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Impulse control symptoms in patients with Parkinson's disease: The influence of dopaminergic agonist☆

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ABSTRACT

Background: Impulse control disorders and punding are common in Parkinson's disease patients. Cross-sectional studies suggest an association between dopamine replacement therapy, especially dopaminergic agonists, and impulse control and related disorders in Parkinson's disease. However, some surveys suggest that Parkinson's disease itself does not confer an altered risk for impulse control disorders and related behavior, although these disturbances are more frequently reported in Parkinsonian patients than in healthy controls.

Objective: To ascertain the frequency of impulse control disorders and punding symptoms in Parkinson's disease patients and healthy controls and to determine the influence of dopamine agonist treatment on the prevalence of these disturbances.

Methods: A case-control study was conducted on 207 Parkinson's disease patients (79 taking dopamine agonists) and 230 healthy controls. The outcome measures were the presence of current impulse control disorders and punding symptoms, based on clinical criteria after application of the Minnesota Impulsive Disorders Interview for screening.

Results: The frequency of impulse control disorders in Parkinson's disease patients vs. Healthy controls was 16.9% vs. 15.2% ($p = 0.631$). Punding was more frequent in Parkinson's disease patients ($p = 0.028$); however, impulse control disorders were more frequent in medicated Parkinson's disease patients taking dopamine agonists than in medicated patients not taking dopamine agonists ($p = 0.001$) and healthy controls ($p = 0.014$).

Conclusions: Parkinson's disease itself does not lead to the development of impulse control disorders. Dopaminergic agonist treatment may trigger the disorder in susceptible individuals. Punding may be more prevalent in Parkinson's disease patients.

1. Introduction

In recent years, dopaminergic treatment of Parkinson's disease (PD) has been thought to give rise to impulsive-compulsive behavior (ICB), including the impulse control disorders (ICD) and punding [1–5]. The ICD are characterized by engaging in activities in a repetitive and compulsive manner, despite adverse consequences [1,2]. The patients describe an initial hedonic drive prompting their repetitive behavior, but with time these behaviors may become less pleasurable and more compulsive. ICD have similarities with drug addiction: affected individuals compulsively pursue an activity, development of tolerance, negative effects of withdrawal, and losses in personal life [3]. The mesolimbic dopaminergic pathway is theorized to play a central role in the development of ICD by linking the addictive behavior to reward sensations derived from the release of dopamine [2]. ICD frequently reported in PD patients include gambling disorder, compulsive buying, and abnormal eating (or binge eating) and sexual behaviors. Another ICB reported in PD is punding, a stereotyped, repetitive, non-goal-

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Table 1
Demographic and clinical characteristics of the study population.

	HC n = 230	PD n = 207	NDAPD n = 128	DAPD n = 79	DAPD vs. NDAPD
Age, y, mean (SD)	58.8 (9.6)	64.1 (11.0)	65.6 (10.8)	61.6 (10.9)	
		0.001[a]	**0.001**[b]	0.212[b]	**0.007**
Education,y, mean (SD)	9.0 (5.5)	8.2 (5.1)	7.6 (5.1)	9.3 (5.0)	
		0.188[a]	0.054[b]	> 0.999[b]	**0.042**
Male sex, %	42.6	57.5	55.5	60.8	
		0.002[a]	**0.020**[b]	**0.006**[b]	0.415
GDS ≥ 6, %	19.6	45.4	50.8	36.7	
		0.001[a]	**0.001**[b]	**0.002**[b]	**0.049**
MMSE > 26, %	66.1	69.6	64.8	77.2	
		0.437[a]	0.812[b]	0.067[b]	0.062
At least one ICD, %	15.2	16.9	10.2	27.8	
		0.631[a]	0.181[b]	**0.014**[b]	**0.001**
Two or more ICD, %	2.6	5.8	3.1	10.1	
		0.092[a]	0.777[b]	**0.047**[b]	**0.010**
Punding, %	1.3	5.3	4.7	6.3	
		0.031[a]	0.066[b]	**0.028**[b]	0.610

Abreviations: GDS, Geriatric Depression Scale; ICD, impulse control disorder; MMSE, Mini-mental State Examination; HC, healthy control; DAPD, Parkinson's disease taking dopamine agonist; NDAPD, Parkinson's disease patients not taking dopamine agonist; PD, Parkinson's disease; SD, standard deviation; y, years.
[a] p-values between HC and PD patients: Mann-Whitney (continuous variables) or Likelihood Ratio test (nominal variables).
[b] p-values between PD patients taking and not taking dopamine agonist compared with HC: Kruskal-Wallis test (continuous variables) or logistic regression (nominal variables).

oriented behavior [6].

It is not clear whether PD itself confers an increased risk for ICB. Many studies suggest that these disorders are more frequent in treated PD patients than in healthy controls (HC) [7]. However, other studies, especially those evaluating untreated patients, have shown that the ICB prevalence in PD patients is not higher than that in HC [8,9].

The main aim of this study was to evaluate the prevalence of ICB in a cohort of PD patients and to determine whether these disorders are more frequent in PD patients than in HC. The secondary objectives were 1) to assess whether the types or associations of disorders exhibit different frequencies between PD patients and HC; and 2) to verify the influence of dopaminergic agonist use on the prevalence of ICB.

2. Patients and methods

2.1. Patients

This is a cross-sectional, case-control study. Patients and HC were recruited from two hospitals from the Sarah Network of Rehabilitation Hospitals in Belo Horizonte and Rio de Janeiro between December 2012 and December 2016. All PD patients consecutively admitted at a neurologic outpatient clinic were evaluated. HC within the age range of the PD cohort (40–90 years) were selected among the relatives and caregivers of neurologic and orthopedic patients at the same hospitals. The study was approved by the Hospital's ethics committees, and all participants and controls provided their written informed consent.

The diagnosis of PD was established according to the UK Brain Bank Society criteria [10]. We developed a questionnaire to obtain information about the demographic profile and medication use of the patients and HCs. We also used the Mini-Mental State Examination (MMSE) as a screening instrument for global cognitive dysfunction [11], and Brazilian validate version of the Geriatric Depression Scale (GDS) with a cutoff point of 6, to assess a clinically significant mood disorder [12].

2.2. Assessment of ICB

The diagnosis of ICB was established based on clinical criteria of gambling disorder [13], compulsive buying [14], hypersexuality [2,15], binge eating [13], and punding [16], aided by specific questionnaires. Patients and HC were initially interviewed; however, the relatives and caregivers were also interviewed because the patients often denied or neglected to mention these behavior disorders.

The patients and HC were evaluated to investigate the current or past presence of ICD and related behaviors, such as gambling disorder, compulsive buying, abnormal sexual and eating behaviors, and punding. A modified questionnaire based on the Minnesota Impulsive Disorders Interview was used to screen for ICB [17]. ICD and punding were considered diagnostic when the symptoms persisted for more than one month and induced patient or family stress or interfered with professional or personal activities [8].

2.3. Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 20.0. (IBM Corp. Released 2011, Armonk, NY, USA). The data were submitted to an exploratory analysis to obtain the characteristics of the studied population and the prevalence of the described variables. Frequencies are expressed as absolute values and percentages. Quantitative results are presented as the means with standard deviations (SD). For nominal variables, the differences between PD patients and HC were evaluated with logistic regression, likelihood ratios (LRs) or Fisher's exact test if the expected frequencies were less than 5. Normality assumptions and the homogeneity of variance of continuous variables were verified with the Shapiro-Wilks and Levene's tests. If one of these tests failed, the Mann-Whitney (two groups) or Kruskal-Wallis (more than two groups) tests were performed. All statistical tests were 2-sided. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Description of the study population

The demographic and clinical information for the 207 PD patients and 230 HC is listed in Table 1. No significant differences were found between PD patients and the HC group in education (8.2 [5.1] years vs. 9.0 [5.5] years; $p = 0.188$) and the number of persons that scored higher than 26 on the MMSE (69.6% vs. 66.1%; $p = 0.437$). However, PD patients were more likely to be male (57.5% vs. 42.6%; $p = 0.002$) and older (64.1 [11.0] years vs. 58.8 [9.6] years; $p = 0.001$). More PD patients than HCs screened positive for depression, based on the recommended GDS cutoff score of > 6 (45.4% vs. 19.6%; $p = 0.001$).

In regarding to treatment, 186 (89.9%) PD patients were taking

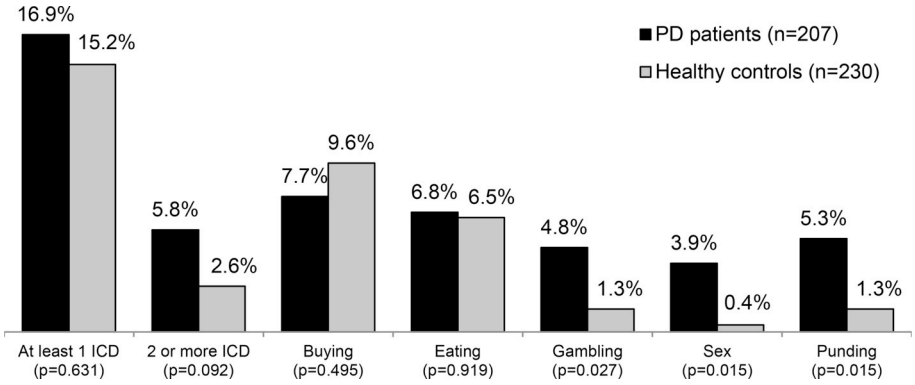

Fig. 1. Frequencies of impulse control disorders (ICD) and punding symptoms in patients with Parkinson's disease (PD) and in healthy controls.

levodopa, and 79 (38.2%) were taking dopamine agonists (immediate release pramipexole 98.7%, transdermal rotigotine 1.3%). In the PD group, those using dopaminergic agonists were younger (61.5 [10.9] years vs. 65.6 [10.8] years, p = 0.007) and had higher education levels (p = 0.042). Fewer patients using dopaminergic agonists had GDS scores indicative of depressive symptoms (36.7% vs. 50.8%, p = 0.049), suggesting that mood disorders are not as frequent in this group. Although more patients had a MMSE score higher than 26 in the group taking dopaminergic agonists (77.2% vs. 64.8%), no statistically significant difference was found among PD patients, regardless of treatment (p = 0.062).

3.2. ICD and punding frequencies

At least one active ICD was identified in 35 (16.9%) PD patients and 35 (15.2%) HC (Fig. 1). Two or more ICD were observed in 5.8% of PD patients and 2.6% of HC. No significant difference was observed regarding the ICD frequency between the two groups. The frequencies of impulse control and related behavior symptoms are illustrated in Fig. 1. Additionally, findings for PD patients vs. HC were as follows: compulsive buying (7.7% vs. 9.6%), compulsive eating (6.8% vs. 6.5%), compulsive gambling (4.8% vs. 1.3%), compulsive sexual behavior (3.9% vs. 0.4%), and punding (5.3% vs. 1.3%). The most frequent types of ICD were not different between PD patients and HC, and compulsive shopping and binge eating were the most commonly observed behaviors in both groups. In PD patients, gambling disorder (p = 0.027) and hypersexuality (p = 0.015) were more common than in HC. PD patients had a higher frequency of punding (p = 0.015) than HC.

ICD were more frequent in PD patients treated with dopamine agonists than in those not treated with these medications (27.8% vs. 10.2%; p = 0.001) and in HC (27.8% vs. 15.2%; p = 0.014). A significant difference was observed between the groups of patients treated with and without dopamine agonists (p = 0.010) and between dopamine agonist-treated patients and HC (p = 0.047) regarding the presence of 2 or more ICD. However, no differences were observed in the frequencies of at least one (10.2% vs. 15.2%, p = 0.181) or two or more ICD (p = 0.777) among PD patients not using dopaminergic agonists and the HC group.

4. Discussion

The primary finding of this study is that the broad range of ICD is equally common in persons with and without PD. Additional finding is that ICD in dopamine agonist treated PD is more frequent than in HCs as well as PD patients non-exposed to dopamine agonists. Epidemiological studies have demonstrated that these disorders are relatively common in PD patients [18]. Nevertheless, it remains unclear whether ICD onset is related to PD pathophysiology, a consequence of individual differences in personality and neuropsychiatric history, or a direct result of dopaminergic therapy [18,19]. Our results suggest that the excess occurrence of ICD in PD is likely driven by exposure to dopamine agonist therapy, a finding also reported by others [3,18,19].

Impulsive disorders are commonly observed in a wide variety of psychiatric and neurological disorders. The lifetime prevalence rate of ICD ranges from 1% to 24.8% in the general population and from 23.5% to 37.8% in psychiatric patients [1]. The lifetime prevalence rate of at least one comorbid ICD was 22.4% in a population of people without neurological disease aged 60 years and older, the same age group as the majority of PD patients [20]. In the present study we verified that the frequency of ICD in HC was in this range, 15.2%. The same trend of similarities of findings in different populations occurs when analyzing the frequencies of particular forms of ICD. Previous findings have demonstrated that 0.1–5.8% of neurologically healthy individuals met diagnostic criteria for gambling disorder across five continents during the year before the survey, and 0.7–6.5% met these criteria during their lifetime [21]. Lifetime gambling disorder was reported in 6.9% of adult psychiatric patients and in 9.2% of healthy individuals aged 60 years and over [1,20]. Rates of hypersexuality among the general population have been estimated to be approximately 3%–5%, with adult males comprising the majority of the affected persons [15]. The prevalence of compulsive shopping ranged from 5% to 8.7% of the healthy adult population [22], and was 9.3% in psychiatric patients [1]. The lifetime rate of compulsive eating disorders ranged from 0.2% to 4.6% in control individuals [23]. The frequencies of gambling disorder, compulsive buying and eating disorders in HC in our study were, respectively 1.3%, 9.6%, and 6.5%. These figures are comparable to what has been reported in other cohorts comprising healthy individuals. In contrast, the frequency of hypersexuality was much lower, 0.4%. Indeed, various studies have shown that the prevalence of ICD in PD patients, ranging from 4.4 to 39%, is not different from that mentioned in other populations [5,18].

Subtypes of ICD also have frequency comparable to those reported in other populations. For instance, gambling disorder, hypersexuality, compulsive buying and eating disorders occur, respectively, in the range of 2–9.3%, 2–11.8%, 1–10.5%, and 4–14% in PD patients [5,18,24]. However, we observed that gambling disorder and hypersexuality were more common in PD patients than in HC. It was suggested that the mechanisms underling gambling disorder and hypersexuality could be not identical to other ICD [2,3,7,19]. Yet hypersexuality and gambling disorder are clearly disabling not only to the patient but also to his family. Sometimes, the caregiver or a relative are more likely to volunteer this information to the physician [2,16,19]. This might be a reason why these more distressing ICD were reported less frequently in HC. The low number of individuals with these disorders may also have influenced the differences observed, so these results should be viewed with caution.

There are studies comparing the prevalence of ICD between individuals with and without PD [8,9,18,25]. Similarly to the results

observed in our study, some of them failed to show a higher prevalence of ICD in PD patients. This happened when different populations of patients (newly diagnosed, drug-naïve PD patients [8,9] or treated PD patients [25]) or controls (unmatched healthy individuals with ages similar to the PD patient cohort) were evaluated [8,9,25]. Others, though, suggest that ICD are more common in treated PD patients than in the general population or in assessed healthy controls subjects [7]. An example was the study of Perez-Lloret et al. [24] that reported an ICD prevalence of 25% in 203 PD patients and no occurrence of ICD in the control group. It is possible that the recruitment of a control group composed of age- and sex-matched, ambulatory, cognitively intact, non-aphasic patients who had recovered from a stroke could explain the absence of ICD in this group, since ICD and punding have been infrequently observed following cerebrovascular disease [24]. A recent cross-sectional population-based study showed that patients with PD have a 4-fold increased odds of ICD compared with age- and gender matched controls [26]. On the other hand, similarly to our study, these authors found that the higher frequency of ICD is limited to patients treated with agonists.

Approximately 38% of the patients evaluated in the present study used dopaminergic agonists. When this subgroup of individuals was analyzed separately, the ICD prevalence was significantly higher than controls. On the other hand, no differences were observed between the frequency of the disorders in patients who did not use agonists and the HC. This is line with most studies that have shown that dopamine agonist use is associated with ICD in PD and in other conditions, such as pituitary adenoma and restless legs syndrome [3–5,24].Similarly to the present study, others have found that exposure to dopamine agonist in PD increases the ICD prevalence rate from 6% to 17% [5]. Many studies suggest that ICD are associated with the use of high doses, and long exposure to dopamine agonists [3,5,7,27]. ICD appear to be related to formulation and route of administration of the medication, being less frequent in patients taking transdermal and extending release dopaminergic agonist [4,19].

More than one-third of our patients with ICD experienced two or more ICD, which was consistent with reports from previous studies that found that multiple ICD simultaneously occurred in PD patients [4,5,24]. Once more the role of dopamine agonist exposure is clear-cut: the prevalence of more than one ICD was higher just in PD patients who were receiving these agents. This finding may suggest that the use of agonists may increase the prevalence of multiple ICD [4].

There is a long list of risk factors for the development of ICD: current cigarette smoking, prior personal or family history of alcohol use and recreational drug use disorder, prior gambling problems, drug-induced mania, a premorbid history of impulsivity disorders or family history of such conditions, strong novelty seeking traits, a lack of concern for the future, and genetic polymorphisms (variants in DRD1, DRD2, DRD3, DRD4, opioid receptor Kappa, the serotonin 2A receptor gene, DOPA decarboxylase, NMDA receptor GRIN2B, and the COMT gene) [3–5,7,18,19,27–29]. Interestingly, these genetic polymorphisms have also been reported to be associated with the development of substance and behavioral addiction disorders in the general population [19,27].Certain psychological factors have been reported to be associated with ICD in the general population and in PD patients [19,25].

Taken together, these results suggest that subclinical behavioral abnormalities occur in the same proportion in individuals with or without PD because of combination of genetic and psychological traits predisposing to addiction [19]. The excess occurrence of these disorders in a subgroup of PD patients is driven by exposure to dopamine agonist therapy and possibly other treatments, such as deep brain stimulation [9]. It is conceivable that the treatment with dopamine agonists, that have greater D2/D3 receptors selectivity, in predisposed individuals may transform a personality trait or subclinical, abnormal behavior, into a clinically relevant disorder [8,19].

The prevalence of punding in PD patients in the present study was not high, just 5.3%, although more prevalent in PD patients than in controls. This figure is comparable to that reported in other studies [3,9,16]. Punding is related to more prolonged PD, dyskinesia, higher daily levodopa dosage, and longer dopamine replacement therapy duration [3]. It has been rarely described in patients without PD, with some reports in patients with stroke, restless leg syndrome, bipolar disorder, and cocaine and amphetamine addiction [3,6,9,19,30]. In our study, only three patients in the HC group had a diagnosis of punding; among these individuals, one had a diagnosis of bipolar disorder, and another was a current amphetamine abuser.

Our study has a few limitations. It was not possible to assess the severity of ICD, since we used structured instruments primarily to diagnose the disturbances. A second issue was that our sample consisted of patients from a rehabilitation hospital, which may limit the generalization of our results. PD patients and HC were not completely matched. The HC group was composed of relatives and caregivers of neurologic patients who may not be representative of the age-matched general population. However, there are several strengths: we used structured interviews based on the diagnostic criteria of each disorder to confirm the diagnosis of ICD, which reduces the impact of not using validated questionnaires as screening instruments. We performed a systematic evaluation of a large number of patients at all stages of PD in routine clinical care. We also assessed gambling, sex, shopping, and eating ICD and punding, using standardized assessment instruments.

5. Conclusion

The results of our study provide additional support to the notion that PD itself does not lead to the development of ICD. Our findings indicate that dopaminergic agonist treatment may trigger the disorder in susceptible individuals. This indicates that prescription of these agents in PD can be done although it is necessary to carefully determine if patients have risk factors for development of ICD. Long-term follow-up of PD patients and matched controls is needed to determine the influence of demographic, clinical and neuropsychiatric characteristics on the development of ICB.

Authors' roles

1. Research project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

A.P.V.: 1A, 1B, 1C, 2A, 2B, 2C, 3A
L.S.V.: 2A, 2B, 2C, 3B
A.R., C.M.C.: 1C, 2C, 3B
F.E.C.C.: 1A, 1B, 2A, 2C, 3B

Financial disclosure/Conflict of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_discosure.pdf (available on request from the corresponding author) and declare no conflict of interest related to the present paper.

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