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Original Article

Pattern of Non-Motor Fluctuations in Patients of Parkinson's Disease

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Abstract

Parkinson's disease is a common disease of old age, whose major symptoms are of motor nature. Apart from the symptoms related to motor activity, patients of PD also experience various other fluctuating symptoms of a non-motor nature. These non-motor fluctuations (NMF) have been classified according to their characteristics into three categories; dysautonomic, mental (cognitive / psychiatric), and sensory / pain. These non-motor fluctuations 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 varied presentations of the non-motor fluctuations in patients of PD are presented in this study.

128 patients of PD from the Movement Disorder Clinic of the Neurology Out Patient Department of BSMMU were included in this study. 106 had motor fluctuations and 111 had non-motor fluctuations. The non-motor fluctuations were classified into sensory in 67 (63.2%) patients, autonomic in 78 (73.6%) patients and psychiatric in 18 (17%) patients. The most frequent sensory fluctuations were akathisia, pain and tingling sensations. Excessive sweating, drooling, oral dryness and flushing were the common autonomic fluctuations while depression and fatigue were the common psychiatric complaints. Most of the non-motor fluctuations were associated with motor fluctuations and with the "off" state.

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Introduction

Parkinson's disease is a common disease of old age with a prevalence of 10 – 400 / 100,000 of the general population but 15 percent of the individuals between 65 and 74 years of age and more than half of all individuals after age 85 were found to have abnormalities on examination consistent with the presence of an extra-pyramidal disorder.[1]

The major symptoms of Parkinson's disease are of motor type. All patients with Parkinson's disease (PD) experience motor fluctuations during the course of the disease, usually related to chronic levodopa therapy. It has been estimated that after initiation of treatment with levodopa, about 10% of patients per year develop motor fluctuations,[2] and in clinical based studies about 50% suffer these complications after 5 years.[3,4,5]

However other fluctuating symptoms of a non-motor nature have also been described in patients of Parkinson's disease and they can be equally disabling.[6,7] Non-motor fluctuations have been classified into three categories according to their clinical manifestations: dysautonomic, mental (cognitive/psychiatric), and sensory/pain.[6] These non-motor fluctuations may have a varied

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presentation and unless recognized by the physicians to be a feature of PD itself, lead to unnecessary and often costly or harmful investigations. This study was done to determine the type and frequency of non-motor fluctuations (NMF) in patients of Parkinson's disease and find out their relationship to motor fluctuations (MF).

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. 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[1] 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, including 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.[10,11,12,13,14,15] This classification was adopted by Riley and Lang[8] and Hillen and Sage[7].

For each symptom, the link with the motor state was specified: the patients were asked whether the fluctuating manifestation seemed to coincide with the "on", "pre-on", "off", "pre-off", or "dyskinetic" state or whether it did not seem to depend on the motor state. Prior to these questions, the exact meanings of motor fluctuations were described to the patient as follows: 'on' period was with the least amount of lowness, stiffness and shakiness, whereas 'Off' period was the period with the highest level of slowness, stiffness and shakiness. The 'dyskinesia' period was characterized as abnormal, non-rhythmical involuntary movements. After determination of nonmotor symptoms, the relation of these to motor fluctuations was questioned. Non-motor symptoms occurring episodically and periodically, rather than continuously, and related to one of the motor fluctuations or independent of motor fluctuations were termed 'nonmotor fluctuation'.

The patients were evaluated by Hoehn and Yahr (H & Y) scale. 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

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 shows distribution of patients by motor fluctuations and their relation with nonmotor fluctuations. Out of 128 patients, 106 (82.8%) had motor fluctuations and 111 (86.7%) had nonmotor fluctuations. Nonmotor fluctuations and their relation with motor fluctuations (n=106) were studied by classifying symptoms into sensory 67 (63.2%), autonomic 78 (73.6%) and psychiatric 18 (17%). All patients with motor fluctuations experienced one or more nonmotor symptoms. Nonmotor symptoms (n=111) with or without association with motor symptoms were sensory in 84 (75.7%), autonomic in 102 (91.9%) and psychiatric in 20 (18.6%) patients.

Table II shows the sensory fluctuations and their association with motor fluctuations. The most frequent sensory fluctuations described by the patients were akathisia (52.4%), pain (39.6%), and tingling sensations (28.3%). Most of the sensory symptoms were associated with motor fluctuations

and most of them were associated with the "off" state, but some of them were independent of motor fluctuations.

Table III shows the autonomic fluctuations and their association with motor fluctuations. The most frequent autonomic fluctuations were excessive sweating (37.6%), drooling (21.3%), oral dryness (20.5%) and flushing (19.2%). Most of these were associated with the motor fluctuations. Most of the autonomic symptoms were associated with the "off" state, but some of them were present independent of motor fluctuations.

The Table IV shows the psychiatric fluctuations and their association with motor fluctuations. The most frequent psychiatric fluctuations were depression (24.6%) and fatigue (21.3%). Most of these were associated with motor fluctuations and most of the psychiatric symptoms were associated with "off" state, except elevated mood (9.7%) which was 100 percent associated with "on" period, but some of them were also present independent of motor fluctuations.

Table V shows most non-motor fluctuations (NMF) and their rate of association with the motor fluctuations (MF). The most frequent nonmotor fluctuations were akathisia (52.4%), pain (39.6%), excessive sweating (37.6%), tingling sensation (28.3%), depression (25%), drooling (21.3%), oral dryness (20.5%), flushing (19.2%) and tightening sensation (16.5%). Most of these were associated with motor fluctuations.

Table I: Distribution of patients by motor fluctuations (MF) and nonmotor fluctuations (NMF), and relation of NMF with MF and nonmotor fluctuations with or without association with motor fluctuations

Fluctuations	**Number of patients**	**Percentage**
Total patients (n=128)*		
Motor fluctuations present	106	82.8
Nonmotor fluctuations present	111	86.7
Nonmotor fluctuations and their association with motor fluctuations (n-106)*		
Sensory	67	63.2
Autonomic	78	73.6
Psychiatric	18	17.0
Nonmotor fluctuations associated with or without motor fluctuations (n=111)*		
Sensory	84	75.7
Autonomic	102	91.9
Psychiatric	20	18.0

*Multiple respons

Table II: Frequency of sensory fluctuations and their corresponding motor state (n = 128)

Sensory Symptoms	Sensory fluctuations (%)	Sensory fluctuations associated with motor fluctuations (%)	Sensory fluctuations independent of motor fluctuations (%)	Sensory fluctuations associated with different types of motor fluctuations		
				"Off' period (%)	"On' period (%)	Dyskinesia (%)
Akathisia	52.4	79.8	20.2	77.6	15.3	7.1
Pain	39.6	80.7	19.3	87.8	8.2	4.0
Tingling Sensation	28.3	79.7	20.3	74.4	13.5	12.1
Tightening sensation	16.5	80.6	19.4	70.6	21.1	8.3
Burning sensation	11.7	82.3	17.7	89.8	10.2	0
Restlessness	8.2	79.5	20.5	89.5	10.5	0

Table-III: Frequency of autonomic fluctuations and their corresponding motor state (n=128).

Autonomic Symptoms	Autonomic fluctuations (%)	Autonomic fluctuations associated with motor fluctuations (%)	Autonomic fluctuations independent of motor fluctuations (%)	Autonomic fluctuations associated with different types of motor fluctuations		
				"Off' period (%)	"On' period (%)	Dyskinesia (%)
Excessive Sweating	37.6	81.7	18.3	67.5	18.4	14.1
Drooling	21.3	86.9	13.12	64.6	20.3	15.1
Flushing	19.2	84.6	13.1	64.6	20.3	15.1
Oral dryness	20.54	82.8	17.2	70.6	17.1	12.3
Dysphagia	17.4	83.7	16.3	77.5	15.4	7.1
Urinary urgency	15.7	88.0	1.46	77.7	18.1	4.2
Abdominal Bloating	13.1	78.9	21.1	91.6	5.1	3.3
Abdominal pain	11.2	75.5	24.5	92.8	7.2	0
Constipation	16.3	82.6	17.4	82.8	8.1	9.1
Impotence	11.5	79.7	20.3	82.5	12.3	5.2
Urinary frequency	14.7	81.6	18.4	88.7	11.3	0
Belching	7.3	79.8	20.2	93.7	4.2	2.1
Distal cold Sensation	6.4	90.5	9.5	100.0	00	00
Palpitation	5.2	84.7	15.3	93.6	3.3	3.1
Pallor of skin	4.5	91.6	8.4	95.9	4.1	00
Sensation of being hot	6.8	82.8	17.2	93.6	4.3	2.1

Table-IV: Frequency of psychiatric fluctuations and their corresponding motor state (n = 128)

Symptoms	Psychiatric fluctuations (%)	Psychiatric fluctuations associated with motor fluctuations (%)	Psychiatric fluctuations independent of motor fluctuations (%)	Psychiatric fluctuations associated with different types of motor fluctuations		
				"Off' period (%)	"On' period (%)	Dyskinesia (%)
Depression	25.0	80.0	20.0	75.7	14.2	10.1
Fatigue	20.0	90.0	10.0	78.	9.1	12.2
Confusion	18.8	90.0	10.0	80.0	20.0	0
Irritability	12.3	100.0	0	80.0	20.0	0
Elevated mood	10.0	100.0	0	0	100.0	0
Hallucination	5.0	100.0	0	50.0	50.0	0

Table-V: The most frequent nonmotor fluctuations and their rate of association with the motor fluctuations.

Non-motor fluctuations	Nonmotor fluctuations associated with or without motor fluctuations (n=111) (%)	Nonmotor fluctuations associated with motor motor fluctuations (n-106) (%)
Akathisia	52.4	79.8
Pain	39.6	80.7
Excessive sweating	37.6	81.7
Tingling sensation	28.3	79.7
Depression	25.0	80.0
Drooling	21.3	86.9
Oral dryness	20.5	82.8
Flushing	19.2	84.6
Tightening sensation	16.5	80.6

Discussion

Motor fluctuations and non-motor fluctuations both are common in Parkinson's disease. Non-motor fluctuations have been described for more than 30 years[6] but they have been under assessed. Few data are available about their prevalence in general, their characteristics and their relationships to duration of disease or treatment.

In this study, 106 (82.8%) patients out of 128 had motor fluctuations and 111 (86.7%) patients out of 128 had non-motor fluctuations. All the patients with motor fluctuations experienced one or more non-motor fluctuations. These are sensory 67 (63.2%), autonomic 78 (73.6%), and psychiatric 18 (17%). The results of this study are in agreement with the study done by Gunal et al.[15]

Non-motor fluctuations were generally linked to motor fluctuations but also occurred regardless of their motor state. In these 111 patients sensory fluctuations were present in 84 (75.7%), autonomic fluctuations in 102 (91.9%), and psychiatric fluctuations in 20 (18%) patients. These results are also in agreement with other studies.[14,15] However in this study more sensory and autonomic fluctuations and less psychiatric fluctuations were present in comparison to above studies.

In this study, the common sensory fluctuations were akathisia (52.4%), pain (39.6%), and tingling sensation (28.3%). Most of these symptoms were associated with "off" period but also occurred during "on" period, period of dyskinesia and independent of motor fluctuations. This finding is similar to other studies. Among the sensory fluctuations, akathisia was reported to be the most frequent (54%).[14] One study found a prevalence of 43% (pure akathisia and restlessness), but akathisia did not depend on any specific motor state.[16] Goetz et al[12] reported having akathisia mostly during the "off" period. Koller[17] opined that sensory phenomena may cause greater distress than motor symptoms. Witjas et al[14] reported that in their 6 patients (12%), the most incapacitating type of fluctuations was the sensory. Pain and subjective sensory symptoms were quite often described, although they may be initial symptoms, having higher frequencies during "off" period.[18]

In this study, autonomic symptoms were frequent among Parkinson's disease patients and most of them were associated with motor fluctuations. Majority of these were associated with "off" period, but also occurred with "on" period, period of dyskinesia and independent of motor fluctuations (Table III). This finding is similar to the findings of Gunal et al[15] who found that the autonomic fluctuations seen during "off" periods were increased salivation, abdominal bloating, sweating, facial flushing and postural lightheadedness. Parkinson[19] himself reported autonomic dysfunction in Parkinson's disease, and a variety of fluctuating symptoms have been described since then. These include change in blood pressure, dyspnoea, stridor, abdominal bloating, animus, facial flushing, bladder dysfunction and drenching sweats.[12,20] These fluctuations are mainly associated with the "off" state but also with peak of dose dyskinesia.[12] Drenching sweats were the second most common non-motor fluctuation reported (64%) by Witjas et al.[14] This symptom occurred mostly during "off" state (62%), but could also occur during severe dyskinetic states (18%).[12,21]

Fluctuating psychiatric symptoms have been frequently reported in Parkinson's disease. Delis et al[22] found a moderate impairment of neurophyschological tests during "off" periods. Gunal et al,[15] observed a mood decline during the period of worsening in the motor symptoms. Mood fluctuations seen in Parkinson's disease patients have been studied extensively, and a depressive mood has also been shown during the dyskinesia period.[22,23] These results are in agreement with this study. Similar to this study, cognitive and neuropsychiatric disturbances were reported to be common in Parkinson's disease and quite often mood swings related to motor fluctuations have been reported.[18] Also similar to this study, most often improvement in depression and anxiety during "on" phase were reported but in the same patient also mania and depression associated with "on" and "off" phases.[24] Fatigue is a common symptom in Parkinson's disease in this study and most of the patients reported a fluctuating sensation of fatigue during "off" state. This result is in agreement with other studies describing the high frequency of this symptom and the disability it entails.[25,26] In this study, psychiatric fluctuations were less common than above studies.

The most frequent non-motor fluctuation in this study were akathisia (52.4%), pain (39.6%), excessive sweating (37.6%), tingling sensation (28.3%), depression (25%), drooling (21.3%), oral dryness (20.5%), flushing (19.2%), and tightening sensation (16.5%). Most of these symptoms were associated with motor fluctuations (Table V). These results are in agreement with other studies, but differs in symptoms and their frequencies. This is probably due to inclusion of different parameters in this study.

This study shows that patients of Parkinson's disease suffer from different types of non-motor symptoms with fluctuations similar to the motor fluctuations. Recognition of these symptoms as part of Parkinson's disease will prevent unnecessary investigations to exclude other causes.

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