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CLINICAL AND COGNITIVE PREDICTORS OF IMPULSE CONTROL DISORDERS IN DRUG NAIVE PATIENTS WITH PARKINSON'S DISEASE

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BACKGROUND AND AIM

Impulse control disorders (ICD) can be triggered by dopamine replacement therapies, especially dopamine-agonists, in patients with Parkinson's disease (PD). PD itself does not confer an increased risk for the development of ICD in the absence of treatment. Only a specific subset of patients with PD will eventually develop ICD under dopaminergic treatment. In the present study, we investigated clinical and cognitive features at baseline in a cohort of drug-naïve PD patients, which successively developed ICD over a 36-months follow-up period compared with patients who did not.

METHODS

We consecutively enrolled a study cohort of drug-naïve PD patients who underwent a comprehensive assessment of clinical (i.e. motor, non-motor, cognitive and behavioral) functioning. One week after the baseline assessments, all patients started a dopaminergic replacement therapy and were followed for an observation period of 36 months by two blinded and trained clinicians, with a clinical follow-up every 6-months. The ICD presence and severity was assessed by means of the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale. A multivariate analysis of variance was used to compare clinical and cognitive features between the two study groups at baseline. To determine the independent predictors of ICD overtime, a multivariable logistic regression was ran including demographic (i.e. gender, age at the disease onset), motor (i.e. H&Y stages, disease duration, UPDRS III total and subscores, total LEDD and use of dopamine-agonist at treatment initiation), non-motor (i.e. Non-motor symptoms scale, REM behavioral disorders questionnaire, Epworth Sleepiness scale, Parkinson Fatigue Scale, PFS), cognitive and behavioral (i.e. standardized neuropsychological battery scores, Beck Depression Inventory) measures. A $p<0.05$ was considered statistically significant. Analyses were performed with SPSS version 13.

Parameter	ICD+ (n=18) mean±SD	ICD- (n=57) mean±SD	p -value
Age	57±9.7	61.9±9.4	**0.007**
Gender (M/F)	10/8	35/22	0.198
Education	8.7±5.1	10.8±3.8	0.324
Disease duration	1.4±0.5	1.4±0.6	0.867
H&Y stage	1.1±0.3	1.4±0.5	0.245
BDI II	11.2±3.2	9.2±7.4	0.367
UPDRS III	15.7±6	17.9±7	0.521
NMSS (total score and single domains)	13.3±17.8	14.9±14.4	0.751
PFS	2.9±1.1	2.2±0.8	**0.027**
RBD quest	7.3 ±3.4	4.7±3.2	**0.041**
ESS	5.1 ±3.2	3.1 ±2.5	**0.021**
LEDD at treatment initiation			
-Total LEDD (mg daily)	202.7±58.1	229±56.1	0.234
-LEDD-DA (mg daily)	96±65.5	79±60.7	0.523
LEDD at the end of the observation period			
-Total LEDD (mg daily)	312.3±113.5	377.3±94.7	0.121
-LEDD-DA (mg daily)	165.6±111.8	110.7±128.6	0.201
LEDD at ICD emergence			
-Total LEDD (mg daily)	312.3±113.5		
-LEDD-DA (mg daily)	165.6±111.8		

Tab. 1. H&Y stage: Hoehn & Yahr stage; UPDRS: Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; PFS: Parkinson Fatigue scale; NMSS, Non-motor Symptoms Scale; RBD quest: REM behavioural disorders questionnaire; ESS: Epworth Sleepiness Scale; LEDD: Levodopa Equivalent Daily Dose; DA: dopamine agonist. Significant results are reported in bold..

Cognitive Tasks	ICD+ (n=18) (mean±SD)	ICD- (n=57) (mean±SD)	p-value
MMSE	28.8±1.6	27.8±2.7	0.557
MoCA	24.6±4.1	23.4±3.7	0.212
TMT-A	39.7±13.1	36.5±31.7	0.954
TMT-B	93.5±33.6	84.2±76.1	0.712
Digit Span forward	5.0±0.8	5.3±0.9	0.967
RAVLT-immediate recall	36.9±7.9	38.4±7.9	0.412
RAVLT-delayed recall	6.0±2.3	6.9±2.8	0.892
RAVLT-recognition	1.5±1.8	1.7±2.2	0.441
ROCF recall	10.7±5.6	10.8±6.3	0.852
Prose recall test	13.3±12.1	9.9±3.9	0.474
Letter fluency task	28.0±10.1	27.1±7.8	0.526
Category fluency task	38.0±5.3	36.8±6.1	0.374
MCST-perseverative errors	0.8±1.4	2.4±1.8	**0.081**
MCST-number of categories achieved	5.8±0.4	6.2±0.1	0.384
10 points CDT	8.3±1.3	7.9±1.9	0.567
FAB	16±2.6	15±1.9	0.443
ROCF-copy	21.9±10.8	22.6±4.4	0.967
BNT	42.5±4.6	48.6±7.9	0.519

Tab. 2. MMSE: Mini Mental State Examination; WCST: Wisconsin Card Sorting Test; ROCF: Rey-Osterrieth Complex Figure Test; RCPM: Raven's 47 Coloured Progressive Matrices. IST: Interference of Stroop Test.

RESULTS

Demographic and clinical features of PD patients are summarized in Table 1-2. Seventy-five patients were enrolled in the study. During the observation period, 18 patients with PD (24%) develop ICD. At baseline, PD patients who will eventually develop ICD were presented with younger age ($p = 0.007$), more severe fatigue ($p = 0.027$), RBD ($p = 0.041$) and sleepiness ($p = 0.021$). They also showed a trend of higher cognitive performances at the modified card sorting test scores at baseline ($p = 0.081$). No differences in LEDD and LEDD-DA were detected between ICD+ and ICD- patients at the treatment initiation. No differences were detected between LEDD and LEDD-DA of ICD+ and ICD- patients at the end of the observation period (time of ICD emergence for ICD+ patients and 36-months follow-up visit for ICD- patients). Longitudinal predictors of ICD development in multivariable models were only age ($p = 0.042$), PFS scores (0.019) and modified card sorting test scores at baseline ($p = 0.032$).

DISCUSSION AND CONCLUSIONS

In our longitudinal sample, age, presence of fatigue and executive performances at the time of the diagnosis are associated with an increased risk of developing symptoms of ICD after treatment initiation. These findings suggest that a fronto-striatal cognitive more than limbic dysfunction may be present in early drug-naïve PD patients more prone to develop ICD.