Research article

A descriptive study on symptoms of Parkinson's disease in an Indian cohort from Karnataka

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ABSTRACT

Introduction and Aim: Parkinson's Disease (PD) is a multifactorial neurodegenerative disorder with ever-changing motor and nonmotor symptoms. Disease treatment is modified accordingly with the progression of the disease. The present study was carried out to understand the symptoms reported by PD subjects in different phases of the disease.

Materials and Methods: Demographic and clinical details were obtained using questionnaires to evaluate the frequency and severity of various motor and nonmotor symptoms experienced by the PD subjects.

Results: Ageing was strongly associated with the onset of disease, whereas the BMI category adversely correlated with other motor symptoms (OMS), nonmotor symptoms (NMS), and specifically gastrointestinal symptoms. Tremors were the most troublesome cardinal motor symptoms, followed by stiffness and bradykinesia. The most common NMS were fatigue/tiredness, anxiety/depression, insomnia, constipation, and cognitive impairment. Anxiety and depression were positively associated with other NMS symptoms such as insomnia, fatigue and exhaustion, apathy, and gastrointestinal problems. More than half of our patients reported gastrointestinal discomfort, early satiety, appetite decrease, and bloating. In our present investigation, the most common gastrointestinal symptoms linked with constipation were straining evacuation, lumpy hard stool, and incomplete evacuation.

Conclusion: We have analysed the frequency and trend of various symptoms associated with PD in an Indian population from Karnataka. A significant correlation exists between motor and nonmotor symptoms, which impacts the quality of life in PD during the course of the disease.

Keywords: Constipation; gastrointestinal symptoms; motor symptoms; neurodegenerative disorder; nonmotor symptoms; Parkinson's disease.

INTRODUCTION

Parkinson's disease is a multifactorial, slow-progressive neurodegenerative movement disorder. PD is described as an idiopathic disease with no identifiable cause. Several risk factors have been closely studied and associated with PD. It is often proposed that genetics and exposure to environmental toxins could initiate neurodegeneration in PD. Ageing, genetics, gender, environmental factors and head injury have been linked with the aetiology of PD (1). A prevalence of 33 PD cases per lakh individuals is reported in India (2). According to the most recent WHO data, PD mortality in India reached 43,398 in 2020 or 0.51 percent of all deaths. India is ranked 65th in the world, with a PD mortality rate of 4.57 per lakh people adjusted to age (3).

Although PD was once thought to be a motor system disease, it is now understood to be a complex disorder with various clinical manifestations, including neuropsychiatric, gastrointestinal, and various other nonmotor symptoms (NMS), in addition to bradykinesia, stiffness, resting tremors and other motor symptomatology (4). Due to the lack of a definitive diagnostic test, clinical categorisation criteria are used to define PD by the occurrence of both motor and only a few nonmotor symptoms. The majority of symptoms are progressive, and in present clinical practice, monitoring these defining characteristics is the key to identifying PD. A favourable response to dopaminergic medication serves as the primary verification of PD diagnosis and is a prominent sign of diagnostic reliability. Every patient is distinct in terms of their symptoms, severity, and rate of progress; as a result, every case of PD is unique (5). We conducted a cross-sectional descriptive study of Indian PD subjects residing in Karnataka to compare and analyse the association and correlation of various symptoms with different attributes.

MATERIALS AND METHODS

Institutional ethics committee of Kasturba Hospital approved this cross-sectional observational study. This study is registered in the clinical trial registry of India (CTRI/2018/04/013333). Subjects were recruited from the neurology clinic with written informed consent. PD subjects diagnosed by a clinical neurologist based on the United Kingdom brain bank society of PD criteria were included in the study. Subjects with secondary Parkinsonian symptoms and unstable neurological or psychiatric illness were excluded from the study (5).

Data on potential risk factors associated with PD, such as occupation, well water drinking, and living habitat, were collected. Occupation-wise, subjects were classified into physical and non-physical workers (6). Subjects were scored for the severity of motor symptoms reported using UPDRS-III (Unified Parkinson's Disease Rating Scale- part III specific for motor symptoms). Subjects were grouped into different stages based on the symptoms using Modified Hoehn and Yahr Staging (7,8). Subjects were treated accordingly to ease their motor symptoms. Medication details of individual subjects were collected, and the levodopa equivalent dose was calculated (9). Detailed questionnaires were used to understand the frequency of cardinal motor symptoms (CMS) and other motor symptoms (OMS) reported in our PD subjects. Similarly, data on the severity of nonmotor symptoms (NMS), with a special focus on gastrointestinal symptoms and the frequency of symptoms related to constipation, were also collected (10–12). We have included (OMS) sialorrhea and dysphagia in the gastrointestinal symptoms as these symptoms are associated with the gastrointestinal tract.

SPSS version 20 was used to determine the statistical significance. Different statistical tests such as descriptive statistics to get the frequency, mean and standard deviation, Spearman correlation, One-way ANOVA and Kruskal-Wallis were carried out to evaluate the statistical association and differences.

RESULTS

Forty subjects were enrolled by considering the inclusion and exclusion criteria described in the methodology. Approximately 60% of the subjects were above 65 years of age (range 41-82 years), body mass index (BMI) (range: 17.72 kg/m^2-24.77 kg/m^2), age at onset of disease (range: 34-78 years), duration on treatment (range: 3 months to 14 years), other descriptive data collected from the subjects with respect to demographic and medical history are tabulated (Table 1). 30% of the subjects belonged to the early onset group (<50 years at onset), and 70% were late-onset PD (≥50 years at onset). Some of our subjects had comorbidities; 7.5% had heart ailments, 2.5% had hypothyroidism, 2.5% had hyperthyroidism, and 5% suffered from arthritis other than hypertension and T2DM. 30% of the subjects were homemakers, 17.5% were with clerical office work, 5% were teachers, 10% had small-scale businesses, the rest were physical labourers, 22.5% were farmers, and 15% were day labourers such as tailors, welders and others.

Table 1: Demographic and clinical data of the subjects

Descriptive		**Mean ± SD or n (%)**
Age (years)		58.32 ±11.05
Age at Onset of PD (years)		55.45 ±11.68
Treatment Duration (years)		1.9 ±2.8
UPDRS III Score		20.35 ±8.33
LEDD mg		462.35 ±292.06
BMI		22.26 ±2.05
Family History of PD		4 (10)
Hypertension		13 (32.5)
T2DM		5 (12.5)
Other Medical History		5 (17.5)
Drinking well water		19 (47.5)
Physical Activities		5 (12.5)
Other Natural Therapies		5 (12.5)
Nutritional Supplements		4 (10)
Coffee Intake		14 (35)
Gender	Male	27 (67.5)
	Female	13 (32.5)
Diet	Veg	18 (45)
	Mixed	22 (55)
BMI Category	Underweight	1 (2.5)
	Healthy	21 (52.2)
	Overweight	18 (45)
Occupation	Non-Physical	25 (62.5)
	Physical	15 (37.5)
Residence	Rural	32 (80)

	Urban/Semi-Urban	8 (20)
Alcohol Consumption	Never	35 (87.5)
	Current	2 (5)
	Former	3 (7.5)
Tobacco Chewing / Smoking	Never	35 (87.5)
	Occasionally	2 (5)
	Former	3 (7.5)
Modified Hoehn and Yahr Staging	Stage 1	19 (47.5)
	Stage 1.5	10 (25)
	Stage 2	3 (7.5)
	Stage 2.5	8 (20)

BMI: Body Mass Index; LEDD: Levodopa Equivalent Daily Dose; T2DM: Type II Diabetes Mellitus; UPDRS III: Unified Parkinson's Disease Rating Scale III- Motor Symptoms

Data collected on the medications revealed only one subject was on treatment with an individual drug (acting as a dopamine agonist), and 27.5% of the subjects were only on Syndopa. In contrast, the rest of the 70% of subjects were on multiple combination therapy. 90% of the subjects were prescribed Syndopa, and 45% were on varying combinations of various other drugs. We also noted that 60% of the subjects were on dopamine agonists, 40% were on monoamine oxidase-B (MAOB) Inhibitor, 12.5% used drug acting as glutamate antagonists and 22.5% on cholinergic system in combination with other drugs. Higher LEDD (Levodopa Equivalent Daily Dose) was recommended for subjects with severe motor symptoms, specifically tremor ($\chi^2(3) = 3.65$, p= 0.05), rigidity ($\chi^2(3) = 7$, p=0.03) and bradykinesia ($\chi^2(3) = 2.93$, p=0.08[#]).

Frequency of CMS and various OMS reported in our PD subjects are depicted in Fig. 1. Severity of NMS, precisely gastrointestinal symptoms and frequency of symptoms related to constipation are also diagrammatically represented in Fig. 2, 3 and 4. A Kruskal-Wallis H test showed that there was a statistically significant difference in CMS [$\chi^2(3) = 10.537$, $p = 0.015$] and OMS [$\chi^2(3) = 10.023$, $p = 0.018$] between the different stages of the disease based on Modified H&Y Stages.

Statistical analysis disclosed that advancing age positively correlated with age at the onset of disease (r=0.444, p=0.004) and enhanced NMS (r=0.444, p=0.004). Similarly, CMS positively correlated with OMS (r=0.570, p=0.000), NMS (r=0.553, p=0.000) and specifically gastrointestinal symptoms (r=0.377, p=0.017). Whereas BMI negatively correlated with OMS (r=-0.317, p=0.04), NMS (r=-0.335, p=0.03) and gastrointestinal symptoms (r=-0.483, p=0.002). Non-parametric Spearman's correlation test performed for CMS and OMS are in table 2.

Anxiety and depression positively correlated with other NMS such as insomnia (r=0.554, p=0.000), fatigue and tiredness (r=0.549, p=0.000), apathy (r=0.554, p=0.000), and gastrointestinal symptoms specifically early satiety (r=0.356, p=0.024), abdominal pain (r=0.346, p=0.029), sialorrhea (r=0.319, p=0.045), bloating (r=0.355, p=0.025) along with some of the motor symptoms such as the masked face (r=0.353, p=0.025), dystonia, and freezing (Table 3). Subjects who complained of fatigue and tiredness showed an association with motor symptoms of bradykinesia (r=0.358, p=0.023) and masked face (r=0.346, p=0.031). Rest of the NMS correlations with respect to OMS and NMS are mentioned in Tables 3 and 4, respectively.

Gastrointestinal symptoms, dysphagia positively correlated with tremors (r=0.533, p=0.000), balance impairment (r=0.471, p=0.002), and rigidity (r= 0.467, p=0.002). Appetite loss correlated with tremors (r=0.424, p=0.006) and balance impairment (r=0.446, p=.0.004). Rigidity was also associated with incomplete evacuation (0.430, p=0.006) and constipation (r=0.359, p=0.023). Early satiety positively correlated with anxiety/ depression (r= 0.35, p=0.024), apathy (r= 0.344, p=0.030) and insomnia (r=0.343, p=0.030). Only anxiety and depression correlated with sialorrhea (r=0.319, p=0.045), bloating (r=0.355, p=0.025), abdominal pain (r=0.346, p= 0.029).

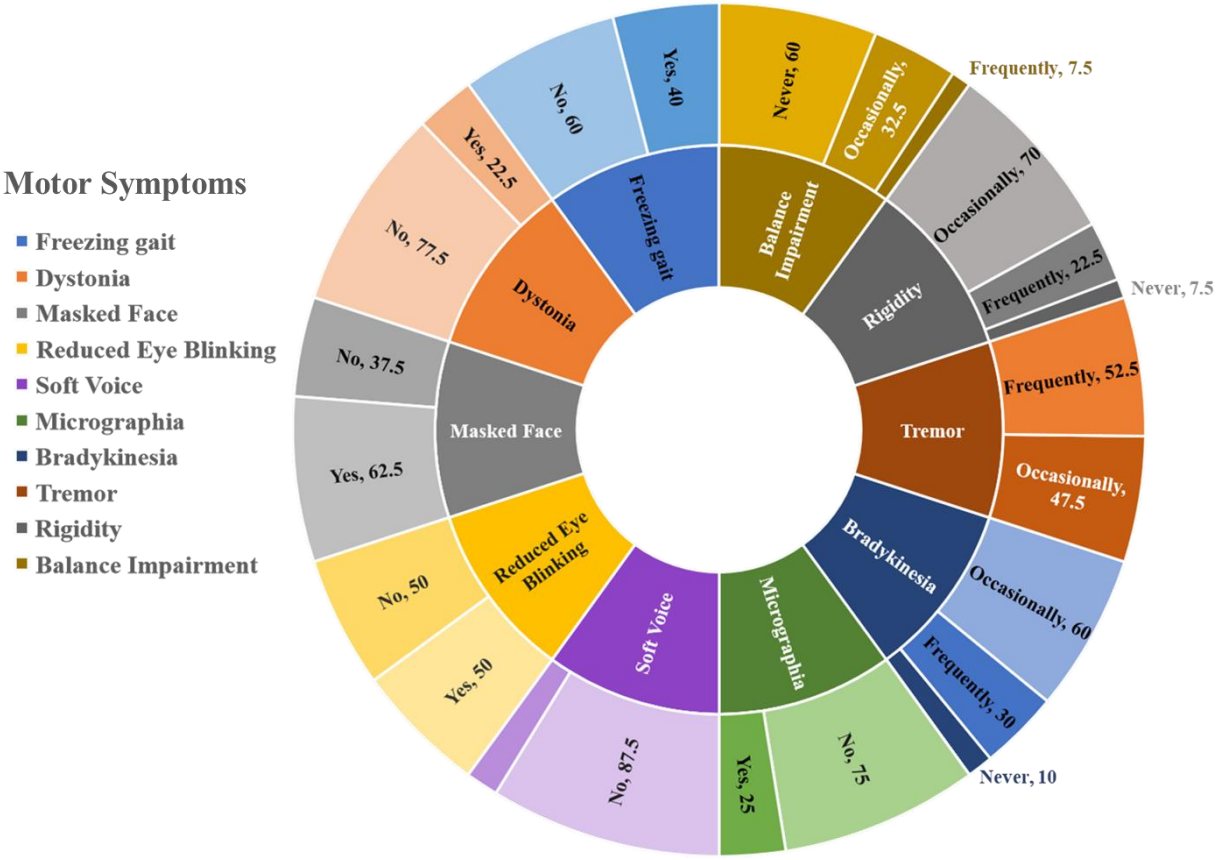

Fig.1: Motor symptoms in PD. Cardinal motor symptoms- Rigidity, Tremors, Bradykinesia and Balance Impairment; Other motor symptoms- Freezing gait, Dystonia, Masked face, Reduced eye blinking, Micrographia, Soft voice

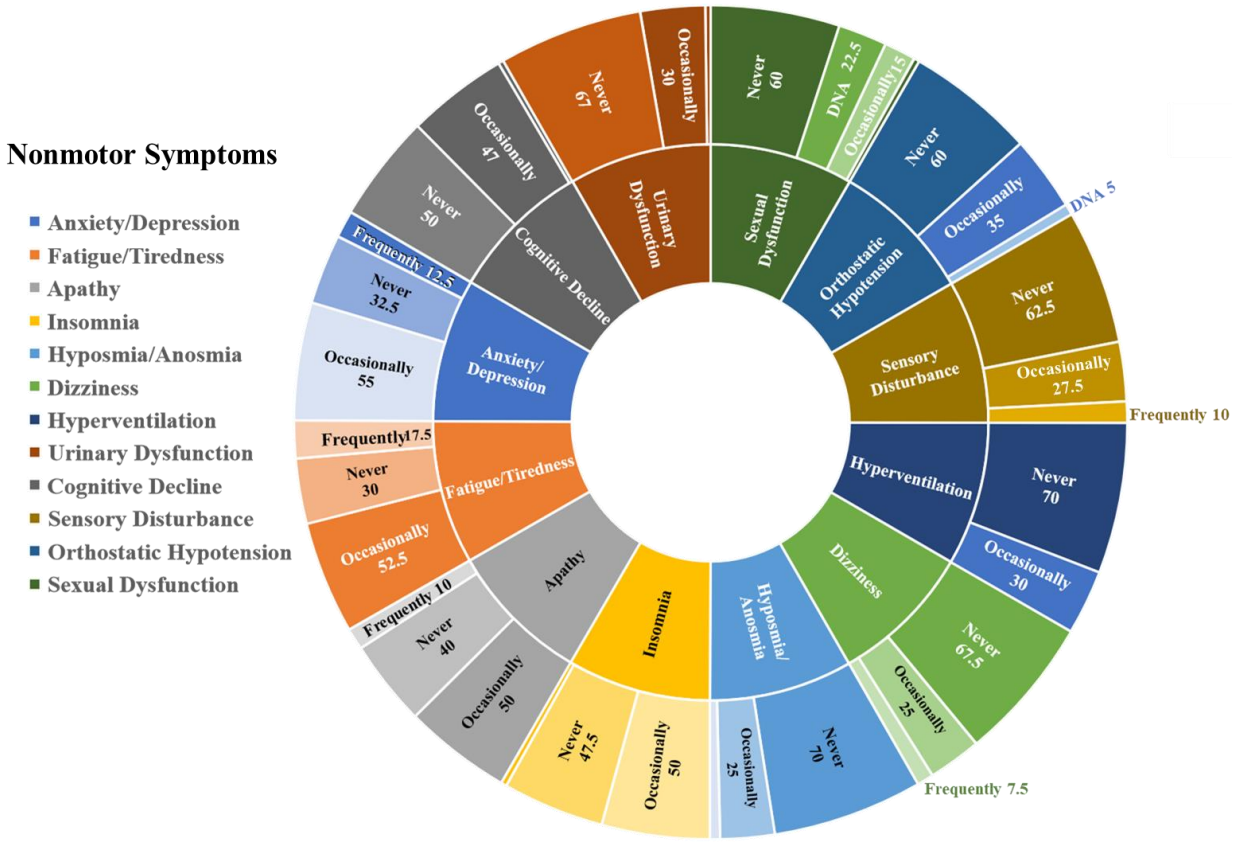

Fig. 2: Nonmotor symptoms in PD. Mood disturbance- Anxiety/Depression, Apathy, Fatigue/Tiredness; Autonomic dysfunction- Orthostatic Hypotension, Hyperventilation, Sexual dysfunction, Urinary dysfunction, Dizziness; Sensory dysfunction- Hyposmia/Anosmia, sensory disturbance (pain); and Cognitive decline

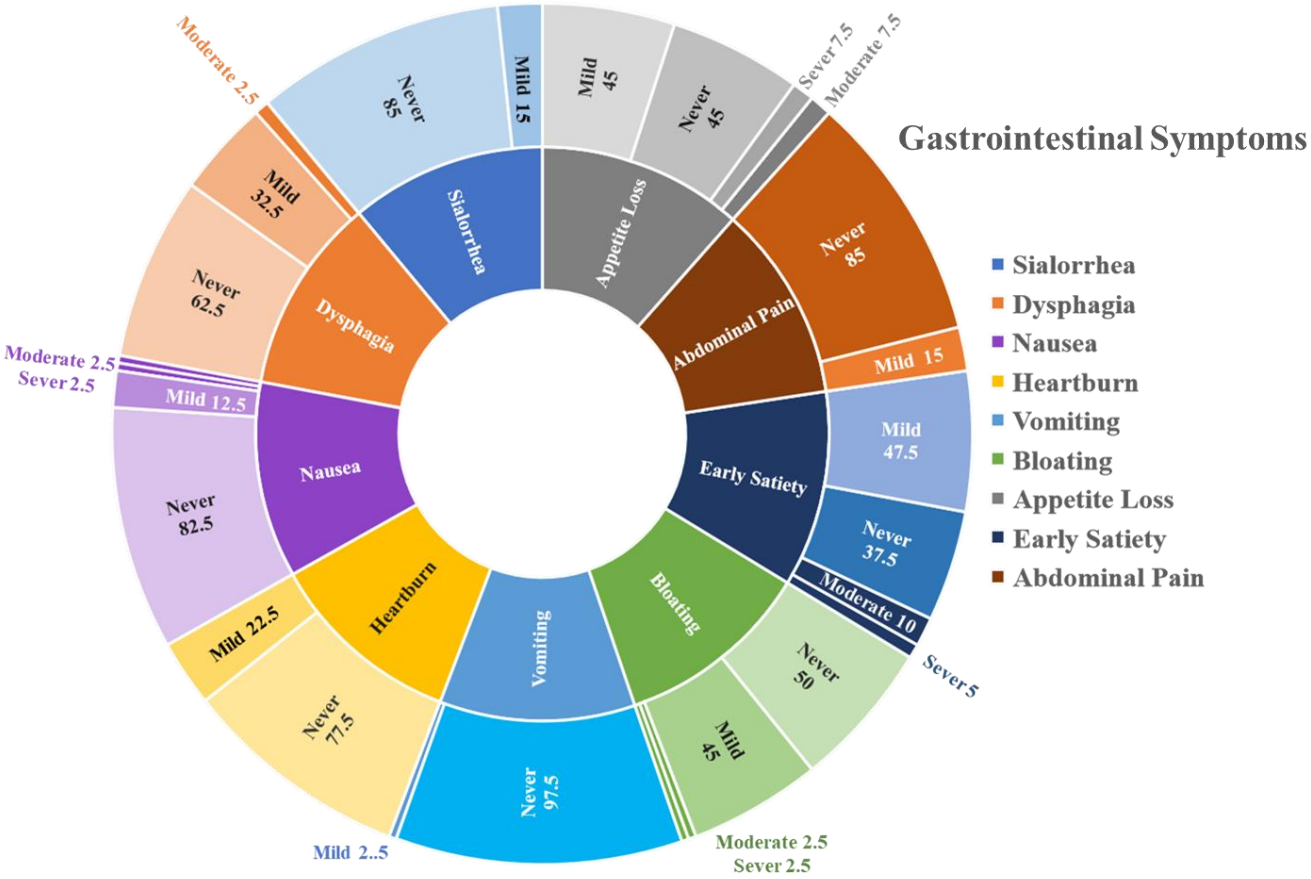

Fig. 3: Gastrointestinal symptoms in PD

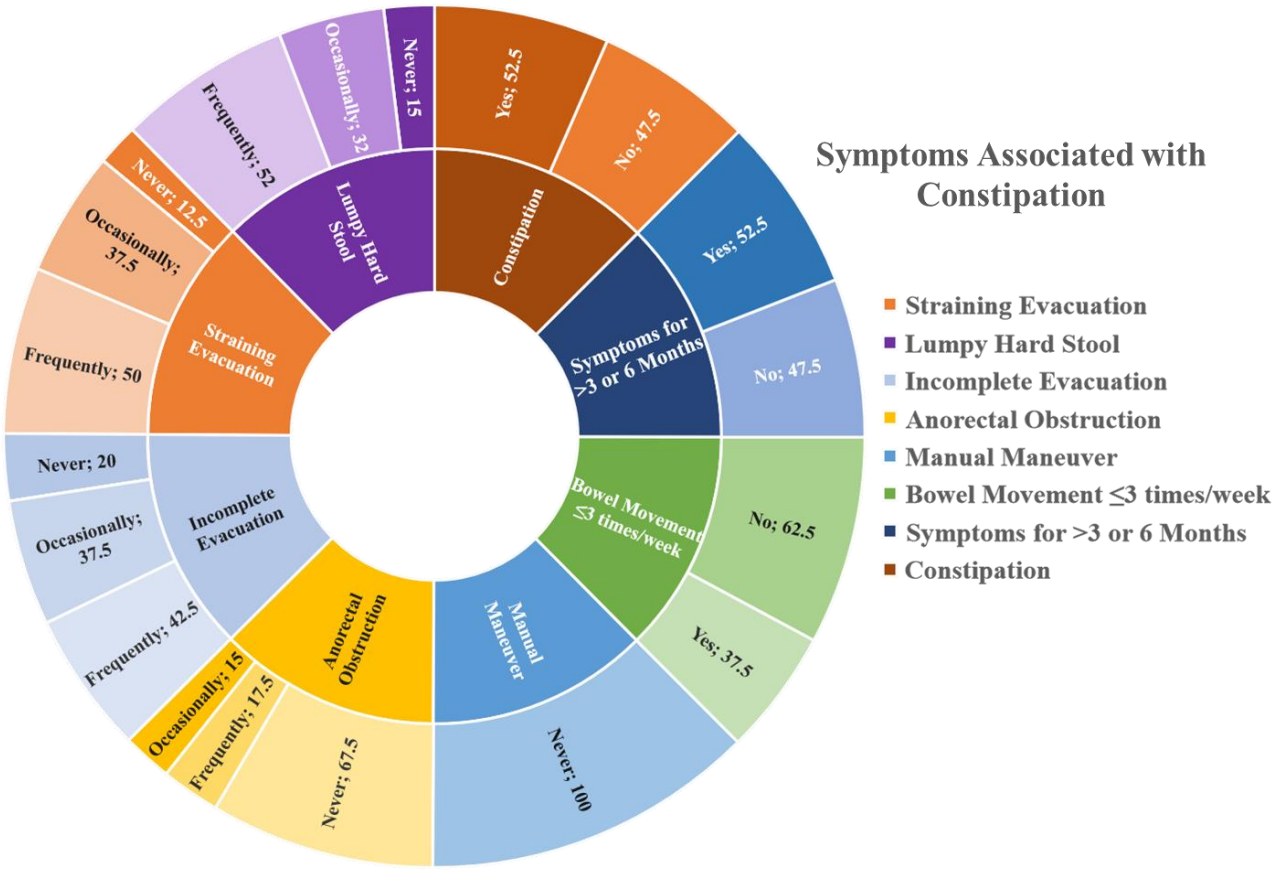

Fig. 4: Symptoms associated with constipation

Table 2: Assessment of Spearman's statistical correlation of cardinal and other motor symptoms

	Bradykinesia		Tremor		Rigidity		Balance impairment	
	r	***p***	***R***	***P***	***r***	***p***	***r***	***p***
Bradykinesia	1		**0.319***	**.045**	0.301	0.059	0.139	0.392
Tremor	**0.319***	**0.045**	1		**0.459****	**0.003**	0.205	0.204
Rigidity	0.301	0.059	**0.459****	**0.003**	1		0.245	0.128
Balance impairment	0.139	0.392	0.205	0.204	0.245	0.128	1	
Micrographia	**0.311***	**0.051**	0.087	0.595	0.177	0.273	**0.425****	**0.006**
Masked Face	**0.411****	**0.008**	0.194	0.231	**0.423****	**0.007**	0.142	0.382
Reduced Eye Blinking	0.249	0.121	0.150	0.355	**0.474****	**0.002**	0.245	0.127
Soft Voice	0.256	0.111	**0.360***	**0.023**	**0.330***	**0.038**	**0.518****	**0.001**
Freezing	0.315*	0.048	0.164	0.313	0.261	0.103	**0.414****	**0.008**
Dystonia	0.215	0.183	**0.393***	**0.012**	**0.423****	**0.007**	0.219	0.175

*Correlation is significant at the 0.05 level (2-tailed), ** correlation is significant at the 0.01 level (2-tailed).

Table 3: Assessment of Spearman's statistical correlation of NMS against other motor symptoms

	Balance impairment		Freezing		Dystonia	
	r	***P***	***r***	***p***	***r***	***p***
Anxiety/Depression	0.204	0.206	**0.497****	**0.001**	**0.366***	**0.020**
Fatigue/Tiredness	**0.346***	**0.029**	**0.604****	**0.000**	**0.369***	**0.019**
Apathy	0.214	0.185	**0.619****	**0.000**	**0.449****	**0.004**
Insomnia	0.276	0.085	**0.583****	**0.000**	**0.479****	**0.002**
Dizziness	0.201	0.214	**0.406****	**0.009**	0.255	0.112
Hyperventilation	**0.617****	**0.000**	**0.356***	**0.024**	0.300	0.060
Urinary Dysfunction	0.097	0.553	**0.317***	**0.046**	0.165	0.308
Sexual Dysfunction	0.202	0.211	**0.325***	**0.041**	0.257	0.109
Cognitive Decline	0.154	0.342	**0.424****	**0.006**	**0.450****	**0.004**
Sensory Disturbance	**0.428****	**0.006**	0.108	0.506	0.227	0.159
Orthostatic Hypotension	0.127	0.435	**0.026**	0.875	0.024	0.883

*Correlation is significant at the 0.05 level (2-tailed), ** correlation is significant at the 0.01 level (2-tailed)

DISCUSSION

The mechanisms of dopaminergic neuronal death in PD are embellished and accelerated by ageing, possibly through interactions with both genetic and environmental factors. The majority of researchers have found that the incidence of PD rises with age and is more common in the older population (6,13). Spearman's rank correlation was computed to assess the relationship between various symptoms and to understand the association of severity and frequency with each other. Our analysis is consistent with other studies that advanced age had a higher incidence of PD. NMS were observed to be positively correlated with age in our subjects. Previous studies statistically reported NMS to be more prevalent in PD patients than in age and gender-matched old individuals (14). Most of our subjects lived in rural areas (80%), ~50% consumed well water, and 22.5% practised agriculture. Rural residence, farming and well water use during early life are associated with PD (6,15).

One-way ANOVA and Kruskal Wallis test indicated that modified H&Y Stage is positively associated with CMS and OMS. However, there was no significant difference in NMS and gastrointestinal symptoms reported by subjects in different stages of the disease. H&Y staging has been designed based on the motor symptoms manifested by cases; hence we did not observe any correlation between NMS and H&Y staging. Most of our subjects were in the healthy BMI category (52.5%). We observed BMI negatively correlated with NMS and OMS. That is, most of our subjects from a rural background and lower BMI (low body weight) had more severe NMS and OMS, which is an interesting new observation made in our subjects that must be confirmed in a larger population. We did not note any significant correlation between BMI and different H&Y staging. Other studies have reported lower BMI associated with the advancing stages of the disease (16). According to previous research, approximately half of PD patients experience weight loss, which is mainly caused by disease advancement (17). Some of our subjects suffered from comorbidities such as T2DM (12.5%), hypertension (32.5%) and other chronic medical conditions (17.5%). According to recent observational research, individuals with T2DM have a higher probability of developing PD and experiencing quick progression and severe forms of clinical manifestations (18). Similarly, meta-analyses have disclosed a history of hypertension as a potential risk factor in motor PD (19). In our study, we noted only a small proportion of PD were also diagnosed with T2DM and hypertension.

Table 4: Assessment of Spearman's statistical correlation of nonmotor symptoms

	Anxiety Depression		Fatigue Tiredness		Apathy		Insomnia		Dizziness		Urinary Dysfunction		Sexual Dysfunction		Cognitive Decline	
	r	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***	***r***	***p***
Advancing age	0.132	0.417	0.227	0.159	**.325***	**0.041**	**.388***	**0.013**	0.275	0.086	**.389***	**0.013**	0.21	0.193	**.355***	**0.024**
LEDD mg	0.261	0.103	**.345***	**0.029**	0.243	0.13	0.267	0.096	**.335***	**0.034**	0.19	0.241	**.323***	**0.042**	0.139	0.393
Anxiety Depression	1		**.594****	**0.000**	**.523****	**0.001**	**.516****	**0.001**	**.368***	**0.02**	0.254	0.114	0.131	0.421	**.374***	**0.018**
Fatigue Tiredness	**.594****	**0.000**	1		**.690****	**0.000**	**.470****	**0.002**	**.338***	**0.033**	0.221	0.17	**.535****	**0.000**	**.546****	**0.000**
Apathy	**.523****	**0.001**	**.690****	**0.000**	1		**.756****	**0.000**	**.349***	**0.027**	**.349***	**0.027**	**.458****	**0.003**	**.612****	**0.000**
Insomnia	**.516****	**0.001**	**.470****	**0.002**	**.756****	**0.000**	1		**.339***	**0.032**	**.339***	**0.032**	**.368***	**0.02**	**.651****	**0.000**
Dizziness	**.368***	**0.02**	**.338***	**0.033**	**.349***	**0.027**	**.339***	**0.032**	1		**.430****	**0.006**	0.196	0.225	**.374***	**0.018**
Urinary Dysfunction	0.254	0.114	0.221	0.17	**.349***	**0.027**	**.339***	**0.032**	**.430****	**0.006**	1		0.196	0.225	**.374***	**0.018**
Sexual Dysfunction	0.131	0.421	**.535****	**0.000**	**.458****	**0.003**	**.368***	**0.02**	0.196	0.225	0.196	0.225	1		**.510****	**0.001**
Cognitive Decline	**.374***	**0.018**	**.546****	**0.000**	**.612****	**0.000**	**.651****	**0.000**	**.374***	**0.018**	**.374***	**0.018**	**.510****	**0.001**	1	

*Correlation is significant at the 0.05 level (2-tailed), ** correlation is significant at the 0.01 level (2-tailed)

A large number of individuals develop tremors at some time over the course of the disease (4). We reported tremors as the most bothersome CMS, followed by rigidity and slow movement. Though the symptoms of tremors did not affect the functionality of the subjects, instead, it is reported to be a symptom responsible for the subjects to get anxious and restless, which intensified the symptoms in public gatherings leading to low self-estimate and distressing oneself and family, impacting mental wellbeing. In contrast, rigidity and bradykinesia made the subjects inactive functionally. We report CMS positively correlated with NMS & OMS. A combination of CMS, for example, slowness of movement and stiffness, may cause a decline in spontaneous correlated movements, such as loss of hand gestures during speaking, reduced eye blinking, or expression. Similarly, bradykinesia of pharyngeal muscles causes dysphagia leading saliva to collect in the mouth and drool (4). 87.5% of our subjects were on drugs acting on the dopaminergic system, while 22.5% were on combination therapy affecting both the dopaminergic and cholinergic systems of the brain, though none were on antihistamines.

NMS, fatigue/tiredness, anxiety/depression, insomnia, constipation and cognitive decline were the most predominant nonmotor symptoms identified in our study. Nearly all earlier research shows a prevalence of symptoms in the categories of sleep, mood, cognition, urine function, and sexual function among PD. However, there is variation in the proportional frequency of these symptoms (20). Anxiety and depression positively correlated with insomnia. Depression and anxiety go hand in hand and are responsible for distress in PD. In a survey of subjects with both early-stage and late-stage PD, mood disorders such as depression, anxiety, and apathy were listed as some of the most problematic NMS. Certain NMS are exhibited in some PD cases, although not all the different symptoms, whereas NMS may not be reported or may be of less concern in some individuals. The clinical presentation of various NMS emphasises the ubiquitous brain and peripheral nervous system Lewy pathology and varying rate of neurodegeneration rather than depletion of just the dopaminergic neuron (21). 70% of the subjects in our study reported fatigue or tiredness, and 12.5% experienced anxiety frequently, although 55% felt depressed or anxious occasionally. We also noted a positive correlation between these symptoms. Tiredness and lack of interest are regarded as the initial signs of depression. Depression is a primary NMS, affecting ~50% of PD, leading to anxiety and panic episodes with the progression of the disease (5).

Gastrointestinal clinical manifestations were most bothersome and constantly reported by our patients. Gastrointestinal symptoms, early satiety, appetite loss and bloating were experienced by more than fifty percent of our subjects. In our study, straining evacuation, lumpy hard stool, and incomplete evacuation were the most prominent gastrointestinal symptoms associated with constipation. Sung HY et al. report a similar finding in their study population though the frequency and severity vary (22). In our study population, we observed constipation in ~52% of the subjects using the Bristol stool chart. Constipation may result from a dysfunctional autonomic nervous system, and it is linked with the aggregation of alpha-synuclein (23). It is one of the most prevalent prodromal NMS, impacting over 60% of PD cases (24). Previous studies have reported an association between motor symptoms and NMS, explicitly involving the autonomic nervous system (25). We observed a significant correlation between gastrointestinal symptoms and CMS, specifically tremors and rigidity.

CONCLUSION

Our study highlights the need to include NMS as an important component of clinical examination in order

to prevent NMS from being overlooked in the therapy, which is focused on motor evaluation and results in inadequate treatment. A significant, well-designed prospective community-based investigation is required in the Indian population to determine the prevalence, symptom categorisation based on the NMS and UPDRS, treatment effectiveness, and temporal progression of NMS in PD. Such a study will serve as a foundation for bettering the standard of care given to these individuals by medical personnel.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Olanow, C.W., Klein, C., Schapira, A.H.V. Parkinson's Disease. In: Jameson, J.L., Fauci, A.S., Kasper, D.L., Hauser, S.L., Longo, D.L., Loscalzo, J., editors. Harrison's Principles of Internal Medicine. 20th ed. New York, NY: McGraw-Hill Education; 2018.
2. Gourie-Devi, M., Gururaj, G., Satishchandra, P., Subbakrishna, D.K. Prevalence of Neurological Disorders in Bangalore, India: A Community-Based Study with a Comparison between Urban and Rural Areas. Neuroepidemiology. 2004;23(6):261-268.
3. Parkinson's Disease in India [Internet]. World Life Expectancy. [cited 2022 Jun 13]. Available from: https://www.worldlifeexpectancy.com/india-parkinson-disease
4. Chou, K.L. Clinical manifestations of Parkinson disease - UpToDate [Internet]. 2022 [cited 2022 Oct 14]. Available from: https://www.uptodate.com/contents/clinical-manifestations-of-parkinson-disease/print
5. Váradi, C. Clinical Features of Parkinson's Disease: The Evolution of Critical Symptoms. Biology. 2020 May;9(5):103.
6. Behari, M., Srivastava, A.K., Das, R.R., Pandey, R.M. Risk factors of Parkinson's disease in Indian patients. Journal of the Neurological Sciences. 2001;190(1-2):49-55.
7. Goetz, C.G., Fahn. S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stebbins, G.T., *et al.*, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Process, format, and clinimetric testing plan. Mov Disord. 2007 Jan;22(1):41-47.
8. Goetz, C.G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G.T., Counsell, C., *et al.*, Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations The Movement Disorder Society Task Force on rating scales for Parkinson's disease. Mov Disord. 2004;19(9):1020-1028.
9. Tomlinson, C.L., Stowe, R., Patel, S., Rick, C., Gray, R., Clarke, C.E. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord. 2010 Nov 15;25(15):2649-2653.
10. Park, H., Lee, J.Y., Shin, C.M., Kim, J.M., Kim, T.J., Kim, J.W. Characterisation of gastrointestinal disorders in patients with parkinsonian syndromes. Parkinsonism Relat Disord. 2015 May;21(5):455-460.
11. Schrag, A., Anastasiou, Z., Ambler, G., Noyce, A., Walters, K. Predicting diagnosis of Parkinson's disease: A risk algorithm based on primary care presentations. Mov Disord. 2019 Apr;34(4):480-486.
12. Srinivas, M., Srinivasan, V., Jain, M., Rani Shanthi, C.S., Mohan, V., Jayanthi, V. A cross-sectional study of stool form (using Bristol stool chart) in an urban South Indian population. JGH Open. 2019 Dec;3(6):464-467.
13. Collier, T.J., Kanaan, N.M., Kordower, J.H. Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. Nat Rev Neurosci. 2011 Jun;12(6):359-366.
14. Krishnan, S., Sarma, G., Sarma, S., Kishore, A. Do nonmotor symptoms in Parkinson's disease differ from normal aging? Mov Disord. 2011 Sep;26(11):2110-2113.
15. Sanyal, J., Chakraborty, D.P., Sarkar, B., Banerjee, T.K., Mukherjee, S.C., Ray, B.C., *et al.*, Environmental and familial risk factors of Parkinson's disease: case-control study. Can J Neurol Sci. 2010 Sep;37(5):637-642.
16. Van der Marck, M.A., Dicke, H.C., Uc, E.Y., Kentin, Z.H.A, Borm, G.F., Bloem, B.R., *et al.*, Body mass index in Parkinson's disease: a meta-analysis. Parkinsonism Relat Disord. 2012 Mar;18(3):263-267.
17. Cersosimo, M.G., Raina, G.B., Pellene, L.A., Micheli, F.E., Calandra, C.R., Maiola, R. Weight Loss in Parkinson's Disease: The Relationship with Motor Symptoms and Disease Progression. Biomed Res Int. 2018;2018:9642524.
18. Cheong, J.L.Y., de, Pablo-Fernandez, E., Foltynie, T., Noyce, A.J. The Association Between Type 2 Diabetes Mellitus and Parkinson's Disease. J Parkinson's Dis. 2020;10(3):775-789.
19. Hou, L., Li, Q., Jiang, L., Qiu, H., Geng, C., Hong, J.S., *et al.*, Hypertension and Diagnosis of Parkinson's Disease: A Meta-Analysis of Cohort Studies. Front Neurol. 2018 Mar 19;9:162.
20. Ravan, A., Ahmad, F.M.H., Chabria, S., Gadhari, M., Sankhla, C.S. Non-motor symptoms in an Indian cohort of Parkinson's disease patients and correlation of progression of non-motor symptoms with motor worsening. Neurology India. 2015 Mar 1;63(2):166.
21. Sauerbier, A., Jenner, P., Todorova, A., Chaudhuri, K.R. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disord. 2016 Jan;22 Suppl 1:S41-S46.
22. Sung, H.Y., Park, J.W., Kim, J.S. The Frequency and Severity of Gastrointestinal Symptoms in Patients with Early Parkinson's Disease. J Mov Disord. 2014 Apr;7(1):7-12.
23. Cersosimo MG, Benarroch EE. Pathological correlates of gastrointestinal dysfunction in Parkinson's disease. Neurobiol Dis. 2012 Jun;46(3):559-564.
24. Yu, Q.J., Yu, S.Y., Zuo, L.J., Lian, T.H., Hu, Y., Wang, R.D., *et al.*, Parkinson disease with constipation: clinical features and relevant factors. Sci Rep. 2018 Jan 12;8(1):567.
25. Berganzo, K., Tijero B., González-Eizaguirre, A., Somme, J., Lezcano, E., Gabilondo, I., *et al.*, Motor and non-motor symptoms of Parkinson's disease and their impact on quality of life and on different clinical subgroups. Neurologia. 2016 Dec;31(9):585-591.