syndrome (n=3) was significantly more in age ≤40 years (p-value=0.015), while olfactory disturbance (n=19), sexual dysfunction (n=23), and constipation (n=50) were significantly more in age >60 years (p-value=0.038, 0.027, 0.009 respectively) [Table/Fig-2].

Variables	Male patients n (%)	Female patients n (%)	p-value
<b>Age (years)</b>			
≤40	6 (8%)	5 (18.5%)	0.104
41-60	22 (29.3%)	9 (33.4%)	
>60	47 (62.7%)	13 (48.2%)	
Mean age (Mean±SD)	61.93±12.77	55.15±14.61	
<b>Hoehn and Yahr stage</b>			
Mild (1, 1.5, 2)	38 (50.7%)	16 (59.3%)	0.607
Moderate (2.5, 3)	35 (46.7%)	6 (22.2%)	
Severe (4, 5)	2 (2.7%)	5 (18.5%)	
<b>Motor symptoms</b>			
Bradykinesia	65 (86.7%)	24 (88.9%)	0.532
Resting tremors	62 (82.7%)	19 (70.4%)	0.141
Rigidity	42 (56%)	16 (59.3%)	0.475
Postural instability	17 (22.7%)	7 (25.9%)	0.557

<b>Non motor symptoms</b>			
Depression	47 (62.67%)	16 (59.26%)	0.755
Anxiety	45 (60%)	21 (77.78%)	0.097
Apathy	12 (16%)	6 (22.22%)	0.467
Delusion	2 (2.67%)	-	0.391
Delirium	1 (1.33%)	-	0.547
Cognitive impairment	9 (12%)	3 (11.11%)	0.902
Impulse control disorder	3 (4%)	-	0.291
REM sleep behaviour disorder	15 (20%)	1 (3.70%)	0.046*
Excess daytime somnolence	6 (8%)	1 (3.70%)	0.449
Narcolepsy type sleep attack	1 (1.33%)	-	0.547
Restless leg syndrome	4 (5.33%)	3 (11.11%)	0.309
Insomnia	31 (41.33%)	7 (25.93%)	0.156
Sleep disordered breathing	7 (9.33%)	4 (14.81%)	0.431
Fatigue	41 (54.67%)	11 (40.74%)	0.215
Pain	36 (48%)	14 (51.85%)	0.731
Olfactory disturbance	19 (25.33%)	5 (18.52%)	0.474
Visual disturbance	8 (10.67%)	5 (18.52%)	0.294
Urgency	24 (32%)	5 (18.52%)	0.183
Frequency	26 (34.67%)	6 (22.22%)	0.232
Nocturia	22 (29.33%)	4 (14.81%)	0.138
Sexual dysfunction	28 (37.33%)	1 (3.70%)	0.001*
Sweating abnormality	2 (2.67%)	4 (14.81%)	0.021*
Dribbling of saliva	3 (4%)	-	0.291
Dysphagia	1 (1.33%)	-	0.547
Ageusia	2 (2.67%)	-	0.391
Constipation	57 (76%)	17 (62.96%)	0.193
Nausea	27 (36%)	8 (29.63%)	0.550
Vomiting	2 (2.67%)	2 (7.41%)	0.276
Psychosis	-	1 (3.70%)	0.094
Delusion	1 (1.33%)	-	0.547
Ankle swelling	-	1 (3.70%)	0.094
Dysautonomia	3 (4%)	1 (3.70%)	0.946
Weight loss	5 (6.67%)	-	0.169

**[Table/Fig-1]:** Distribution of non motor symptoms according to gender of PD patients.

## DISCUSSION

Non motor symptoms of PD has received relatively little attention, despite diverse presentation of these conditions and their impact on the quality of life. NMS is often not reported by patients himself thinking that it is not related to disease per se despite its high prevalence.

The NMS were present in 95.09% of presents patients similar to published studies showing prevalence of NMS ranging from more than two-third patients to involving all patients [6-23]. The most common NMS in this study was constipation, similar to studies by Mukhtar S et al., Azmin S et al., and Kumar NSS et al., [11,12,18]. Constipation has been found to be the most common NMS in Asian studies which might be due to the dietary differences. Anxiety was the most prevalent NMS in study by de Souza A et al., while it was second most common NMS in study by Mukhtar S et al., and also in the present study [11,17].

The mean NMS value was lower compared to a previous multicenter study and the study by Mukhtar S et al., [6,11]. The mean presence of NMS progressively increased from mild to severe modified Hoehn and Yahr stages, similar to various published studies [13,15,17]. The higher number of NMS is thought to be related to worsening of motor symptoms; however, it may vary and some symptoms can be seen in earlier stages or others in later stages. There was an

Non motor symptoms	Number of patients in modified Hoehn and Yahr stage				p-value
	Mild {n=54 (52.94%)}	Moderate {n=41 (20.40%)}	Severe {n=7 (6.86%)}	Total n (%)	
Depression	27 (50%)	30 (73.17%)	6 (85.71%)	63 (61.76%)	0.028
REM sleep behaviour disorder	5 (9.26%)	11 (26.83%)	-	16 (15.69%)	0.033
Olfactory disturbance	6 (11.11%)	17 (41.46%)	1 (14.29%)	24 (23.53%)	0.002
Visual disturbance	2 (3.7%)	7 (17.07%)	4 (57.14%)	13 (12.75%)	0.000
Urgency	8 (14.81%)	17 (41.46%)	4 (54.14%)	29 (28.43%)	0.004
Sweating abnormality	2 (3.7%)	2 (4.88%)	2 (28.57%)	6 (5.88%)	0.030
Constipation	32 (59.26%)	36 (87.80%)	6 (85.71%)	74 (72.55%)	0.006
Vomiting	-	4 (9.76%)	-	4 (3.92%)	0.045
Psychosis	-	-	1 (14.29%)	1 (0.98%)	0.001
Visual blurring	1 (1.85%)	8 (19.51%)	1 (14.29%)	10 (9.80%)	0.015
Number of patients in age groups					
	≤40 years {n=11 (10.78%)}	41-60 years {n=31 (30.39%)}	>60 years {n=60 (58.82%)}	Total (102)	
Restless leg syndrome	3 (27.27%)	2 (6.45%)	2 (3.33%)	7 (6.86%)	0.015
Olfactory disturbance	-	5 (16.13%)	19 (31.67%)	24 (23.53%)	0.038
Sexual dysfunction	1 (0.09%)	5 (16.13%)	23 (38.33%)	29 (28.43%)	0.027
Constipation	5 (45.45%)	19 (61.29%)	50 (83.33%)	74 (72.55%)	0.009

**[Table/Fig-2]:** Significant association of various non motor symptoms to modified Hoehn and Yahr stage and age distribution.

increased prevalence of NMS with advancing age, similar to the study by de Souza A et al., [17]. The increased prevalence of NMS in older patients could be due to physiological aging or comorbid conditions.

Depression, RBD, olfactory disturbance, visual disturbance, urinary urgency, sweating abnormality, constipation, vomiting, psychosis, and visual blurring significantly association with HY staging in present study. Kumar NSS et al., found that urinary disturbances, sexual problems, sleep related problems like difficulty to sleep, falls and double vision had significant statistical correlation with Hoehn and Yahr staging among the all NMS [18].

The RBD and sexual dysfunction were found to be more prevalent in male patients while sweating abnormality were significantly more in female patients in present study. Mukhtar S et al., also found that sexual dysfunction was more prevalent in male patients as females are not comfortable discussing these issues [11]. While, Martinez-Martin P et al., found that sweating disturbances were

more prevalent in female population [26]. RBD is found to be more prevalent in male patients in study by Zhou J et al., but a study by Haba-Rubio J et al., found no gender differences for RBD [27,28]. Restless Legs Syndrome (RLS) was more prevalent in age ≤40 years while olfactory disturbance, sexual dysfunction and constipation was significantly more prevalent in age >60 years. Similar to the present study, Breen KC et al., showed in their study that sexual dysfunction was more common in older PD patients whereas restless legs were common in young PD patients [29]. Spica V et al., also found that olfactory disturbances and sexual dysfunction were significantly more prevalent in older PD patients while RLS were more prevalent in young patients [14].

All the previous studies from India show predominance of constipation, sleep disturbances, anxiety and urinary disturbances [Table/Fig-3] [15-23]. There is variation in most common NMS and frequency of each NMS but pattern of NMS looks quite similar in all studies.

Authors (year)	Population size	Mean age (years)	Most common non motor symptoms (three most common)	Association
Krishnan S et al., [15] (2011)	174	59.5	Sleep/fatigue, mood/cognition, miscellaneous	NMSS scores correlated with Hoehn and Yahr stage, NMS burden is greater in women
Ravan A et al., [16] (2015)	81	62.93	Nocturia, constipation, fatigue	Correlation between NMS and motor symptoms in the disease progression
de Souza A et al., [17] (2015)	171	67.1	Anxiety, urinary urgency, constipation	NMS number increases with Hoehn and Yahr stage, age >70 years, duration and later onset of PD
Kumar NSS et al., [18] (2019)	45	64.7	Constipation, anxiety, urgency of bladder	Frequency of NMS correlated with Hoehn and Yahr stage
Shakthi C et al., [19] (2019)	100	59.39	Nocturnal sleep disturbances, constipation, unexplained pain	Most common NMS in males constipation, urinary urgency and nocturia. In females sleep disturbances and neuropsychiatric symptoms
Pappala K et al., [20] (2019)	64	56.1	Difficulty in falling asleep, urinary urgency, memory impairment	Significant impact of NMSs on quality of life
Karri M et al., [21] (2020)	100	68.35	Fatigue, pain, lightheadedness	NMS have impact on health-related quality of life in PD and on caregiver's life
Chaudhuri JR et al., [22] (2021)	75	59.2	Gastrointestinal symptoms, cardiovascular dysfunctions, sexual dysfunction	NMS frequency increased with disease duration
Sahu S et al., [23] (2021)	150	59.01	Unexplained pain, anxiety, constipation	NMS had a significant impact on quality of life
Present study	102	60.14	Constipation, anxiety, depression	RBD and sexual Dysfunction more prevalent in male patients. Significant association was noted between NMS and modified Hoehn and Yahr stage

**[Table/Fig-3]:** Indian studies on non motor symptoms of Parkinson's disease [15-23].

## Limitations(s)

The study recruited a relatively small number of patients and was conducted at single centre, so there may be possibility of selection bias. The differentiation of NMS whether it is due to PD or the antiparkinsonism medication could not be done and also effect of co-morbid illnesses could not be estimated.

## CONCLUSION(S)

To conclude, NMS are highly prevalent in the present study and well recognition of these symptoms along with motor symptoms would help in diagnosis and management of PD patients. Though, the prevalence of NMS in this study is similar and consistent with other studies, there are differences in the frequency of individual symptoms which may relate to cultural and geographic differences.

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