Original Article

Frequency Of Non-Motor Symptom In Patients Presenting With Parkinson's Disease At Tertiary Care Hospital In Pakistan

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Abstract

Parkinson's Disease (PD) is the second most common neurodegenerative disorder. Its risk increases with advancing age. Prevalence of Parkinson's disease in Pakistan has been estimated to be 0.4 million by Pakistan Parkinson Disease Society.[1] The exact etiology has not been fully elucidated but there is evidence of involvement of non-dopaminergic pathways (such as cholinergic and serotonergic). Non-motor symptoms (NMS) often precede motor symptoms by up to several decades, most commonly olfactory dysfunction (hyposmia), Rapid Eye Movement (REM) sleep behavior disorder (RBD), constipation, depression, and pain.[2] The NMS of parkinsonism can occur both during early and late stage and are due to non-dopaminergic cell dysfunction such as serotonin.[3]

Introduction:

The NMS have been recognized globally and previous literature has shown the frequency of NMS to change geographically.[4] Similarly, other factors such as environmental factors and genetics also play a vital role in NMS among PD patients.[5] These factors indicate the necessity of geographical studies carried out in South east Asian countries. Karri et al.[6] have reported an audit study regarding NMS in PD patients from India. The non-motor symptoms are an integral part of the disease but are under recognized by the treating physician and under reported by the patients.

The rationale of the study was to find the frequency of non-motor symptoms (NMS) in patients presenting with Parkinson's disease to establish the local perspective as the data from international and local study show variance.[7-10] They also are in considered to be a problem of severe disease. Early recognition of these symptoms could be used as preclinical markers of PD and lead to earlier diagnosis and treatment.

Material & methods

Study design:

This is a cross-sectional study conducted in Dr. Ruth K.M Pfau Municipal Hospital, Karachi, Pakistan, after receiving IRB approval. Data collection took place for 6 months after approval of the study protocol. Informed consents were obtained from all patients for inclusion in the sample and for the use of their data in the study. Non-probabilistic and continuous sampling technique was used collecting data.

Inclusion criteria/Exclusion criteria

Candidates between the ages of 50 and 80 who had been diagnosed with PD according to the UK PD Brain Bank criteria and had been suffering from the condition for at least 3 months were enrolled. Exclusion from study was carried out if (1) patients without informed consent, (2) history of hypothyroidism and hyperthyroidism, (3) dating scan-confirmed pregnant patients, (4) ischemic/hemorrhagic stroke (5) Patients with a history of sinus thrombosis (6) Patients with a history of epilepsy. h/o CNS disease (e.g., patients with head trauma, multiple sclerosis (7) renal impairment, chronic obstructive pulmonary disease, asthma, congestive heart failure, myocardial infarction, chronic liver disease).

Outcomes:

Brief historical and demographic information for the duration of PD was collected. All participants in the study were required to complete an NMS questionnaire by themselves or with the help of family members. When language was an issue, researchers helped the patient complete her PD-NMS questionnaire. Answers were recorded as 'yes' or 'no'. Patients only ticked yes if they had experienced the symptom/problem in the past month. Quantitative variables such as (age and duration of PD) and qualitative variables such as gender, PD stage, hypertension, type II diabetes, economic income status, educational status, occupational status, non-motor symptoms. Variable findings are recorded in the form.

Statistical analysis

Data were analyzed with SPSS version 23.0. Means and standard deviations were calculated for age and duration of PD. Frequencies and percentages were calculated for gender, PD stage, hypertension, type II diabetes, income status, education status, occupational status, and non-motor symptoms (yes/no). We stratified for age, gender, hypertension, type II diabetes, financial income status, educational status, occupational status, and duration of PD to determine their effects on outcome variables. Post-stratification chi-square test was applied and p-values < 0.05 were considered significant. The sample size was determined using the WHO sample size software, considering the lowest frequency of NMS fecal incontinence (P) = (6%), margin of error (d) = 4%, and confidence level (C.I) = 95% was calculated. Estimated sample size was (n) = 136 patients.

Results

Patient characteristics:

In this study 136 patients were included to assess the status of non- motor symptoms (NMS) in patients presenting with PD at our institution and the results were analyzed as Mean ± SD of age was 65.3±8.24 years. Mean ± SD of duration of PD was 59.9±26.9 with months. In distribution of gender, 97 (71.3%) were male while 39 (28.7%) were female. Diabetes mellitus type II was documented in 50 (36.8%) patients. Hypertension was noted in 75 (55.1%) patients. Stage of PD showed that 15 (11.0%) patients were included in stage I, 19 (13.9%) in stage II, 27 (19.8%) in stage III, 46(33.9%) in stage IV while 29 (21.4%) were included in stage V. These characteristics are shown in Table 1.

Table 1: Baseline characteristics of included participants.

Characteristic	**Mean±SD / Frequency (%)**
Age	65.3±8.24 years
Duration of disease	59.9±26.9
Gender Male Female	 97 (71.3%) 39 (28.7%)

Diabetes Mellitus	50 (36.8%)
Hypertension	75 (55.1%)
Stages	
Stage I	15 (11.0%)
Stage II	19 (13.9%)
Stage III	27 (19.8%)
Stage IV	46(33.9%)
Stage V	29 (21.4%)

Social status:

Out of 136 patients, 80 (58.8%) patients were employed while 56 (41.2%) were unemployed. Educational status showed that 19 (13.9%) patients were illiterate, 45 (33.2%) had primary education, 38 (27.9%) had secondary education while 34 (25.0%) had higher education. Financial income status showed that 27 (19.8%) patients belong to lower income group, 31 (22.8%) in Lower Middle-Income Group, 43 (31.6%) in Middle-Income Group, 20 (14.8%) in Upper Middle-Income Group while 15 (11.0%) were included in Upper Income Group. These social statuses are shown in Table 2.

Table 2: Social status of included participants.

Characteristic	**Mean±SD / Frequency (%)**
Employment status	
Employed	80 (58.8%)
Unemployed	56 (41.2%)
Educational status	
Illiterate	19 (13.9%)
Primary	45 (33.2%)
Secondary	38 (27.9%)
Higher	34 (25.0%)
Financial status	
Lower-Income Group	27 (19.8%)
Lower Middle-Income Group	31 (22.8%)
Middle-Income Group	43 (31.6%)
Upper Middle-Income	20 (14.8%)
Upper Income Group	15 (11.0%)

Symptoms:

Nocturia was found to be most common non-motor symptoms i.e.135 (99.2%) followed by constipation 123 (90.4%), loss of libido 120 (88.2%), forgetfulness in 112 (82.3%), taste/smelling in 107 (78.6%), insomnia 102 (75.0%), restless leg 101 (74.2%), daytime sleep 100 (73.5%), dizzy 99 (72.8%), urgency 85 (62.5%), sex difficulty 82 (60.3%), depression 79 (58.0%), falling 75 (55.1%), bowel emptying 74 (54.4%), vivid dream 73 (53.7%), sweating 71 (52.2%), pains 71 (52.2%), dribbling 69 (50.7%), swallowing 66 (48.5%), acting dream 63 (46.3%), loss concentration 62 (45.5%), anxiety 59 (43.3%), loss in interest 49 (36.0%), weight change 44 (32.3%), delusion 44 (32.3%), hallucination 40 (29.4%), swelling 39 (28.6%), diplopia 36 (26.4%), vomiting 33 (24.2%), bowel incontinence was found to be the least common non-motor symptoms i.e. 30 (22.0%). This data is represented in Table 3. Stratification of age groups, gender, hypertension, diabetes mellitus type II, occupational status, duration of PD, educational status and financial income status was done with respect to non-motor symptoms to assess significant difference.

Table 3: Non-motor symptoms in included participants with Parkinson's disease.

Characteristic	Mean±SD / Frequency (%)
Nocturia	135 (99.2%)
constipation	123 (90.4%)
loss of libido	120 (88.2%)
forgetfulness	112 (82.3%)
taste/smelling	107 (78.6%)
insomnia 102 (75.0%)	102 (75.0%)
restless leg	101 (74.2%)
daytime sleep	100 (73.5%)
dizzy	99 (72.8%)
urgency	85 (62.5%)
sex difficulty	82 (60.3%)
depression	79 (58.0%)
falling	75 (55.1%)
bowel emptying	74 (54.4%)
vivid dream	73 (53.7%)
sweating	71 (52.2%)
pains	71 (52.2%)
dribbling	69 (50.7%)
swallowing	66 (48.5%)

acting dream	63 (46.3%)
loss concentration	62 (45.5%)
anxiety	59 (43.3%)
loss in interest	49 (36.0%)
weight change	44 (32.3%)
delusion	44 (32.3%)
hallucination	40 (29.4%)
swelling	39 (28.6%)
diplopia	36 (26.4%)
vomiting	33 (24.2%)
bowel incontinence	30 (22.0%)

Post stratification analysis:

In present study, stratification of confounders / effect modifiers with respect to non-motor symptoms, insignificant difference was reported in age group (P=0.385), gender (P=0.978) and financial income status (P=0.054), whereas significant difference was documented in hypertension (P=0.0001), diabetes mellitus type II (P=0.0001), occupational status (P=0.0001), duration of Parkinson's disease (P=0.0001) and educational status (P=0.001). Statistically significant results are shown in Table 4, 5, 6, 7, and 8.

Table 4: Stratification of hypertension with non-motor symptoms

NON-MOTOR SYMPTOMS	**HYPERTENSION**		**P-VALUE**
	Hypertensive	Non-Hypertensive	
Constipation	80 (3.6%)	43 (1.9%)	
Bowel emptying	50 (2.2%)	24 (1.1%)	
Dribbling	49 (2.2%)	20 (0.9%)	
Swallowing	40 (1.8%)	26 (1.2%)	
Taste/smelling	60 (2.7%)	47 (2.1%)	
Vomiting	22 (1.0%)	11 (0.5%)	
Bowel incontinence	20 (0.9%)	10 (0.4%)	
Nocturia	65 (2.9%)	70 (3.1%)	
Urgency	50 (2.2%)	35 (1.6%)	

Forgetfulness	70 (3.1%)	42 (1.9%)	0.0001
Loss concentration	40 (1.8%)	22 (1.0%)	
Loss of interest	35 (1.6%)	14 (0.6%)	
Dizzy	60 (2.7%)	39 (1.7%)	
Sweating	58 (2.6%)	13 (0.6%)	
Falling	40 (1.8%)	35 (1.6%)	
Daytime sleepiness	68 (3.0%)	32 (1.4%)	
Insomnia	67 (3.0%)	35 (1.6%)	
Restless leg	66 (2.9%)	35 (1.6%)	
Vivid dream	40 (1.8%)	33 (1.5%)	
Acting dream	50 (2.2%)	13 (0.6%)	
Delusion	22 (1.0%)	22 (1.0%)	
Hallucination	22 (1.0%)	18 (0.8%)	
Depression	60 (2.7%)	19 (0.8%)	
Anxiety	40 (1.8%)	19 (0.8%)	
Loss of libido	70 (3.1%)	50 (2.2%)	
Sex difficulty	62 (2.8%)	20 (0.9%)	
Pains	40 (1.8%)	31 (1.4%)	
Weight change	29 (1.3%)	15 (0.7%)	
Diplopia	26 (1.2%)	10 (0.4%)	
Swelling	10 (0.4%)	29 (1.3%)	

Applied chi-square test

Table 5: Stratification of diabetes mellitus type II with non-motor symptoms

NON-MOTOR SYMPTOMS	**DIABETES MELLITUS**		**P-VALUE**
	Diabetic	Non-Diabetic	
Constipation	40 (1.8%)	83 (3.7%)	
Bowel emptying	35 (1.6%)	39 (1.7%)	
Dribbling	30 (1.3%)	39 (1.7%)	
Swallowing	42 (1.9%)	24 (1.1%)	
Taste/smelling	41 (1.8%)	66 (2.9%)	
Vomiting	22 (1.0%)	11 (0.5%)	
Bowel incontinence	20 (0.9%)	10 (0.4%)	
Nocturia	35 (1.6%)	100 (4.5%)	
Urgency	30 (1.3%)	55 (2.5%)	
Forgetfulness	45 (2.0%)	67 (3.0%)	
Loss concentration	38 (1.7%)	24 (1.1%)	
Loss of interest	37 (1.6%)	12 (0.5%)	
Dizzy	30 (1.3%)	69 (3.1%)	
Sweating	38 (1.7%)	33 (1.5%)	
Falling	35 (1.6%)	40 (1.8%)	
Daytime sleepiness	50 (2.2%)	50 (2.2%)	

Insomnia	48 (2.1%)	54 (2.4%)	0.0001
Restless leg	47 (2.1%)	54 (2.4%)	
Vivid dream	32 (1.4%)	41 (1.8%)	
Acting dream	20 (0.9%)	43 (1.9%)	
Delusion	15 (0.7%)	29 (1.3%)	
Hallucination	14 (0.6%)	26 (1.2%)	
Depression	30 (1.3%)	49 (2.2%)	
Anxiety	20 (0.9%)	39 (1.7%)	
Loss of libido	40 (1.8%)	80 (3.6%)	
Sex difficulty	35 (1.6%)	47 (2.1%)	
Pains	30 (1.3%)	41 (1.8%)	
Weight change	12 (0.5%)	32 (1.4%)	
Diplopia	10 (0.4%)	26 (1.2%)	
Swelling	5 (10.2%)	34 (1.5%)	

Applied chi-square test

Table 6: Stratification of occupational status with non-motor symptoms

NON-MOTOR SYMPTOMS	**OCCUPATIONAL STATUS**		**P-VALUE**
	Employed	Unemployed	
Constipation	70 (3.1%)	53 (2.4%)	
Bowel emptying	40 (1.8%)	34 (1.5%)	
Dribbling	35 (1.6%)	34 (1.5%)	
Swallowing	45 (2.0%)	21 (0.9%)	
Taste/smelling	60 (2.7%)	47 (2.1%)	
Vomiting	20 (0.9%)	13 (0.6%)	
Bowel incontinence	23 (1.0%)	7 (0.3%)	
Nocturia	65 (2.9%)	70 (3.1%)	
Urgency	50 (2.2%)	35 (1.6%)	
Forgetfulness	60 (2.7%)	52 (2.3%)	
Loss concentration	35 (1.6%)	27 (1.2%)	
Loss of interest	40 (1.8%)	9 (0.4%)	
Dizzy	39 (1.7%)	60 (2.7%)	
Sweating	44 (2.0%)	27 (1.2%)	
Falling	42 (1.9%)	33 (1.5%)	
Daytime sleepiness	55 (2.5%)	45 (2.0%)	0.0001
Insomnia	48 (2.1%)	54 (2.4%)	
Restless leg	46 (2.1%)	55 (2.5%)	
Vivid dream	39 (1.7%)	34 (1.5%)	
Acting dream	45 (2.0%)	18 (0.8%)	
Delusion	30 (1.3%)	14 (0.6%)	
Hallucination	28 (1.2%)	12 (0.5%)	
Depression	35 (1.6%)	44 (2.0%)	

Anxiety	25 (1.1%)	34 (1.5%)	
Loss of libido	46 (2.1%)	74 (3.3%)	
Sex difficulty	40 (1.8%)	42 (1.9%)	
Pains	38 (1.7%)	33 (1.5%)	
Weight change	35 (1.6%)	9 (0.4%)	
Diplopia	20 (0.9%)	16 (0.7%)	
Swelling	19 (0.8%)	20 (0.9%)	

Applied chi-square test

Table 7: Stratification for duration of Parkinson's disease with non-motor symptoms

NON-MOTOR SYMPTOMS	**DURATION** [In Months]		**P-VALUE**
	7 - 60	>60	
Constipation	85 (3.8%)	38 (1.7%)	0.0001
Bowel emptying	44 (2.0%)	30 (1.3%)	
Dribbling	39 (1.7%)	30 (1.3%)	
Swallowing	50 (2.2%)	16 (0.7%)	
Taste/smelling	65 (2.9%)	42 (1.9%)	
Vomiting	16 (0.7%)	17 (0.8%)	
Bowel incontinence	20 (0.9%)	10 (0.4%)	
Nocturia	68 (3.0%)	67 (3.0%)	
Urgency	56 (2.5%)	29 (1.3%)	
Forgetfulness	66 (2.9%)	46 (2.1%)	
Loss concentration	40 (1.8%)	22 (1.0%)	
Loss of interest	49 (2.2%)	0 (0.0%)	
Dizzy	50 (2.2%)	49 (2.2%)	
Sweating	40 (1.8%)	31 (1.4%)	
Falling	40 (1.8%)	35 (1.6%)	
Daytime sleepiness	59 (2.6%)	41 (1.8%)	
Insomnia	44 (2.0%)	58 (2.6%)	
Restless leg	45 (2.0%)	56 (2.5%)	
Vivid dream	37 (1.6%)	36 (1.6%)	
Acting dream	46 (2.1%)	17 (0.8%)	
Delusion	32 (1.4%)	12 (0.5%)	
Hallucination	26 (1.2%)	14 (0.6%)	
Depression	38 (1.7%)	41 (1.8%)	
Anxiety	22 (1.0)	37 (1.6%)	
Loss of libido	43 (1.9%)	77 (3.4%)	
Sex difficulty	38 (1.7%)	44 (2.0%)	
Pains	35 (1.6%)	36 (1.6%)	
Weight change	33 (1.5%)	11 (0.5%)	

Diplopia	25 (1.1%)	11 (0.5%)	
Swelling	29 (1.3%)	10 (0.4%)	

Applied chi-square test

Table 8: Stratification of educational status with non-motor symptoms

NON-MOTOR SYMPTOMS	EDUCATIONAL STATUS				P-VALUE
	Illiterate	Primary	Secondary	Higher	
Constipation	16 (0.7%)	40 (1.8%)	35 (1.6%)	32 (1.4%)	0.001
Bowel emptying	10 (0.4%)	38 (1.7%)	20 (0.9%)	6 (0.3%)	
Dribbling	4 (0.2%)	25 (1.1%)	22 (1.0%)	18 (0.8%)	
Swallowing	5 (0.2%)	19 (0.9%)	19 (0.9%)	23 (1.0%)	
Taste/smelling	11 (0.5%)	39 (1.7%)	30 (1.3%)	27 (1.2%)	
Vomiting	3 (0.1%)	10 (0.4%)	9 (0.4%)	11 (0.5%)	
Bowel incontinence	2 (0.1%)	11 (0.5%)	7 (0.3%)	10 (0.4%)	
Nocturia	18 (0.8%)	45 (2.0%)	38 (1.7%)	34 (1.5%)	
Urgency	6 (0.3%)	32 (1.4%)	21 (0.9%)	26 (1.2%)	
Forgetfulness	10 (0.4%)	40 (1.8%)	31 (1.4%)	31 (1.4%)	
Loss concentration	4 (0.2%)	29 (1.3%)	22 (1.0%)	7 (0.3%)	
Loss of interest	0 (0.0%)	19 (0.9%)	15 (0.7%)	15 (0.7%)	
Dizzy	4 (0.2%)	39 (1.7%)	24 (1.1%)	32 (1.4%)	
Sweating	2 (0.1%)	16 (0.7%)	22 (1.0%)	19 (0.9%)	
Falling	6 (0.3%)	18 (0.8%)	20 (0.9%)	31 (1.4%)	
Daytime sleepiness	10 (0.4%)	40 (1.8%)	29 (1.3%)	21 (0.9%)	
Insomnia	15 (0.7%)	37 (1.7%)	30 (1.3%)	20 (0.9%)	
Restless leg	15 (0.7%)	37 (1.7%)	26 (1.2%)	23 (1.0%)	
Vivid dream	3 (0.1%)	32 (1.4%)	27 (1.2%)	11 (0.5%)	
Acting dream	4 (0.2%)	28 (1.3%)	22 (1.0%)	9 (0.4%)	
Delusion	8 (0.4%)	11 (%)	15 (0.7%)	10 (0.5%)	
Hallucination	4 (0.2%)	12 (0.5%)	16 (0.7%)	8 (0.4%)	
Depression	7 (0.3%)	30 (1.3%)	24 (1.1%)	18 (0.9%)	
Anxiety	4 (0.2%)	29 (1.3%)	19 (0.9%)	7 (0.3%)	
Loss of libido	12 (0.5%)	44 (2.0%)	31 (1.4%)	33 (1.5%)	
Sex difficulty	8 (0.4%)	34 (1.5%)	28 (1.3%)	12 (0.5%)	
Pains	9 (0.4%)	10 (0.4%)	21 (0.9%)	31 (1.4%)	
Weight change	4 (0.2%)	18 (0.8%)	12 (0.5%)	10 (0.5%)	
Diplopia	2 (0.1%)	15 (0.7%)	13 (0.6%)	6 (0.3%)	
Swelling	3 (0.1%)	12 (0.5%)	16 (0.7%)	8 (0.4%)	

Applied chi-square test

Discussions:

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease with a reported prevalence rate of approximately 1% in people aged 60 years and over.[11] This prevalence rate increases with

advancing age. While traditionally believed to be a disorder producing only motor symptoms, this understanding has since been proven unequivocally false, with the disease also involving a large and varied number of non-motor symptoms that can have a significant impact on quality of life, ability to conduct activities of daily living, and career burden.

While most motor symptoms involved in PD are generally well understood, with a number of effective treatment options having been developed over recent years, non-motor symptoms still provide an area of significant debate. This is particularly the case with regard to the pathophysiology of mild cognitive decline and Parkinson's disease dementia, the accurate assessment of mood symptoms, and the exact nature of the complicated relationship that exists between motor and non-motor symptom presentation.

In this study we highlight the overall high frequency of NMS in PD in Pakistani population, and their comparison between mild and severe disease. Some of the components differ in frequency compared to other studies carried out around the world which will be discussed below. In our study the highest overall NMS was found to be nocturia at 135 (99.2%), comparatively higher than other studies.[12]

Constipation was another NMS found in this study in 123 (90.4%) patients. This was higher than study of Bonnet et al (45 to 60%), but similar conducted by Khoo et al and Azmin et al reported (67%) in their studies who looked at Malaysian population.[12-14] The urinary urgency in 85 (62.5%) patients and Khoo et al. described urinary urgency in spectrum of NMS in Early PD at 46%.[12, 13]

Other studies have reported slightly lower incidences of 53-67% [36,37,61,84]. Depression is linked with mortality and morbidity.[15-17] It needs to be addressed properly at every stage of Parkinson's disease and should be treated aggressively.

According to Bonnet et al., the sex difficulty correlated more with severity of motor disease and male gender compared with age, depression and use of L-dopa.[12] The study reported significantly lower incidence of impaired libido and sexual dysfunction (17% and 28% respectively). Similarly, the study reported it to be only 8%.[14] One explanation of such marked difference could be different culture and social norms and biases against reporting. It is pertinent that this topic should be approached with due respect with the patient and managed appropriately.

Among all the NMS, incidence of falling was 75 (55.1%) in our study. Fear of falling has been shown to be directly related to actual falling.[18] The incidence of these symptoms was extremely low in PRIAMO study (14.2% and 1% respectively).[15] Khoo et al. reported somewhat higher number but still lower than our population (33% and 23% respectively).[13] Sleep related problems i.e. insomnia and restless leg were present in 102 (75%) and 101 (74.2%). This is similar to some studies such as study in Norwegian population reported incidence of sleep problems to be 60%.[19, 20]

In present study, stratification of confounders / effect modifiers with respect to non-motor symptoms, insignificant difference was reported in age group (P=0.385), gender (P=0.978) and financial income status (P=0.054), whereas significant difference was documented in hypertension (P=0.0001), diabetes mellitus type II (P=0.0001), occupational status (P=0.0001), duration of Parkinson's disease (P=0.0001) and educational status (P=0.001).

It is to be concluded that non-motor symptoms are very common in Pakistani population of PD. Nocturia was most common non-motor symptom followed by constipation. Furthermore, there may be the likely need for a culturally appropriate screening scale for our population. However, there is a need to conduct more studies using large sample size with multiple study sites in Pakistan to validate these results.

References:

1. Politis, M., et al.(2010): Parkinson's disease symptoms: the patient's perspective - Mov Disord, 25: 1646-51.
2. Munawar, M., et al.(2012): Parkinson disease and its association between China and Pakistan - Pakistan Journal of Medical and Health Sciences, 6: 1058-1061.
3. Khealani, B.A. and S.M. Baig.(2006): Clinical spectrum of Parkinson's disease from Pakistan - Singapore Med J, 47: 1075-9.
4. van Wamelen, D.J., et al.(2021): Cross-sectional analysis of the Parkinson's disease Non-motor International Longitudinal Study baseline non-motor characteristics, geographical distribution and impact on quality of life - Sci Rep, 11: 9611.
5. Pang, S.Y., et al.(2019): The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease - Transl Neurodegener, 8: 23.
6. Karri, M., B. Ramasamy, and R. Kalidoss.(2020): Prevalence of Non-motor Symptoms in Parkinson's Disease and Its Impact on Quality

of Life in Tertiary Care Center in India - Ann Indian Acad Neurol, 23: 270-274.
7. Durcan, R., et al.(2019): Prevalence and duration of non-motor symptoms in prodromal Parkinson's disease - Eur J Neurol, 26: 979-985.
8. Saad, S.N., Ali Zohair; Badshah, Mazhar; and Afzal, Aamir.(2017): Frequency of non-motor symptoms in parkinson disease: experience from Pakistan - Pakistan Journal of Neurological Sciences (PJNS), 12.
9. Tanveer, K., et al.(2018): Non-motor Symptoms in Patients with Parkinson's Disease: A Cross-sectional Survey - Cureus, 10: e3412.
10. Mukhtar, S., et al.(2018): Frequency of non-motor symptoms in Parkinson's disease presenting to tertiary care centre in Pakistan: an observational, cross-sectional study - BMJ Open, 8: e019172.
11. Mhyre, T.R., et al.(2012): Parkinson's disease - Subcell Biochem, 65: 389-455.
12. Bonnet, A.M., et al.(2012): Nonmotor symptoms in Parkinson's disease in 2012: relevant clinical aspects - Parkinsons Dis, 2012: 198316.
13. Khoo, T.K., et al.(2013): The spectrum of nonmotor symptoms in early Parkinson disease - Neurology, 80: 276-81.
14. Azmin, S., et al.(2014): Nonmotor symptoms in a malaysian Parkinson's disease population - Parkinsons Dis, 2014: 472157.
15. Barone, P., et al.(2009): The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease - Mov Disord, 24: 1641-9.
16. Hussein, A., et al.(2023): Non-Motor Symptoms of Parkinson's Disease: The Neurobiology of Early Psychiatric and Cognitive Dysfunction - Neuroscientist, 29: 97-116.
17. Pessoa Rocha, N., et al.(2014): Depression and cognitive impairment in Parkinson's disease: a role for inflammation and immunomodulation? - Neuroimmunomodulation, 21: 88-94.
18. Castro, P., et al.(2021): Case Report: Acute Onset Fear of Falling and Treatment With "Cognitive Physical Therapy" - Front Neurol, 12: 707840.
19. Bryant, M.S., et al.(2015): Relationship of falls and fear of falling to activity limitations and physical inactivity in Parkinson's disease - J Aging Phys Act, 23: 187-93.
20. Avidan, A., et al.(2013): Associations of sleep disturbance symptoms with health-related quality of life in Parkinson's disease - J Neuropsychiatry Clin Neurosci, 25: 319-26.