THE CLINICAL PROFILE OF NONMOTOR FLUCTUATIONS IN PARKINSON'S DISEASE PATIENTS

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ABSTRACT

Objective: Recently described nonmotor fluctuations may cause disability in Parkinson's disease patients. These fluctuations are generally grouped as sensory, autonomic and cognitive/psychiatric. The clinical spectrum and frequency of these symptoms among patients with fluctuating Parkinson's disease are unknown.

Methods: We studied the correlation of nonmotor fluctuations with motor symptoms and determined the effect of age at disease onset, duration of disease, dosage and duration of levodopa treatment to the occurrence of nonmotor fluctuations.

Results: The statistical analysis showed a positive correlation of all above criteria with sensory and autonomic fluctuations. Whereas, cognitive-psychiatric fluctuations were found to be only correlated with the duration of levodopa usage. The nonmotor fluctuations included in the study were observed during "on" period as well as "off" and "end dose off" periods.

Conclusion: The variability of nonmotor fluctuations in clinical presentation and coappearance of these fluctuations with different types of motor fluctuations were considered as the effect of other neurotransmitter systems acting syncronously with dopamine. In this study, we determined the high risk factors for nonmotor fluctuations in patients with Parkinson's disease.

Key Words: Parkinson's disease, Nonmotor, fluctuations, Dopamine, Levodopa

INTRODUCTION

Actually all patients with Parkinson's disease (PD) experience motor fluctuations usually related to chronic levodopa therapy in progression of disease. These fluctuations constitude the greatest problem during the long term management of the patients(1). It is estimated that approximatelly 10% of all patients treated with levodopa will develop motor fluctuations per year, so that 50% are affected after five years of sustained levodopa therapy(2). Recently, in addition to motor fluctuations, nonmotor fluctuations have been described as sensory, autonomic and cognitive/psychiatric fluctuations(3). In our study we planned to estimate the nonmotor symptoms and then fluctuations in these symptoms. The age at disease onset, duration of disease, dosage and duration of levodopa usage were determined and the correlation between these parameters and nonmotor fluctuations were studied.

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Methods: During six months period (November 1998 - April 1999) we evaluated 85 consecutive PD patients. The ethical approval of the study was granted by the university ethical committee and the informed concent was given. The symptoms were classified in sensory, autonomic and cognitive/psychiatric groups by questionnaire as described in table I. If the symptoms were positive, the patient was asked to describe the correlation of these symptoms with motor symptoms (on, off states, dyskinesia, end-dose off, predose). We determined the age at disease onset, duration of the disease, dosage and duration of levodopa usage of the patients. The Unified Parkinson's disease rating scales (UPDRS) and Hoehn and Yahr (H&Y) scales of the patients were evaluated. The patients were also evaluated by minimental status scale to exclude the cognitive decline interfering with interview performance.

Table I. The nonmotor symptoms and relation with motor fluctuations were studied according to this questionnaire.

Noncorrelated with motor fluctuations	"On"	"Off"	"End dose off"	"Predose"
Sensory Symptoms:				
1. Pain				
2. Paresthesis				
3. Akathisia				
4. Restless leg				
Autonomic symptoms:				
1. Pallor of skin				
2. Drooling				
3. Difficulty with swallowing				
4. Excessive gas with frequent burbing				
5. Bloating (excessive fullness)				
6. Episodic spasm of the anus				
7. Shortness of breath				
8. Excessive sweating				
9. Flushing or chilling				
10. Frequent urination				
11. Orthostatic hypotension				
Cognitive/psychiatric symptoms:				
1. Hallucinations				
2. Moaning or screaming				
3. Elevated mood				
4. Depressed mood				
5. Panic attack				

Statistics: The nonmotor fluctuations classified as sensory, autonomic and cognitive/psychiatric were studied statistically to determine the correlation with age at disease onset (year), duration of disease and levodopa usage (year) by t test. For levodopa doses (mg/day), chi square test was used. H&Y and UPDRS scales of the patients with nonmotor fluctuations and without fluctuations were studied statistically by t test. $P<0.05$ was considered statistically significant.

Patients and Results: The 85 patients included in the study csisted of 50 male and 35 female. The mean age of the patients was 66.19±9.35 (38-85). The age at disease onset, duration of disease, dosage and duration of levodopa usage and scales were given in table II. The minimental status scales of all patients were over 25/30.

Table II. Demographic characterization of the patients with Parkinson's disease in this study.

	Mean	Range
Age	66	(38-85)
Age of disease onset	62	(31-83)
Disease duration (year)	5	(0.5-33)
Duration of levodopa usage (yr)	3	(0.5-25)
Levodopa dose/day (mgr)	500	(62.5-750)
H&Y	2.16	(1-5)
UPDRS	40.49	(5-122)

H&Y: Hoehn and Yahr scale
UPDRS: Unified Parkinson's Disease Rating Scale

Seventy two of 85 patients (84.7%) had motor fluctuations. All of these patients experienced one or more nonmotor symptoms. The fluctuations of these nonmotor symptoms and relation with motor fluctuations were studied by classifying symptoms into sensory, autonomic, cognitive/psychiatric since the coexistence of different nonmotor symptoms in the same patient would cause conflicts in statistical evaluation.

Sensory fluctuations: Fifty nine of 72 patients (69.4%) had sensory symptoms. These symptoms were correlated with motor fluctuations in 28 patients (38.8%) and called sensory fluctuations. Regarding the sensory fluctuations, 88.88% was during "off" period, 11.11% was during "end-dose off" period. We found a statistically significant difference between patients with sensory fluctuations and without sensory fluctuations in the aspect of age of disease onset, duration of disease, the duration of levodopa usage and dosage. ($p<0.005$, $p<0.05$, $p<0.05$, $p<0.05$ respectively).

The sensory fluctuations were significantly high in the patients with early age of disease onset, long disease duration, high levodopa dosage and long duration of levodopa usage. The results were shown in table III.

Autonomic fluctuations: Sixty one of 72 patients (84.7%) had autonomic symptoms. Only 29.16 % (21 patients) told correlation with motor fluctuations. These autonomic fluctuations were present during "off" period in 75% of the patients, during "on" peroid in 25.8% of the patients, during "end-dose off" period in 15% and during "predose" period in 15%. Seven patients reported to have more than one autonomic symptom. For the autonomic fluctuations similar to sensory fluctuations, the early age of disease onset, long disease duration, high levodopa dosage and long duration of levodopa usage were the risk factors ($p<0.05$, $p<0.05$, $p<0.05$, $p<0.05$ respectively). The results were shown in table III.

Cognitive and psychiatric fluctuations: Thirty four of 72 patients (47.2%) had cognitive/psychiatric symptoms and 11 (15.27%) of the patients had correlated their symptoms with motor fluctuations. These cognitive/psychiatric fluctuations were during "off" period in 81.81% of the patients, during "on" period in 18.18% of the patients. We did not find a statistically significant difference between patients with cognitive/psychiatric fluctuations and without these fluctuations in the aspect of age at disease onset, duration of disease and levodopa usage. However, levodopa dose between patients with cognitive/psychiatric fluctuations and without fluctuations showed a statistically significant difference ($p<0.05$). The high levodopa dosage was found to be correlated with the occurrence of cognitive/psychiatric fluctuations(table III).

H&Y and UPDRS results of the patients with nonmotor fluctuations and without fluctuations were compared statistically and both scales were significantly high in nonmotor fluctuating patients ($p<0.05$). The disease progression has increased the occurrence of nonmotor fluctuations.

Table III. Table shows correlation of disease related parameters with the occurrence of nonmotor fluctuations.

	Age at disease onset	Disease duration (year)	Duration of levodopa usage (year)	Levodopa dose mg/d
The patients with sensory fluctuations	54.78±11.14**	8.75±7.64*	6.10±5.63*	564.9±177.2*
The patients without sensory fluctuations	62.17±9.61	5.34±3.96	3.37±3.44	458.75±183.68
The patients with autonomic fluctuations	54.95±10.46*	9.16±6.68*	6.54±6.10*	571.4±191.9*
The patients without autonomic fluctuations	61.31±10.32	5.57±5	3.43±3.35	465.9±178.74
The patients with cogn/psyhiatric fluctuations	60.27±12.18	10.27±8.51	4.7±3.34	650±129.1*
The patients without cog/psyhiatric fluctuations	59.66±10.50	5.89±4.92	4.28±4.65	475.74±185.9

* $p<0.05$
** $p<0.005$

DISCUSSION

The most common fluctuations seen in PD patients consist of changes in motor functions presumably associated with alterations in the concentration and efficacy of striatal dopaminergic activity. These motor fluctuations may result in degrees of disability at least equal to that caused by the disease itself(2). Newly described nonmotor fluctuations are thought to be frequent and can be grouped as sensory, autonomic and cognitive/psychiatric fluctuations(3). The clinical spectrum and frequency of these nonmotor symptoms among patients with fluctuating PD patients are unknown. Hillen et al(3) studied the nature and occurrence of nonmotor fluctuations in 130 consecutive PD patients. They emphasized the recognition of these symptoms as "off" phenomena. In our study group, the sensory fluctuations were present during "off" and "end dose off" periods. Whereas the autonomic fluctuations were determined during "on" and "predose" periods as well as "off" period. These findings were considered that nonmotor fluctuations could not be described as "off" phenomena. "On" and "predose" period fluctuations and unresponsiveness of some of the nonmotor fluctuations to dopaminergic treatment strategies might indicate the effect of other neurotransmitter systems onto the nonmotor fluctuations.

The correlation between nonmotor fluctuations and disease related parameters were evaluated in our study to determine the patient groups having high risk for nonmotor fluctuations. Our statistical analysis showed that nonmotor sensory fluctuations were mostly present in patients with early age of disease onset as well as the patient with long disease duration and long duration of levodopa usage. The dosage of levodopa used was found statistically high in these patients.

Autonomic symptoms were quite frequent in our patients (84.7%) but, only 33% of the patients' complaints were correlated with motor fluctuations. Although sensory fluctuations were mostly seen during "off" or "end-dose off" periods, autonomic fluctuations were reported during "off" (75%), "on" (25,8%) and "predose" periods (15%). The autonomic fluctuations mostly seen during "off" period were increased salivation, abdominal bloating, sweating, facial flushing and orthostatic hypotension. The patients with autonomic fluctuations had the similar clinical characteristics with the patients having sensory fluctuations. The early age of disease onset, long disease duration and levodopa usage, high levodopa doses were found to be important in the occurrence of autonomic fluctuations. In Goetz (4) and Langston (5) studies about autonomic dysfunction in PD, it was reported that autonomic dysfunction could not be explained only by nigral degeneration.

Fluctuating cognitive and psychiatric symptoms were frequently reported in PD(6). Two thirds of patients receiving chronic levodopa treatment experience fluctuations in mood(1). Any combination of depression, anxiety(7), panic(8), irritability or apathy during "off" periods has been reported. Delis(9) found a moderate decline in of neuropsychological tests during "off" period. In our patients like other reports in the literature, we observed a mood decline during worsening period of the motor symptoms. These fluctuations of mood in PD patients have been thought to be a phenomenon related with motor fluctuations rather than a reactive phenomenon to the motor disability. However, in later reports mood fluctuations seen in PD patients have been studied extensivelly and depressive mood has been shown also during "dyskinesia" period other than "off" period(9,10). This data supports the importance of motor disability and reactive process hypothesis about mood fluctuations. In our study, the patients with cognitive/psychiatric fluctuations did not show any statistically significant difference between nonfluctuating patients in the aspect of the age of disease onset, the duration of disease or levodopa usage, but the levodopa dosage was significantly high in fluctuating patients. The positive correlation found between the levodopa dose and cognitive/psychiatric fluctuations might be the direct effect of levodopa. We could not explain why the duration of levodopa usage was not correlated with cognitive/psychiatric fluctuations since we excluded the cognitive decline of the patients interfering with interview performance by minimental state examination. The lack of

correlation found between the age of disease onset, the duration of disease or levodopa usage might indicate that the cognitive/psychiatric fluctuations progress in a different manner than sensory and autonomic fluctuations.

Newly described nonmotor fluctuations are not clearly explained in their mechanism of action. Some authors blame other neurotransmitters fluctuating syncronously with dopamine since a variety of fluctuating symptoms have been reported(11,12). Our study results support the hypothesis of other neurotransmitters fluctuating syncronously with dopamine. We thought that to clarify the exact mechanisms underlying in nonmotor fluctuations, the studies including large samples with more homogenous patient groups are needed.

REFERENCES

1. *Quinn NP. Classification of fluctuations in patients with Parkinson's disease. Neurology 1988;51(suppl 2), 25-29.*
2. *Poewe WH. Clinical aspects of motor fluctuations in patients with Parkinson's disease. Neurology 1994;44(suppl 6):6-9.*
3. *Hillen ME, Sage JI. Nonmotor fluctuations in patients with Parkinson's disease. Neurology 1996;47:1180-1183.*
4. *Goetz CG, Lutge J, Tanner CM. Autonomic dysfunction in Parkinson's disease. Neurology 1996;36:73-75.*
5. *Langston JW, Forno LS. Hypothalamus in Parkinson's disease. Ann Neurol 1978;3:129-133.*
6. *Olanow CW, Koller WC. An algoritm for the management of Parkinson's disease. Treatment guidelines. Neurology 1988;50(suppl 3):23-30.*
7. *Routh LC, Black JL, Ahlshog JE. Parkinson's disease complicated with anxiety. Mayo Clin Proc 1987;62:733-735.*
8. *Vasquez A, Jimenez FJ, Garcia-Ruiz P. Panic attacks in Parkinson's disease. Acta Neurol Scand 1993;87:14-18.*
9. *Delis D, Direnfeld L, Alexander MP, Kaplan E. Cognitive fluctuations associated with on-off phenomenon in Parkinson's disease. Neurology 1982;32:1049-1052.*
10. *Siemers ER, Shekhar A, Quaid K, Dickson H. Anxiety and motor performance in Parkinson's disease. Mov Disord 1993;8:501-506.*
11. *Nissenbaum H, Quinn NP, Brown RG, Toone B, Gotham AM, Marsden CD. Mood swings associated with the 'on-off' phenomenon in Parkinson's disease. Psychol Med 1987;17:899-904.*
12. *Sage JI, Mark MH. Basic mechanism of motor fluctuations. Neurology 1994;44(suppl 6):10-14.*

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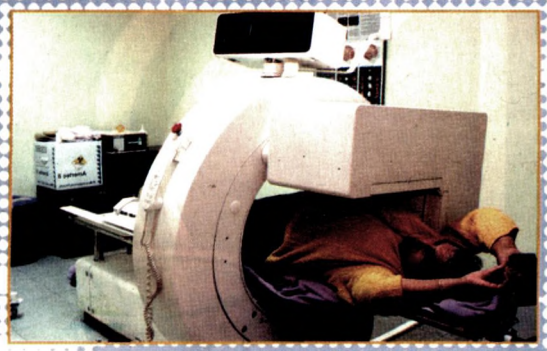

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