Compulsive sexual behaviour in Parkinson's disease is associated with higher doses of levodopa

Authors

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INTRODUCTION

Previous research estimates the lifetime prevalence of compulsive sexual behaviour (CSB) in individuals with PD to be 2.7%. CSB has also been associated with male gender and earlier onset of PD.[1] Although both dopamine agonists and to a lesser extent levodopa have been associated with impulsive compulsive behaviours (ICBs) [2], it is still unclear whether higher levodopa doses are a risk factor for the development of CSB in PD patients.

METHODS

Patients with ICBs were identified from a database of individuals with PD and ICBs who were seen at the National Hospital for Neurology and Neurosurgery, Queen Square, London, UK and who had participated in 3 previous research projects over an eight-year period (from 2008 to 2016). Each project received approval from the local research ethics committee. All the ICB cases were recruited to research studies from PD clinics at the National Hospital and selected due to the reporting of ICBS. All cases underwent a thorough clinical investigation as well as a detailed semi-structured interview conducted by one of the authors. Hospital notes were reviewed by a movement disorder specialist (P.B.) for clinical and demographic data. Levodopa equivalent daily dose (LEDD) was calculated according to previously published guidelines.[3] Data was analysed using the software SPSS© 24.

RESULTS

In total, 128 patients with PD and ICBs were identified. Seventeen cases were excluded because data on dopaminergic treatment when the ICB was most active was incomplete. The remaining 111 patients were included in the analysis. Nearly 75% of the patients were males. The average age of PD onset for the entire cohort was 46.3 years, mean PD duration 11.3 years and mean age at ICBs 56.9 years. Dopamine agonists were used by 91% of the patients.

CSB was the most frequent ICB identified, present in 49.5% of the patients, followed by punding (43.2%), compulsive shopping (38.7%), pathological gambling (32.4%), dopamine dysregulation syndrome (24.3%) and compulsive eating (19.8%). Multiple ICBs were present in 69 patients (62.1%).

For statistical analysis we divided the cohort into two groups based on the presence of CSB: CSB^+ (N = 55) and CSB^- (N = 56). The proportion of male individuals was higher in the CSB^+ group ($p < 0.001$) and these individuals developed ICBs at younger age ($p = 0.02$) (Table 1).

We did not find any differences between groups in the proportion of patients using levodopa, dopamine agonists, MAO inhibitors (MAOi), amantadine or COMT inhibitors (COMTi). Nine patients had not been exposed to dopamine agonists, 3 with CSB and 6 without. The CSB^+ group was using a higher dose of dopaminergic treatment and levodopa as measured by total LEDD ($p = 0.014$), levodopa daily dose ($p = 0.043$), combined levodopa and COMTi LEDD ($p = 0.039$), and isolated COMTi LEDD ($p = 0.026$). DA LEDD ($p = 0.802$) and MAOi LEDD ($p = 0.934$) were similar between groups. Multiple ICBs were present in 48.2% of individuals without and 76.3% of individuals with CSB ($p = 0.002$) (table 1).

Table 1 – Clinical and demographic characteristics divided by groups

	CSB^+	CSB^-	p
N = 111	55	56	
Proportion of males	94.5	60.7	**<0.001***
Mean age of PD onset in years	44.6	48.0	0.079**
Mean PD duration at onset of ICBs in years	10.8	11.8	0.471**
Mean PD duration at assessment in years	11.8	13.2	0.344**
Mean age at ICBs onset in years	54.6	59.1	**0.02****
Multiple ICBs (%)	76.3	48.2	**0.002***
Patients using levodopa (%)	98.1	91	0.206*
Patients using DA (%)	94.5	89.2	0.48*
Patients using MAOi (%)	36.3	26.7	0.312*
Patients using amantadine (%)	49	44.6	0.705*
Patients using COMTi (%)	49	53.5	0.706*
Levodopa daily dose (mg)	994.5	704.9	**0.043****
DA LEDD (mg)	385	357.8	0.802**
MAOi LEDD (mg)	97.5 (N = 20)	96.67 (N = 15)	0.934**
Levodopa + MAOi LEDD (mg)	911.5 (N = 20)	696.7 (N = 15)	0.114***
COMTi LEDD (mg)	265.2 (N = 27)	215.6 (N = 30)	**0.026****
Levodopa + COMTi LEDD (mg)	1068.5 (N = 27)	874.5 (N = 30)	**0.039****
Total LEDD (mg)	1400.1	1163.6	**0.014****
Punding	38.1	48.2	0.34*
Compulsive shopping	43.6	33.9	0.333*
Pathological gambling	30.9	33.9	0.840*
Dopamine dysregulation syndrome	21.8	26.7	0.659*
Compulsive eating	14.5	25	0.234*

PD – Parkinson's disease; SD – standard deviation; ICBs – impulsive compulsive behaviours; DA- dopamine agonist; MAOi – monoamine oxidase inhibitor; COMTi – Catechol-O-methyl transferase inhibitor; LEDD – levodopa equivalent daily dose. *Chi-square test. **Mann-Whitney test. *** Independent samples t-test. Significant results in bold

The number of patients with DDS did not differ between the groups (p = 0.659), suggesting that the higher dose of levodopa in the CSB^+ group was not being driven by a higher proportion of dysregulators (Table 1).

DISCUSSION

CSB was the most frequently identified ICB in our cohort, affecting almost 50% of people with PD-associated ICBs. We report, for the first time, that PD patients with CSB tend to develop this abnormal behaviour at an earlier age and are more likely to develop multiple ICBs compared to PD patients with other ICBs.

Another novel finding is that patients with CSB were on higher doses of dopaminergic treatment as measured in LEDD. DA and MAOi dose, and the proportion of patients using DA, amantadine and MAOi did not differ between groups. However, patients with CSB were using a higher levodopa daily

dose and higher COMTi doses than patients without CSB, although the proportion of patients using COMTi did not differ between groups. This suggests that higher dopaminergic stimulation, particularly higher doses of levodopa are a risk factor for the development of CSB. It is likely that higher doses of COMTi are not directly related to ICBs but are rather contributing to excessive dopaminergic stimulation by increasing the bioavailability of levodopa. This is corroborated by the fact that only half of the patients were using COMTi.

The association of abnormal sexual behaviour and levodopa was reported in the early days of levodopa use, years before dopamine agonists started being used for PD. Barbeau and colleagues treated 80 patients with Parkinson's disease with an average dose of 4.8 g of levodopa per day and reported that at least 4 males developed an increase in libido.[4]

Although the main risk factor for the development of impulse controls disorders in PD is the use of DAs[2], levodopa has been found to be an important contributor to the development of ICBs in patients with PD receiving treatment with DAs.[5] Interestingly, despite finding that patients with CSB were on higher doses of levodopa, the proportion of other types of ICBs was similar between groups, indicating that even though higher levodopa doses are associated with CSB and DDS, these abnormal behaviours are not more likely to occur together.

By including only patients that participated in previous research projects, it is possible that we have missed patients with ICBs that were diagnosed during a regular outpatient's appointment. However, since we were interested in assessing the prevalence of CSB among patients with established ICBs we believe this approach minimised the possibility of including false positives.

CONCLUSION

The data from this study suggest that CSB is more frequent in males and tends to appear earlier than other ICBs. CSB may be the most frequent ICB associated with PD. Furthermore, patients with CSB are more likely to develop multiple ICBs. When compared to other types of ICBs, this behavioural addiction appears to be driven by higher levodopa doses. Data from larger studies are needed to confirm these novel findings.

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Contributors Study concept and design: PB, AJL, SOS, AD, TTW. Gathering of data: PB, TG, SOS, AD. Analysis and interpretation of data: PB, TG, AJL, SOS, AD, TTW. Drafting of the manuscript: PB. Critical revision of the manuscript: TG, AJL, SOS, AD, TTW.

Competing Interests

Pedro Barbosa received support to attend academic meetings from Britannia Pharmaceuticals and the Movement Disorders Society, and has received a grant from Britannia Pharmaceuticals.

Talyta Grippe has nothing to disclose.

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Atbin Djamshidian has nothing to disclose.

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REFERENCES

1. Nakum S, Cavanna AE. The prevalence and clinical characteristics of hypersexuality in patients with Parkinson's disease following dopaminergic therapy: A systematic literature review. *Parkinsonism & related disorders* 2016;25:10-6. doi: 10.1016/j.parkreldis.2016.02.017
2. Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Archives of neurology* 2010;67(5):589-95. doi: 10.1001/archneurol.2010.65
3. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society* 2010;25(15):2649-53. doi: 10.1002/mds.23429
4. Barbeau A. L-dopa therapy in Parkinson's disease: a critical review of nine years' experience. *Canadian Medical Association journal* 1969;101(13):59-68. [published Online First: 1969/12/27]
5. Hassan A, Bower JH, Kumar N, et al. Dopamine agonist-triggered pathological behaviors: surveillance in the PD clinic reveals high frequencies. *Parkinsonism & related disorders* 2011;17(4):260-4. doi: 10.1016/j.parkreldis.2011.01.009