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Short communication

Past smoking and current dopamine agonist use show an independent and dose-dependent association with impulse control disorders in Parkinson's disease

Guilherme T. Valença [a,b], Philip G. Glass [a], Nadja N. Negreiros [a], Meirelayne B. Duarte [a], Lais M.G.B. Ventura [b], Mila Mueller [b], Jamary Oliveira-Filho [b,*]

[a] Movement Disorders and Parkinson's Disease Clinic, Bahia State Health Attention Center for the Elderly, Salvador, BA, Brazil
[b] Post-Graduate Program in Health Sciences, Federal University of Bahia, Salvador, BA, Brazil

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ABSTRACT

Background: Previous studies have described the association between dopamine replacement therapy in Parkinson's disease and impulse control disorders.
Methods: A case–control study was performed to establish the prevalence of four of these behaviors in Brazilian patients with Parkinson's disease on stable dopamine replacement therapy and the possible associated risk factors. We investigated 152 patients and 212 healthy controls for pathological gambling, compulsive sexual behavior and compulsive buying and eating.
Results: Overall, patients had more impulsive control disorders than controls (18.4% vs. 4.2%, $P < 0.001$). Impulse control disorders were more common in younger patients ($P = 0.008$) and in those taking dopamine agonist ($P < 0.001$) and levodopa ($P = 0.02$). Higher Unified Parkinson's Disease Rating Scale motor score ($P = 0.03$) and past smoking ($P = 0.02$) were also associated in the univariate analysis. Variables independently associated with impulse control disorders were history of smoking (odds ratio = 1.059 for each year of smoking, $P = 0.010$) and current use of pramipexole (odds ratio = 2.551 for each increase in 1 mg, $P < 0.001$).
Conclusions: Dopaminergic stimulation and previous exposure to smoking are independently associated with impulse control disorders in a dose-dependent manner.

1. Introduction

Antiparkinson therapy, based on dopaminergic stimulation, has been very effective in reducing motor symptoms in PD. However, in addition to motor complications, this therapy can also result in aberrant or excessive stimulation of the dopamine receptors that is related to a complex of nosological entities characterized by psychomotor disinhibition [1]. They are connected by their repetitive and reward natures, stimulus-dependency and include impulse control disorders (ICDs) [1]. Because of the potential link to dopamine replacement therapy (DRT) and the functional impairment related to these behaviors, in recent years, the interest on the topic has become apparent and published studies demonstrate its relevance [2,3].

Systematic surveys have estimated the prevalence of the most common ICDs (pathological gambling, compulsive sexual behavior, compulsive buying and compulsive eating) in DRT/PD patients. Recently, a large cross-sectional study with 3090 PD patients showed a prevalence of any ICD of 13.6% and 3.9% had two or more ICDs [4]. Risk factors in Caucasian populations include history of ICD and drug abuse prior to the development of PD, young patient and/or single status, bipolar disorder, impulsivity, depression, family history of ICD, male gender, genetic factors, smoking and especially the use of dopamine agonists [4–6]. In the context of potential genetic and environmental factors affecting the expression of ICD, studying other multiethnic populations may bring insights into the mechanisms of these disorders. Thus, in the present study, we investigated the prevalence of impulse control disorders in Brazilian PD patients on dopamine replacement therapy and the possible risk factors associated with these conditions.

2. Patients and methods

2.1. Study population

We investigated consecutive PD patients, diagnosed according to UK PD Society Brain Bank criteria [7], from a movement disorders clinic in Salvador, Brazil; and healthy controls, recruited among relatives, spouses, partners, friends and caregivers

* Corresponding author. Federal University of Bahia, Rua Waldemar Falcão, 2106, apt. 201: Horto Florestal, Salvador, BA 40295-710, Brazil. Tel.: +55 71 33535156.
E-mail address: jamaryof@ufba.br (J. Oliveira-Filho).

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of these patients. Patients and controls were assessed for the most common forms of impulse control disorders (i.e. pathological gambling, compulsive sexual behavior, compulsive buying and compulsive eating). Patients with atypical parkinsonism and dementia were excluded.

Once included in the study, patients were examined by a neurologist and, after informed consent, a structured interview for clinical and demographic variables was performed. Data concerning the type and dosages of dopamine replacement therapy and related complications were also recorded. In order to determine possible risk factors for ICDs, ICD/PD patients were compared with the control group. Levodopa equivalent unit (LEU) for each patient was calculated as previously described, as follows: L-dopa dose + L-dopa dose × 1/3 if on entacapone; bromocriptine (mg) × 10; cabergoline or pramipexole (mg) × 67; ropinirole (mg) × 20; pergolide (mg) × 100; apomorphine (mg) × 8 [8]. The study was approved by the local ethics committee.

2.2. Survey instrument

We performed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease in its shortened version (QUIP-S), a validated screening questionnaire for ICDs [9]. This instrument has 3 sections: Section 1 assesses four ICDs: pathological gambling, compulsive buying, compulsive sexual behavior and eating disorder; Section 2 other compulsive behaviors: punding, hobbysm and walkabout; and Section 3 compulsive medication use. Although it was designed to be self-administered, we decided to apply the complete QUIP-S by the patients' side, regardless of their reading level, in order to avoid educational bias because two thirds of them had not completed twelve years of formal education. No patient was illiterate and the same investigator applied the questionnaire in all cases.

2.3. Statistical analysis

Data was entered into an electronic database for statistical analysis (SPSS, version 14.0). Categorical variables were compared using the chi-square test or Fisher exact test and continuous variables using Student's t test. Variables with a possible ($P < 0.1$) association with ICD in univariable analyses were included in a multivariable logistic regression model, searching for predictors of ICD as a binary dependent variable.

3. Results

A total of 152 PD patients attending our movement disorders clinic were recruited. Of these, 66 (43.4%) were female and 86 (56.6%) were male. Their mean age was 67.3 years (standard deviation [SD] 10.4; range, 33–89 years), mean disease duration 7.2 years (SD 5.3; range, 1–35 years), mean UPDRS motor section score 36.4 (SD 15.8; range, 8–79), and mean Hoehn and Yahr score 2.5 (SD 0.7, range, 1–4). Control group consisted of 212 individuals with similar sex and age as the PD group ($P > 0.1$): 144 (66%) male, mean age 68 years (SD 10.9; range, 35–81).

Overall, PD patients had more ICDs (at least one) when compared to controls (18.4% vs. 4.2%, respectively, $P < 0.001$). When we analyzed separately the different forms of ICDs, these were more frequent in PD than in controls (Table 1). Of those 28 PD/ICD patients, we found 2 with pathological gambling (1.3%), 18 with compulsive sexual behavior (11.8%), 16 with compulsive buying (10.5%) and 12 with compulsive eating (7.9%). Frequencies are shown in Table 1. Regarding the compulsive behaviors and compulsive medication use, we found a frequency of 14.2% and 0.65%, respectively.

As a group, ICDs were more common in men than women ($M = 20$, 75.2%), although not significantly different ($P = 0.08$). Patients with ICD were significantly younger than those without ICD (62.6 [SD 9.1 vs. 68.4 [SD 10.4] years, $P = 0.008$). Pramipexole, the only dopamine agonist available in our State, was used by 89.3% of patients with ICD and 11.7% of those without this condition ($p < 0.001$). Daily dopamine agonist dose (mg) was higher in PD with ICDs (2.9 [SD 1.2] vs. 0.85 [SD 1.4], $P < 0.001$). Furthermore, we found a slight association with the UPDRS motor score ($P = 0.03$), levodopa therapy ($P = 0.02$) and past smoking ($P = 0.02$). No PD patients were current smokers. There was no correlation between ICD and H & Y or S & E scores, LEU, duration of illness, motor fluctuation, dyskinesia as well as amantadine and selegiline dosages. The variables tested for association with the ICD are shown in Table 2.

In the multivariable analysis, history of smoking (odds ratio = 1.059 for each year of smoking, 95% confidence interval 1.014–1.107, $P = 0.010$) and current dose of pramipexole (odds ratio = 2.551 for each increase in 1 mg, 95% confidence interval 1.786–3.636, $P < 0.001$) remained independent variables associated with the presence of ICD.

Table 1
Results of the QUIP in 152 PD patients and 212 controls.

	PD, *n* (%)	Controls, *n* (%)	*P*
Any ICD	28 (18.4)	9 (4.2)	<0.001
Pathological gambling	2 (1.3)	0 (0)	0.094
Compulsion by sex	18 (11.8)	1 (0.5)	<0.001
Compulsive buying	16 (10.5)	4 (1.9)	<0.001
Binge eating	12 (7.9)	5 (2.4)	0.014

ICD = impulse control disorders; QUIP = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease.

4. Discussion

The present study is the first case–control study determining the prevalence of ICDs and compulsive behaviors in PD patients in Brazil. Overall, prevalence of ICD varied from 6.3% to 13.6%, or up to 17.7% in patients treated with dopamine agonists [3,4]. In our study, we found a higher prevalence (18.4%), due, perhaps, to a high proportion of dopamine agonist use among our patients (89.3%). This could also explain the high frequency of compulsive behaviors in our PD population.

Regarding the predictors of ICD, the most relevant finding of our study was its association with dopamine agonist use and previous smoking. Both associations were independent of age, gender, PD stage and family history. Moreover, a significant dose-relationship was demonstrated for both variables. Univariable analyses in different studies showed that ICDs are associated with younger age, a history of similar disorders and drug abuse prior to the development of PD, family history, male gender, smoking, and

Table 2
Demographic and clinical characteristics of PD patients with and without ICDs.

Characteristic	ICD, $n = 28$	Non ICD, $n = 124$	*P*
Male sex, *n* (%)	20 (71.4)	66 (53.2)	0.080
Past smoking, *n* (%)	11 (39.3)	24 (19.4)	0.020
Family history of PD, *n* (%)	8 (28.6)	21 (16.9)	0.160
Diabetes mellitus, *n* (%)	4 (14.3)	16 (12.9)	0.840
Hypertension, *n* (%)	10 (35.7)	49 (39.5)	0.710
Coronary heart disease, *n* (%)	1 (3.6)	3 (2.4)	0.730
L-dopa therapy, *n* (%)	22 (78.6)	116 (93.5)	0.020
Amantadine use, *n* (%)	4 (14.3)	14 (11.3)	0.660
Pramipexole use, *n* (%)	25 (89.3)	14 (11.3)	<0.001
Selegiline use, *n* (%)	0 (0)	2 (8.3)	0.550
Wearing off, *n* (%)	14 (50)	50 (40.7)	0.360
On-off, *n* (%)	5 (17.9)	22 (17.9)	0.990
Dyskinesia, *n* (%)	8 (28.6)	17 (13.8)	0.220
RSBD, *n* (%)	7 (28)	30 (29.1)	0.880
Constipation, *n* (%)	14 (50)	71 (57.3)	0.480
Age, mean (SD), y	62.6 (9.1)	68.4 (10.4)	0.008
UPDRS motor score, mean (SD)	30.7 (14.3)	37.7 (15.9)	0.030
H&Y score, mean (SD)	2.3 (0.66)	3.2 (7.0)	0.490
LEU, mean (SD)	732.8 (404.1)	644.4 (397.6)	0.790
Disease duration in years, mean (SD)	7.4 (4.2)	7.2 (5.5)	0.840
Daily pramipexole dosage in mg, mean (SD)	2.9 (1.2)	0.85 (1.4)	<0.001

PD = Parkinson's disease; DA = dopamine agonist; RSBD = REM sleep behavior disorder; H&Y = Hoehn & Yahr, S&E = Schwab & England; LEU = levodopa equivalent unit, ICD = impulse control disorders, SD = standard deviation.

particularly the use of dopamine agonist, the latter being considered the main predictor of ICDs [4–6]. Besides dopamine agonist treatment, levodopa therapy, single status, family history of gambling problems and current smoking were found to be independent predictors of these behaviors [4].

Similarly to others, our results showed that dopamine agonist was the most important predictor. Interestingly, duration of smoking in the past in years was an independent variable associated with ICDs (OR, 1.059 for each increase of 1 year). It is worth noting that none of our PD patients were smokers at the time of the evaluations. The reason for this association is not well known but may be explained by a constant reduction in the number of D2 receptors combined with a decreasing dopaminergic cell activity in addicted individuals, leading to a decreased sensitivity in the striatal and prefrontal reward circuits [1,10,11]. Therefore, we believe that former smoker PD patients on DRT are more susceptible to develop ICDs. Surprisingly, no former smoker PD patient became smoker again, even those with multiple ICDs.

Analyzing ICDs separately, prevalence numbers vary. Many studies have estimated the prevalence of pathological gambling between 1.3 and 9.3% [3,4,12]. Cultural and social factors may influence these results (35). Perhaps this explains our low prevalence (1.3%), since in our country gambling is illegal. Conversely, compulsive sexual behavior was more prevalent in our study (11.8%) when compared to others (2.8% and 3.5%) [3,4]. Concerning compulsive buying and eating, we estimated the prevalence in 10.5% and 7.9% respectively, while in a large cohort these were estimated at 5.7% and 4.3% [4]. Again, cultural and social issues may explain these numbers.

We believe there are some limitations in our study. The QUIP questionnaire was rated at 12th grade reading level. Only a third of our patients had that level of formal education. Thus, we are not sure if this could affect the screening of our PD patients. However, our screening method using a single investigator for all ratings is expected to have minimized this bias. As is any single center study, our results may not be generalizable to other populations and thus larger sample size population studies are needed. Finally, our sample size did not allow for detailing predictors of each type of ICD, but only for ICD as a group.

Our results suggest that dopaminergic stimulation predisposes to the occurrence of ICDs, converging to those found in literature. Moreover, the specific behavior depends on cultural, social and patient access to the particular habit. Finally, ICDs clearly are an underrecognized condition which health professionals should be aware of.

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