MOTOR, NONMOTOR AND COGNITIVE PREDICTORS OF EARLY TREATMENT-RELATED MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE PATIENTS

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OBJECTIVES. Treatment-related motor fluctuations may emerge in patients with Parkinson's disease (PD) within the first few years after levodopa introduction, but may go initially unrecognized, particularly in patients with a shorter disease duration. In this study, we aimed at investigating motor, nonmotor and cognitive predictors that may be identified at the time of PD diagnosis and associated with later development of motor fluctuations after 2 years of treatment.

MATERIALS. The study sample was recruited from an ongoing longitudinal project enrolling consecutive drug-naive PD patients. These patients underwent an extensive motor, nonmotor and cognitive assessments by means of validated scales at the time they were diagnosed with PD.

METHODS. Following baseline assessments, PD patients were initiated on dopaminergic therapy and underwent annual clinical follow-up. At each visit, the total levodopa equivalent daily dose (LEDD) was calculated. At the 2-year follow-up, 73 patients had developed early signs of wearing-off (defined as at least 1 hour of daily OFF time lasting for a minimum of 4 weeks) and were classified as PD early-fluctuators (PD-EF). These patients were automatically matched with 77 patients who did not exhibit motor fluctuations (PD non-fluctuators, PD-NF). Baseline motor, nonmotor, and cognitive data were compared between groups. A multivariate regression model was run to identify baseline clinical predictors associated with development of motor fluctuations at 2 years.

RESULTS. At baseline, PD-EF and PD-NF groups were similar in age, sex, disease duration, and motor symptom severity (Table 1). However, PD-EF patients showed significantly greater severity of pain, depression, and autonomic dysfunction compared to PD-NF (Table 2). Moreover, compared to PD-NF, PD-EF patients performed significantly worse in neuropsychological tests assessing memory, executive, language and visuospatial functioning at baseline (Table 3). Non-motor symptoms scale domain 5 (attention/memory), z-score from executive domain tests as well as total LEDD at 2-year were found to be independent predictors of early motor fluctuations development (Table 4).

DISCUSSION. Our results show that early executive dysfunction and total LEDD are associated with faster development of treatment-related motor fluctuations 2 years after the diagnosis. Dysfunction within fronto-striatal and cortico-subcortical circuits, induced by neurodegenerative processes and perhaps exacerbated by chronic dopaminergic stimulation, may be considered a shared pathophysiological mechanism between these phenomena.

Variables	PD-EF (mean±SD)	PD-NF (mean±SD)	p-value
Baseline			
Age (years)	64.30±9.45	62.10±8.49	0.136
Education	11.68±4.08	12.70±3.62	0.11
Sex (M/F)	44/30	52/24	0.25
Disease duration (m)	14.17±8.86	16.84±12.37	0.133
mH&Y	1.65±0.48	1.72±0.52	0.45
UPDRS III	22.18±8.92	21.12±9.28	0.48
2-year follow-up			
UPDRS IV	1.56±1.75	-	-
Dyskinesia (yes/no)	9/73	-	-
Wearing-off (yes/no)	73/73	-	-
LEDD-Total	362.53±156.62	287.44±111.55	**0.006**
LEDD-Dopa	254.74±180.97	150.51±144.20	**0.001**
LEDD-DA	61.87±94.04	71.22±94.40	0.54
Dopa yes/no	57/16	49/28	0.06

Table 1. Demographic and motor variables. Significant differences are reported in bold (p<0.05).

Variables	PD-EF (mean±SD)	PD – NF (mean±SD)	p-value
Hyposmia (yes/no)	39/34	28/49	**0.03**
NMSS-5 *(Att/WM)*	2.52±3.49	1.21±2.10	**0.007**
NMSS-7 *(Urinary)*	5.74±6.14	3.02±3.87	**0.002**
NMSS-9 *(Miscellaneous)*	4.01±4.47	2.38±3.17	**0.01**
King's PD Pain scale	4.49±6.54	2.34±3.97	**0.03**
PD Sleep scale	113±25.02	128±15.18	0.11
RBD single question	26/42	38/37	0.13
SCOPA-OUT	9.65±5.96	7.47±4.75	**0.03**
BDI	9.14±8.44	6.61±5.96	**0.03**
PFSS	5.11±2.62	2±1.63	0.05

Table 2. Nonmotor symptoms at baseline. Significant differences are reported in bold (p<0.05).

Variables	PD-EF (mean±SD)	PD-NF (mean±SD)	p-value
MoCA	21.08±3.75	23.4±2.95	**<0.001**
Education	12.3±3.9	12.5±.6.1	0.66
MCI II level (yes/no)	31/35	17/48	**0.01**
z-score executive	-0.69±1.05	-0.26±0.82	**0.01**
z-score visuospatial	-0.77±1.60	-0.008±1.16	**0.001**
z-score attention/WM	-0.003±0.60	0.04±0.53	0.65
z-score language	-0.23±1.05	0.20±0.34	**0.001**
z-score memory	-0.82±0.85	-0.42±0.71	**0.003**

Table 3. Neuropsychological data at baseline. Significant differences are reported in bold (p<0.05).

	Treatment-related motor complications at 2 years		
	Predictors	**B**	**p-value**
PD patients (n=150)	NMSS – 5 *(attention/memory)*	0.277	0.017
	z-score executive	-0.944	0.004
	LEDD total at 2 years	0.006	0.008

Table 4. Significant predictors from the multivariate regression model.

CONCLUSION. Our findings demonstrated that specific nonmotor and cognitive features may characterize drug-naïve PD patients more prone to develop early treatment-related motor fluctuations. Identifying at-risk PD population prior to starting any dopaminergic treatment may help clinical management and foster prevention strategies.

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