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Original Article

Non – motor Symptoms in Parkinson's Disease: It's Relationship with Age of Onset, Duration and Stage of Disease and the Dose and Duration of Levodopa Usage

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Abstract

Parkinson's disease is a disease of motor manifestations but non-motor symptoms are also common in Parkinson's disease. Little emphasis is put on non-motor symptoms of PD and there is little data on the relationship of non-motor symptoms to different aspects of the patient and the disease. In this study the relationship of non-motor symptoms to age at onset, duration and stage of the disease, and dose and duration of levodopa use are studied.

128 patients of PD were studied for non-motor symptoms. 111 patients had different types of sensory, autonomic or psychiatric symptoms. Sensory and autonomic symptoms were significantly more common in patients with early age of disease onset and more prolonged duration of the disease, but psychiatric symptoms had no relationship with these factors. In this study it was also found that the frequencies of non-motor symptoms were related to the stage of the disease, longer the duration of the disease more and more non-motor symptoms appear so that 100% patients in stage 5 of the disease had non-motor symptoms. Also sensory and autonomic symptoms were significantly more common in patients with longer duration and higher dose of levodopa use but psychiatric symptoms were significantly commoner in patients with prolonged duration of levodopa use but not to dose of levodopa used.

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Introduction

Parkinson's disease was cogently described first by James Parkinson in 1817 as a disease characterized 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." The emphasis in Parkinson's disease is on motor manifestations with the diagnostic criteria being the presence of bradykinesia, and one of the following – rigidity, tremor or postural instability. But symptoms of a non-motor nature have also been described in patients of PD and they can be equally disabling.[1,2] Non-motor symptoms have been classified into three categories according to their clinical manifestations: dysautonomic, mental (cognitive / psychiatric), and sensory / pain.[3] These non-motor symptoms may have a varied presentation and unless recognized by the physicians to be a feature of PD itself, lead to unnecessary and often costly or harmful investigations. The type and frequency of non-motor symptoms in patients of Parkinson's

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disease and their relationship to motor fluctuations (MF) have been described elsewhere. In this study the relationship of non-motor symptoms to age at onset, duration and stage of the disease, and dose and duration of levodopa use are studied.

Material and Methods

This was a prospective cross-sectional study carried out in the Movement Disorder Clinic of the Neurology Outpatient Department (NOPD) of Bangabandhu Sheikh Mujib Medical University, Dhaka, during the period from October 2001 to June 2003. Study samples included 128 Parkinson's disease patients. All the patients of Parkinson's disease were examined by at least two doctors working in NOPD of BSMMU to avoid chance of biasness. All 128 patients fulfilled the United Kingdom Parkinson's Disease Brain Bank Criteria[4] for Parkinson's disease. All the patients of Parkinson's disease were staged using the modified Hoehn and Yahr scale. All the patients were taking immediate release levodopa preparation. None of the patients were on antidepressive, antipsychotic, dopamine receptor agonist or anticholinergic medications. All the patients were medically stable, mentally sound without any demonstrable evidence of dementia, and had no evidence of other neurological disease.

In a non-directed fashion, each of the patients was assessed by a structured questionnaire, which included sensory, autonomic and psychiatric symptoms. Each interview consisted of 16 dysautonomic, 6 psychiatric and 6 sensory symptoms. These symptoms were reported in several studies and were collected to create the questionnaire.[5,6,7,8,9,10] This classification of non-motor symptoms was also adopted by Riley and Lang[8] and Hillen and Sage[7]. The patients were also assessed by the Mini-Mental Status Scale to exclude the possibility that cognitive decline interfered with the interview performance (all patients had scales greater than 25/30).

Results

This prospective study of non-motor symptoms in patients of Parkinson's disease is the first of its kind reported from Bangladesh. The study included 128 Parkinson's disease (PD) patients fulfilling the Brain Bank Diagnostic Criteria of the United Kingdom Parkinson's Disease Society.

Table I shows the basic data of the study patients. 128 Parkinson's disease patients between 32 to 85 years of age, of whom 86 were male and 42 female were included in the study. Mean age at onset of disease was 52 years, and mean time of disease duration was 6.34 years. All the patients were on Levodopa therapy for a mean duration of 4.76 years with the dose ranging from 125 to 750 mg per day with the mean dose being 513 mg/day.

Table – I. Basic data of the study patients (n=128)

Parameters	Range	Mean ± SD
Age (years)	32 – 85	58.94 ± 12.14
Age at disease onset (years)	28 – 72	52.61 ± 11.60
Disease duration (years)	0.5 – 16.00	6.34 ± 4.23
Duration of levodopa use (years)	0.50 – 14.00	4.76 ± 3.54
Levodopa dose (mg/day)	125 – 750	513.01 ± 178.19

Table II shows the sex-wise comparison of the basic data. Though there is some difference in the mean age, onset and duration of disease, and duration and dose of levodopa use, the differences between male and female patients are not statistically significant as shown by the P value.

Table – II: Sex-wise comparison of basic data

Parameters	Male (n = 86) (Mean ± SD)	Female (n= 42) (Mean ± SD)	P value[a]
Age (years)	58.21 ± 12.65	60.43 ± 11.00	0.333 [ns]
Age at disease onset (years)	51.63 ± 11.64	54.62 ± 11.38	0.172 [ns]
Disease duration (years)	6.60 ± 4.32	5.81 ± 4.04	0.320 [ns]
Duration of Levodopa use (years)	4.90 ± 3.60	4.48 ± 3.44	0.531 [ns]
Levodopa dose (mg/day)	507.50 ± 180.72	524.29 ± 174.50	0.619 [ns]

[a] Unpaired Student's 't' test
[ns] Not significant

Out of the 128 patients, 111(86.7%) had non-motor symptoms. Of these 84 (75.7%) patients had sensory, 102 (91.9%) patients had autonomic and 20 (18.6%) patients had psychiatric symptoms.

Table III shows the presence of non-motor symptoms in the 128 patients of Parkinson's disease.

Table III: Presence of sensory, psychiatric, and autonomic non-motor symptoms in 128 patients of Parkinson's disease

Sensory Symptoms	**Present in pts.**	**Percentage %**	**Autonomic Symptoms**	**Present In pts.**	**Percentage %**
Akathisia	67	52.34	Excessive sweating	29	37.12
Pain	50	39.06	Drooling	27	21.09
Tingling sensation	36	28.12	Flushing	25	19.53
Tightening sensation	21	16.40	Oral dryness	26	20.31
Burning sensation	15	11.71	Dysphagia	22	17.18
Restlessness	11	8.5	Urinary urgency	20	15.62
Psychiatric Symptoms	**Present in pts.**	**Percentage %**	**Abdominal Bloating**	**17**	**13.28**
Depression	32	25	Abdominal pain	15	11.71
Fatigue	25	19.53	Constipation	21	16.40
Confusion	24	18.75	Impotence	15	11.71
Irritability	16	12.5	Urinary frequency	19	14.84
Elevated mood	13	10.15	Belching	9	7.03
Hallucination	7	5.4	Distal cold sensation	8	6.25
			Palpitation	7	5.46
			Pallor of skin	6	4.68
			Sensation of being hot	8	6.25

The most frequent non-motor symptoms were akathisia (52.34%), pain (39.06%), excessive sweating (37.12%), tingling sensation (28.12%), depression (25%), drooling (21.09%), oral dryness (20.31%), flushing (19.53%) and tightening sensation (16.40%).

Table - IV shows that age at disease onset was significantly higher in patients without sensory (60.14 ± 5.63 years) and autonomic (58.46 ± 3.11 years) fluctuations in comparison to patients with sensory (48.67 ± 11.98 years) and autonomic (51.12 ± 12.58 years) symptoms, whereas, there was no significant difference between patients without (52.15 ± 12.13 years) and with (55.10 ± 7.88 years) psychiatric symptoms.

Table IV: Comparison of age at disease onset between patients with and without sensory, autonomic and psychiatric symptoms

Non-motor symptoms	**n**	**Age (years) (Mean ± SD)**	**P value [a]**
With sensory	84	48.67 ± 11.98	
			<0.001***
Without sensory	44	60.14 ± 5.63	
With autonomic	102	51.12 ± 12.58	
			< 0.01**
Without autonomic	26	58.46 ± 3.11	
With psychiatric	20	55.10 ± 7.88	
			NS
Without psychiatric	108	52.15 ± 12.13	

[a] Unpaired Student's 't' test

Table V shows that the disease duration was significantly higher in patients with sensory (8.52 ± 3.60) and autonomic (7.55 ± 3.90 years) symptoms in comparison to patients without sensory (2.18 ± 0.98 years) and autonomic (1.62 ± 0.73 years). However, there was no significant difference in disease duration between patients with (7.88 ± 3.79 years) and without (6.06 ± 4.27 years) psychiatric symptoms.

Table – V: Comparison of disease duration between patients with and without sensory, autonomic and psychiatric symptoms

Non-motor symptoms	n	Disease duration (years) (Mean ± SD)	P value
With sensory	84	8.52 ± 3.60	
			<0.001***
Without sensory	44	2.18 ± 0.98	
With autonomic	102	7.55 ± 3.90	
			< 0.001**
Without autonomic	26	1.62 ± 0.73	
With psychiatric	20	7.88 ± 3.79	
			NS
Without psychiatric	108	6.06 ± 4.27	

[a] Unpaired Student's 't' test

Table VI shows distribution of patients (n = 128) according to their stage (H&Y scale). According to their frequencies, highest number of patients are in stage 2 (33.6%), then stage 1 (24.2%), stage 3 (20.3%), stage 4 (15.6%), and least number of patients in stage 5 (6.3%). Of the 111 patients with non motor symptoms, all 8 (100%) in stage 5 had NMF, 95% (19/20) in stage 4 had NMF, 88.5% (23/26) in stage 3 had NMF, 88.4% (38/43) in stage 2 and 74.2% (23/31) in stage 1 had non motor symptoms.

Table – VI: Distribution of patients according to their stages (Hoehn and Yahr scale)

Stages of Disease	Patients with Parkinson's disease on Levodopa - No. (%)	Patients with Parkinson's disease associated with non-motor symptoms No. (%)	Patients with Parkinson's disease without associated non-motor symptoms No. (%)
Stage 1	31 (24.2)	23 (74.2)	8 (25.8)
Stage 2	43 (33.6)	38 (88.4)	5 (11.6)
Stage 3	26 (20.3)	23 (88.5)	3 (11.5)
Stage 4	20 (15.6)	19 (95.0)	1 (5.0)
Stage 5	8 (6.3)	8 (100.0)	0

Table VII shows that duration of levodopa use was significantly higher in patients with sensory (6.33 ± 3.40 years) and autonomic (5.64 ± 3.44 years) symptoms in comparison in patients to without sensory (1.75 ± 0.77 years) and autonomic (1.31 ± 0.55 years) symptoms, whereas, there was no significant difference in duration of levodopa use between patients with (5.73 ± 2.65 years) and without (4.58 ± 3.66 years) psychiatric symptoms.

Table – VII: Comparison of duration of levodopa use between patients with and without sensory, autonomic and psychiatric symptoms

Non-motor symptoms	n	Duration of levodopa use (years) (Mean ± SD)	P value[a]
With sensory	84	6.33 ± 3.40	
			<0.001***
Without sensory	44	1.75 ± 0.77	
With autonomic	102	5.64 ± 3.44	
			< 0.001***
Without autonomic	26	1.31 ± 0.55	
With psychiatric	20	5.73 ± 2.65	
			NS
Without psychiatric	108	4.58 ± 3.66	

[a] Unpaired Student's 't' test

Table VIII shows that levodopa dosage was significantly higher in patients with sensory (589.76 ± 153.8 mg/day), autonomic (569.02 ± 147.1 mg/day) and psychiatric (625.75 ± 133.35 mg/day) symptoms in comparison to without sensory (366.48 ± 121.01 mg/day), autonomic (293.27 ± 104.24 mg/day) and psychiatric (492.13 ± 178.09 mg/day) symptoms.

Table – VIII: Comparison of levodopa dose between patients with and without sensory, autonomic and psychiatric symptoms

Non-motor symptoms	n	Levodopa dose (mg/day) (Mean ± SD)	P value[a]
With sensory	84	589.76 ± 153.80	
			<0.001***
Without sensory	44	366.48 ± 121.01	
With autonomic	102	569.02 ± 147.10	
			< 0.001***
Without autonomic	26	293.27 ± 104.24	
With psychiatric	20	625.75 ± 133.35	
			< 0.01**
Without psychiatric	108	492.13 ± 178.09	

[a] Unpaired Student's 't' test

Discussion

This study analyzes the relationship of the non-motor symptoms of Parkinson's disease to the characteristics of the disease and the patients. In this study sensory and autonomic symptoms were significantly more common in patients with early age of disease onset and more prolonged duration of the disease, but psychiatric symptoms had no relationship with these factors. In this study it was also found that the frequencies of non-motor symptoms were related to the stage of the disease, i.e. stage 5 (100%), stage 4 (95%), stage 3 (88.5%), stage 2 (88.4%) and stage 1 (74.2%). Longer the duration of the disease more and more non-motor symptoms appear. These results are in agreement with the study by Gunal et al,[10] who states that non-motor sensory symptoms occur more frequently in patients with an early age at disease onset, patients with long disease duration as well as patients with long duration of levodopa use and higher dose of levodopa. In this study, it was also found that the sensory and autonomic symptoms both were significantly higher in patients with the longer duration of levodopa use ($p < 0.001$).

Non-motor symptoms might be related to dopaminergic mechanisms, but the exact role of dopaminergic stimulation in nonmotor symptoms is not known.[11] The fact that the non-motor symptoms are linked to the motor fluctuations and the generally good response to dopaminergic treatment reported by the patients suggest that the dopaminergic system may be strongly involved.[9] In a number of patients, levodopa or dopaminergic medications have also been found to be useful in managing the non-motor symptoms. This suggests a direct involvement of dopamine. However, "on" period fluctuations and unresponsiveness to dopaminergic treatment strategies may indicate the influence of other neurotransmitter systems on the nonmotor symptoms.[10] The number and variety of non-motor symptoms also suggest the intervention of other neurotransmitters. Some authors suggest that other neurotransmitters fluctuating synchronously with dopamine explain this role, since some of the non-motor symptoms fluctuate in response to dopaminergic therapy but others are unchanged.[12,13] This aspect of non-motor fluctuation may be linked to noradrenergic, serotonergic or other secondary transmitter systems, the roles of which have not yet been clarified.[11,14] The dopaminergic system is known to either directly mediate or modulate some nondopaminergic systems such as the serotoninergic system in the case of mood fluctuations and the adrenergic system in that of dysautonomic symptoms.[15]

We did not find any significant difference between patients with and without psychiatric symptoms with regard to the duration of levodopa use (Table – VII). Similar results were also obtained by Gunal et al. [10] In this study, it was found that all non-motor symptoms, that is, sensory, autonomic and also psychiatric, were significantly higher in patients with higher levodopa dosage ($p<0.01$) (Table –XII). This is similar to the findings by Gunal[10] who reported that psychiatric symptoms were significantly higher depending on levodopa

dosage but could not be associated with age of disease onset, duration of disease or duration of levodopa usage. However, Raudino[16] reported no significant differences between patients with motor and non-motor symptoms regarding age, length of the disease, the Hoehn-Yahr and Webster scale, and the dosage of levodopa. But Quinn[17] reported that two thirds of his patients receiving continuous levodopa treatment experienced mood fluctuations. The significant relationship found between the levodopa dosage and psychiatric symptoms might be a direct effect of levodopa but we could not explain the absence of a significant relationship between duration of levodopa use and psychiatric symptoms. This might indicate that the psychiatric symptoms progress in a different manner from sensory and autonomic symptoms.[7] In the study by Gunal et al,[10] autonomic symptoms showed variability in timing with respect to motor fluctuations also. This may suggest involvement of other neuroanatomic structures beyond nigral degenerations, for instance, hypothalamic involvement has been described in PD.[7,18]

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