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# Prevalence of Non-motor Symptoms in Parkinson's Disease: A Study from South India

## *Parkinson Hastalığında Non-motor Semptomların Prevalansı: Güney Hindistan'dan Bir Çalışma*

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## Abstract

**Objective:** Non-motor symptoms (NMS) play a vital role in managing Parkinson's disease (PD) and have become the leading cause of deterioration of quality of life with the progression of the disease. The aim of the present study was to investigate the prevalence of NMS in PD with disease duration.

**Materials and Methods:** We selected 75 patients with PD prospectively and all patients were diagnosed according to the United Kingdom PD Brain Bank criteria. All patients were trichotomized based on disease duration (≤4 years, 5-8 years and ≥9 years). The NMS screening questionnaire comprising 30 items was completed by all patients.

**Results:** Out of 75 patients, men constituted 82.6%, the mean age was 59.2±1.51 (range, 45-69) years. The overall prevalence of NMS was 100%. Among the patients with a disease duration of ≤4 years, 5-8 years, and ≥9 years, gastrointestinal symptoms were observed in 38%, 48%, and 86.2%; cardiovascular dysfunction in 47.6%, 44%, and 82.7%; urinary problems in 38%, 40%, and 72.4%; poor sexual performance in 42.8%, 40%, and 79.3%; sleep disturbance in 38%, 36%, and 75.8%; anxiety in 33.3%, 40%, and 79.3%; hallucinations in 33.3%, 36%, and 72.4%; and cognition problems in 38%, 32%, and 72.4%, respectively. Significantly higher prevalences of gastrointestinal symptoms (p=0.006), cardiovascular dysfunctions (p=0.007), urinary problems (p=0.03), poor sexual performance (p=0.007), sleep disturbances (p=0.007), anxiety (p=0.007), hallucinations (p=0.03), and cognitive problems (p=0.007) were noted in patients with ≥9 years disease duration.

**Conclusion:** Our study established that 100% of patients with PD had at least one NMS and there was a higher prevalence of NMS among those with disease duration more than 9 years.

**Keywords:** Non-motor symptoms (NMS), Parkinson's disease, disease duration, gastrointestinal symptoms, cardiovascular dysfunctions

## Öz

**Amaç:** Non-motor semptomlar (NMS), Parkinson hastalığının (PH) yönetiminde hayati bir rol oynar ve hastalığın ilerlemesi ile yaşam kalitesinin bozulmasının önde gelen nedeni haline gelmiştir. Bu çalışma, hastalık süresine göre PH'de NMS prevalansını araştırmaktır.

**Gereç ve Yöntem:** Yetmiş beş PH tanısı olan hasta bu prospektif çalışmaya dahil edildi. Bütün hastalara Birleşik Krallık PD Beyin Bankası kriterlerine göre tanı kondu. Hastalar hastalık süresine göre 3 gruba ayrıldı (≤4 yıl, 5-8 yıl ve ≥9 yıl). Otuz sorudan oluşan NMS tarama anketi tüm hastalar tarafından dolduruldu.

**Bulgular:** Yetmiş beş hastanın %82,6'sını erkekler oluşturmaktaydı ve yaş ortalaması 59,2±1,51 yıl idi (45-69 yaş). NMS'nin genel prevalansı %100 idi. Hastalık süresi 4 yıl, 5-8 yıl ve ≥9 yıl olan hastalarda gastrointestinal semptomların prevalansı sırasıyla %38, %48 ve %86,2, kardiyovasküler hastalıkların prevalansı sırasıyla %47,6, %44 ve %82,7, idrar sorunlarının prevalansı sırasıyla %38, %40 ve %72,4, zayıf cinsel performansın prevalansı sırasıyla %42,8, %40 ve %79,3, uyku bozukluklarının prevalansı sırasıyla %38, %36 ve %75,8, anksiyetenin prevalansı sırasıyla %33,3,%40 ve %79,3, halüsinasyonların prevalansı sırasıyla %33,3, %36 ve %72,4, bilişsel problemlerin prevalansı sırasıyla %38, %32 ve %72,4 idi. Hastalık süresi ≥9 yıl olan hastalarda; sindirim sistemi semptomları (p=0,006), kardiyovasküler bozukluklar (p=0,007), idrar sorunları (p=0,03), kötü cinsel performans (p=0,007), uyku bozuklukları (p=0,007), anksiyete (p=0,007), halüsinasyonlar (p=0,03) ve bilişsel sorunlar (p=0,007) anlamlı derecede daha yüksek prevalansta görüldü.

**Sonuç:** Çalışmamız, PH tanılı hastaların %100'ünün en az bir NMS'ye sahip olduğunu ve 9 yıldan fazla hastalık süresi olanlarda daha yüksek NMS prevalansı olduğunu ortaya koymuştur.

**Anahtar Kelimeler:** Non-motor semptomlar, Parkinson hastalığı, hastalık süresi, gastrointestinal semptomlar, kardiyovasküler disfonksiyonlar

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## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, it affects all age groups and both sexes (1). Worldwide, the crude prevalence is around 160 per 100,000 (2), and in India 6-53 per 100,000 (3). PD is characterized by motor symptoms such as rigidity, postural instability, resting tremor, bradykinesia, and non-motor symptoms (NMS) such as cognitive impairment, cardiovascular dysfunction, sleep disturbances, psychiatric, urinary problems, and gastrointestinal symptoms (4). Existing studies have marked the importance of NMS as a major cause of disability and poor quality of life in patients with PD (4,5,6). The present study investigated the prevalence of NMS in patients with PD with varying duration of disease. Limited data are available from South India on this topic.

## Materials and Methods

We prospectively recruited 75 patients with PD from the Department of Neurology Yashoda Hospital, Hyderabad. Yashoda Hospital is a tertiary care center of South India. The study period was between June 2014 and May 2017.

The patients were diagnosed as having PD according to the United Kingdom PD Brain Bank criteria (5). Patients with PD who were wheelchair or bed-bound, had dementia or severe psychiatric disturbances, Hoehn and Yahr stage 5, and atypical and secondary parkinsonism were excluded from the study. Demographic information and clinical findings were collected through face-to-face interviews. Motor symptoms of PD were evaluated with the Unified PD Rating Scale part-III (UPDRS-III).

Detailed neurologic examinations were performed in all patients by two movement disorder specialists and one senior neurologist. Medical history was collected (present and past) from medical records and reviewed by a trained neurology resident for all patients. Non-pharmacologic (e.g. physical, occupational, and speech therapies) and pharmacologic therapies (doses of various dopaminergic drugs) were studied in all patients. Assessment of motor deficits was performed in both "off" (dopaminergic drugs stopped for 12 hours) and "on" (maximum improvement with medication) states using UPDRS-III, which assesses motor functions. We trichotomized the patients based on disease duration, ≤4 years, 5-8 years, and ≥9 years. This study was approved by the Institutional Ethics Committee (file no: RP-18/2011) and informed consent was obtained from the patients.

### Non-motor Symptoms Assessment

NMS Quest is a self-completed 30-item comprehensive questionnaire with "yes" and "no" type answers. All items identify the presence or absence of symptoms (5). The 30 questions were categorized into 9 domains: Urinary, sexual, gastrointestinal, cognition (apathy/attention/memory), anxiety/depression, cardiovascular, hallucinations/delusions, and sleep. Seven questions (dribbling of saliva, reduced taste or smell, dysphagia, nausea, constipation, bowel incontinence and incomplete bowel emptying) were part of the gastrointestinal domain. The cardiovascular domain had two questions (feeling light-headed and falling or syncope), the urinary domain assessed urgency and frequency of micturition. The memory domain included memory problems, loss of interest and difficulty in concentration, and the anxiety/depression domain had single questions in each (feeling sad and feeling anxious/frightened). The sleep domain identified five symptoms [insomnia, increased drowsiness with difficulty in staying awake, vivid dreams, talking or moving in sleep or rapid eye movement (REM) sleep behavioral disorders, unpleasant sensations in the legs or restless leg syndrome]. Difficulty in performing sex or loss of interest in sex was classified into the sexual domain, and the presence of hallucinations and delusions was in the hallucinations/depression domain.

### Cognition Assessment

Cognition in all patients with PD was assessed using the Montreal Cognitive Assessment (MoCA) scale. The time for the administration of MoCA was approximately 10 minutes. The total possible score is 30 points; a score of ≥26 is considered normal (7,8).

### Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social sciences statistical package (SPSS Ver. 12.0, SPSS Inc., Chicago IL, USA). Continuous variables are presented in titer of mean and ± standard deviation. The chi-square test was used to study the difference between the three groups. All tests were two-sided and $p<0.05$ was considered statistically significant.

## Results

In the current study, there were 62 (82.6%) men, the mean age was 59.2±1.51 (range, 45-69), and the duration of PD ranged from 1 to 14 years. The mean UPDRS-III score in the "off" state was 41.3±9.43, the mean UPDRS-III score in the "on" state was 11.2±6.98, motor fluctuations were seen in 13 (17.3%) patients, dyskinesia in 24 (32%), and gait freezing in 20 (26.6%) (Table 1).

Among the NMS domains, gastrointestinal symptoms ($p=0.006$), cardiovascular dysfunction ($p=0.007$), urinary problems ($p=0.03$), sexual dysfunction ($p=0.007$), sleep disturbances ($p=0.007$), anxiety/depression ($p=0.007$) hallucinations/delusions ($p=0.03$), and cognitive problems ($p=0.007$) were significantly associated with ≥9 years' disease duration (Table 2).

## Discussion

In our study we established that at least one NMS was present in all patients with PD (100%), our findings are supported by other authors: Krishnan et al. (9) 100%, Liu et al. (10) 98%, Li et al. (11) 100%, Barone et al. (12) 98.6%, Zhang et al. (6) 99.4%, Ravan et al. (13) 98.4%, and Mridula et al. (5) 98%.

### Gastrointestinal Symptoms

Studies have established that gastrointestinal symptoms are higher in Asian PD patients (14). We also found a significantly higher prevalence of gastrointestinal symptoms with an overall prevalence of 60%. Most studies noted higher than 50% prevalence (5,10,14), but some have shown a lower prevalence (12,15). One-third of our patients had symptoms in early disease, and it increased to 85% when the disease duration was more than nine years.

Gastrointestinal system involvement may start years before the onset of motor symptoms and the presence of constipation is common in PD. The vagus nerve is the main supply of parasympathetic innervation to the gastrointestinal system (16,17). Abnormalities of the cholinergic innervation lead to impaired gut motility. There may be an added component of dystonia involving

| Table 1. Baseline characteristics | |
|---|---|
| **Parameters** | **(n=75)** |
| Men | 62 (82.6%) |
| Mean age | 59.2±1.51 |
| Age range | 45-69 |
| Any non-motor symptoms | 75 (100%) |
| Disease duration | 1-14 |
| Mean UPDRS-III score in "off" state | 41.3±9.43 |
| Mean UPDRS-III score in "on" state | 11.2±6.98 |
| Motor fluctuation | 13 (17.3%) |
| Dyskinesia | 24 (32%) |
| Gait freezing | 20 (26.6%) |
| Family history of PD | 2 (2.6%) |
| Modified Hoehn & Yahr stage ≤2 | 42 (56%) |
| Modified Hoehn & Yahr stage 2-3 | 23 (30.6%) |
| Modified Hoehn & Yahr stage 4 | 10 (13.3%) |
| Tremors as the initial presenting symptom | 45 (60%) |
| Bradykinesia/rigidity as the initial presenting symptom | 30 (40%) |
| Medications | |
| Number of patients on levodopa | 57 (76%) |
| Number of patients on dopamine agonists | 12 (16%) |
| Number of patients on amantadine | 32 (42.6%) |
| Number of patients on anticholinergics | 17 (22.6%) |
| Antidepressant | 20 (26.6%) |
| Monoamine oxidase B inhibitors | 13 (17.3%) |
| Medications dosage | |
| Mean levodopa dose (mg/day) | 473.51±268.00 |
| Total LED (mg/day) | 501.28±391.10 |
| Dopamine agonist-LED (mg/day) | 31.27±72.14 |

UPDRS-III: Unified Parkinson's Disease Rating Scale part-III, PD: Parkinson's disease, LED: Levodopa equivalent daily dose

the striated external anal sphincter. A third contribution may occur from the attrition of dopamine-containing neurons in the enteric plexus innervating the colon (17). Other supporting evidence is in the presence of infections such as *Helicobacter pylori,* which is strongly associated with PD and may lead to chronic inflammation in the gut (18). Other gastrointestinal symptoms apart from constipation, include sialorrhea, dysphagia, nausea, and defecatory dysfunction. Our study also adds to the evidence that gastrointestinal symptoms progress with disease duration. There seems to be no response to levodopa therapy and gastrointestinal symptoms are difficult to treat.

We did not quantify further, but tests such as detailed esophagography, electromyogram of the anal sphincter, intestinal motility and transit studies, and defecating proctography can be studied to find more effective and specific therapies for gastrointestinal symptoms.

**Cardiovascular Dysfunctions**

The association of the cardiovascular system in PD is of high significance because many patients have orthostatic hypotension and the prevalence ranges from 30-58% (19). In our study, orthostatic symptoms were the most prevalent NMS even in early disease with increasing prevalence as the disease duration increased; 83% among patients with longer disease duration (≥9 years) had symptoms. Similar prevalence has been reported in other studies (5); however, few studies have shown less than 50% (15,20).

The pathophysiology of autonomic dysfunction in patients with PD is due to peripheral sympathetic denervation of the heart, as demonstrated with 123I-metaiodobenzylguanidine-based single-photon emission computed tomography. This is in contract to multiple system atrophy where there is a central pathology (21). Unfortunately, orthostatic hypotension may be associated with supine hypertension (22). In normal individuals, there is a diurnal trend in blood pressure (BP) with higher values in the daytime and lower in sleep. Tsukamoto et al. (23) performed 24 hours ambulatory BP monitoring in patients with PD and showed a defect in the normal diurnal variation with increased nocturnal BP, similar to patients with essential hypertension. This leads to double jeopardy with orthostatic hypotension predisposing to falls and supine hypertension leading to end-organ damage with increased risk of cerebrovascular and cardiovascular events (24).

There is a variation of BP in the "off" and "on" stage in patients with PD (25), with higher BP in the "off" state. Although partially explained by the effect of dopaminergic drugs, it is also contributed

| Table 2. Comparison of NMS with disease duration | | | | | |
|---|---|---|---|---|---|
| **NMS** | **Overall (n=75)** | **<4 years PD (n=21)** | **5-8 years PD (n=25)** | **≥9 years PD (n=29)** | **p** |
| Gastrointestinal symptoms | 45 (60%) | 8 (38%)* | 12 (48%)* | 25 (86.2%) | 0.006 |
| Cardiovascular dysfunctions | 45 (60%) | 10 (47.6%)* | 11 (44%)* | 24 (82.7%) | 0.007 |
| Urinary problems | 39 (52%) | 8 (38%)* | 10 (40%)* | 21 (72.4%) | 0.03 |
| Sexual dysfunction | 42 (56%) | 9 (42.8%)* | 10 (40%)* | 23 (79.3%) | 0.007 |
| Sleep disturbance | 39 (52%) | 8 (38%)* | 9 (36%)* | 22 (75.8%) | 0.007 |
| Anxiety/depression | 40 (53.3%) | 7 (33.3%)* | 10 (40%)* | 23 (79.3%) | 0.007 |
| Hallucinations/delusions | 47 (62.6%) | 7 (33.3%)* | 9 (36%)* | 21 (72.4%) | 0.03 |
| Cognitive impairment | 37 (49.3%) | 8 (38%)* | 8 (32%)* | 21 (72.4%) | 0.007 |

*No statistical significant, NMS: Non-motor symptoms, PD: Parkinson's disease

by the disease itself. It is seen that patients with PD who have on-off-type motor fluctuations also demonstrate higher resting heart rate, increased orthostatic hypotension, and decreased responses during the Valsalva maneuver and the cold pressor test during the "off" state when compared with healthy control subjects (26).

**Urinary Symptoms**

Urinary symptoms are a major problem in patients with PD. Nocturia is common, causing impairment in sleep. In this study, the overall prevalence of urinary symptoms was 50.6% with 72.4% when disease duration was greater than 9 years. This falls in the range of prevalence rates shown in previous studies; Liu et al. (10) 56%, Mridula et al. (5) 86.7%, Martinez-Martin et al. (20) 59%, Vongvaivanich et al. (15) 54.6%, and Azmin et al. (14) 32.7%.

A highly complex mechanism underlies urinary dysfunction in PD. It is influenced by dopaminergic neurons both peripherally and in the central nervous system. The use of antiparkinsonian medication, especially anticholinergics, may further cause urinary dysfunction (27). In a single-photon emission computed tomography imaging-based study, Winge et al. (28) established an association of the severity of urinary problems with the relative degeneration of neurons in the caudate nucleus.

**Sexual Dysfunction**

Sexuality is an important part of a healthy life (29). Several reports have found sexual dysfunction to be associated with PD (30) and the prevalence ranges from 22% to 68.4% (30). In our study, we noted an overall prevalence of 56% and 79.3% in patients with ≥9 years of disease duration. Other studies have shown slightly lower prevalences of 28.3% (5) and 33% (20). Studies have established an association of erectile dysfunction and low desire in both sexes of patients with PD with disease and treatment (31). On the other hand, drugs, especially dopamine agonists, as well as deep brain stimulation of bilateral subthalamic nuclei, can result in impulse control disorders and hypersexuality (5). Sexual dysfunction can trigger delusions of infidelity and behavioral issues causing severe caregiver stress.

**Sleep Disturbance**

Sleep disturbances were reported by 39 (52%) patients in our cohort. Among those with disease duration ≥9 years, the prevalence was 75.8%. Similar findings were noted by others (5,12,14).

Sleep is affected by various reasons in PD. Other motor symptoms such as increased rigidity, NMS such as nocturia, depression, and hallucinations can impair sleep. PD in itself leads to degeneration of central regulators of sleep in the brainstem, thalamus, and cortex. Sleep fragmentation is most frequently seen but insomnia and excessive daytime somnolence (with added contribution from medication) are also common, and REM sleep behavioral disorder can predate the motor symptoms by a decade (32). Although sleep dysfunction is not purely due to dopaminergic dysfunction, several studies have suggested that dopaminergic drugs, as well as deep brain stimulation, could improve sleep dysfunction in PD (33).

**Depression/Anxiety**

Depression or anxiety can be secondary to any disease, but in PD, it may be an integral part of the disease. Existing studies have shown the prevalence of depression, psychosis, and anxiety to range from 16% to 70% (5,10,12,14). In our study, we found an overall prevalence of 53.3% with the maximum prevalence in those with ≥9 years' disease duration (79.3%).

Neurodegeneration plays a major role in causing depression in patients with PD. The brain stem structures that degenerate include the locus coeruleus and raphe nucleus, along with the substantia nigra, as has been demonstrated by pathologic studies performed by Braak et al. (34). Involvement of noradrenergic and serotonergic neurons underlie the pathophysiology of depression in PD. This was evidenced by a positron emission tomography (PET) study, which showed lower dopamine and noradrenaline transporter levels in the limbic system, as well as the locus coeruleus (35). Similarly reduced serotonergic 1A receptor availability in orbitofrontal and limbic regions has been demonstrated using $^{18}$F-fluorodeoxyglucose PET (36). Ishihara and Brayne (37) established a two to three-fold increase in the prevalence of depression in patients with PD in comparison with healthy people. Depression can occur before motor symptoms and may be present for 4-6 years before PD is diagnosed (37).

**Hallucinations/Delusions**

Hallucinations and delusions are more common in older patients and those who have a bradykinetic rigid variant. A much higher prevalence was noted in the present study, 49% overall. Others studies have shown varying prevalences, lower 15% by Mridula et al. (5) 17% by Martinez-Martin et al. (20), Vongvaivanich et al. (15) 17.3%, whereas Molho and Factor (38) identified it in 30% and Amar et al. (39) reported a similar prevalence of 45%. Generally, hallucinations occur later in the PD disease course and 72.4% of our patients with ≥9 years of duration of disease had hallucinations and delusions.

Dopaminergic drugs, amantadine and anticholinergics, when used for a long time, can induce psychosis in patients with PD. This is worsened with cognitive impairment. An alternative hypothesis suggests a direct correlation with the disease itself. The "continuum hypothesis" suggests that REM sleep behavioral disorder associated with vivid dreams convert into medication-induced hallucinations and delusions and ends in delirium.

**Cognition**

Cognitive impairment, previously thought to occur only in late disease, is now recognized to occur from the early stages of the disease. In our study, we found 33% with disease duration ≤4 years had cognitive impairment compared with 72.4% of patients with disease of ≥9 years' duration; our findings are supported by others (5,16,22).

Dopamine agonists and levodopa may improve cognition, as seen in better performances in the "on" state compared with the "off" state, and may act by improving corticostriatal outflow (40). However, higher doses and anticholinergics can impair cognition and behavior.

**Study Limitations**

The strength of the study is that all patients were evaluated by a single movement disorder specialist, excluding inter-rater bias and the study population covered the disease duration from early to advanced disease. We have few limitations. The sample size was small and we used only a simple questionnaire in a cross-sectional study. We could not assess the impact of medications on NMS.

## Conclusion

In our study, all patients (100%) had at least one NMS, the most prevalently affected domains were gastrointestinal and cardiovascular, followed by sexual dysfunction, cognition, and anxiety/depression. NMS frequency increased with disease duration (≥9 years). Treatment options are limited, though increased dopaminergic medications or deep brain stimulation may help.

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### Ethics

**Ethics Committee Approval:** This prospective Parkinson disease registry and the registry based study was approved by Institutional Ethics Committee (Yashoda Academy of Medical Education and Research) file no: RP-18/2011.

**Informed Consent:** Informed consent was taken from all participating patients.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: K.R.M., V.S.B., Design: J.R.C., K.R.M., Data Collection or Processing: J.R.C., K.R.M., Analysis or Interpretation: K.R.M., V.S.B., Writing: J.R.C., K.R.M.

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