

SHORT REPORT

Impulse control behaviours in patients with Parkinson's disease after subthalamic deep brain stimulation: de novo cases and 3-year follow-up

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2013-307214>).

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Received 14 November 2013

Revised 21 May 2014

Accepted 14 June 2014

Published Online First

10 July 2014

ABSTRACT

Objective To document the occurrence of impulse control behaviours (ICBs) in patients with Parkinson's disease after 3 years of continuous deep brain stimulation (DBS) of the subthalamic nucleus (STN).

Methods Detailed neurological and ICB assessments were performed before STN DBS and up to 3 years after implant.

Results 13 out of 56 patients (23.2%) had ICBs at baseline; they took higher doses of dopamine agonists (DAA). Three years after implant 11 had fully remitted with a 60.8% reduction of DAA medication; the remaining two, who had a similar medication reduction, had only compulsive eating, having recovered from hypersexuality. Six of the 43 patients without ICBs at baseline (14%) developed transient de novo ICBs after implant; none of them had ICBs at the 3-year observation.

Conclusions ICBs were abolished in patients 3 years after STN DBS and DAA dosages were lowered. New ICBs may occur after implant and are transient in most cases. Compulsive eating may be specifically related to STN stimulation.

INTRODUCTION

Neuropsychiatric symptoms, including impulse control behaviours (ICBs), are common non-motor features across all Parkinson's disease (PD) stages. ICBs are a set of reward-based and repetitive behaviours including pathological gambling, hypersexuality, compulsive shopping, compulsive eating and the related behaviours of hobbyism, punning and compulsive dopaminergic medication use.¹ Such behaviours are especially frequent in patients treated with dopamine agonist (DAA) medication.² In the general PD population, reduction or withdrawal of DAA is considered the first-line approach for ICB management.³

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a potentially useful approach for patients with ICBs, as it provides beneficial effects on parkinsonian motor symptoms, allowing for a long-lasting reduction of dopaminergic medication.⁴ However, the evidences are still inconsistent and limited to short-term follow-up,^{5–7} with some cases reporting ICBs even years after surgery.⁸ We designed a prospective observational study to detect the occurrence of ICBs after STN DBS with a long follow-up outlook.

MATERIALS AND METHODS

Patients with PD underwent STN DBS between 2007 and 2012; they all completed a 3-year follow-up period. Inclusion criteria have already been reported.⁹ Occurrence of ICBs was not considered a reason for exclusion. A bilateral simultaneous STN implant was performed in all patients as previously described.⁹ The Internal Review Board (registered at the Office for Human Research Protections as IORG0006168) approved the study, and all patients gave written informed consent.

Neurological evaluations were performed in the morning, in the practically defined *off* condition at baseline and in the practically defined medically *off* condition with stimulation turned on at follow-up.⁹ Motor assessment was performed using the Unified PD rating scale motor part (UPDRS-III). During follow-up visits dopaminergic medications were annotated and reduced to the minimum level sufficient to achieve the best possible control of motor signs.⁹ The levodopa equivalent daily dose was expressed in milligrams and computed according to standard conversion factors for levodopa, DAA, amantadine and monoamine oxidase inhibitors (MAOIs).¹⁰ The total electrical energy delivered (TEED) was measured in micro Joules according to a standard formula.¹¹

The occurrence of ICBs was collected before surgery and at yearly intervals after surgery using a structured interview based on specific diagnostic criteria.¹ The interview contained questions concerning the occurrence of pathological gambling, hypersexuality, compulsive shopping, compulsive eating, hobbyism, punning and compulsive use of dopaminergic medication. In addition, the patients and their caregivers were instructed to contact us whenever ICBs occurred after surgery.

The patients were grouped based on ICB occurrence at baseline as 'ICB' and 'No-ICB'. Continuous data were expressed as mean±SD. Preoperative and postoperative assessments were compared using a paired t test or a Wilcoxon signed rank test, according to data distribution. Student t tests or Mann-Whitney tests were used for between-group comparison, according to data distribution. Categorical data were expressed as number of patients. Between-group comparisons were carried out with χ^2 tests. The significance level was set at 0.05 (two-sided test). Statistical analysis was carried out with the Statistical Package for the Social Sciences (SPSS) software (release V.15.0).



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To cite: Amami P, Dekker I, Piacentini S, et al. *J Neurol Neurosurg Psychiatry* 2015;**86**:562–564.

Analysis of lead location and volume of tissue activated was performed using Optivise DBS Care Management software (Medtronic, Inc). This fuses preimplant MRI and postimplant CT, allowing identification of the anterior and posterior commissures and electrode location. The volume of tissue activated and the relative position of selected anatomical structures are then calculated based on the stimulation settings and rendered in three-dimensional maps.

RESULTS

STN DBS was performed on 69 consecutive patients with PD, 13 were excluded due to: implant removal (1 patient), death unrelated to surgery (1 patient), intraoperative bleeding (3 patients), development of dementia (2 patients) or loss to follow-up (6 patients). The resulting 56 patients had a mean age at onset of 44 (± 7.7), a mean age at surgery of 55.5 (± 7.2) and a mean disease duration of 11.5 (± 4.2).

The group with ICBs at baseline encompassed 13 patients (23.2%), 8 of whom (14.3%) had more than one ICB; 43 patients had no baseline ICBs. The frequencies of different ICB types are reported in figure 1. Patients in the 'ICB' group took higher baseline doses of DAA ($p=0.005$) compared with the 'No-ICB' group, whereas there were no differences regarding dosage of levodopa, amantadine or MAOIs, UPDRS motor score in the *off* condition, gender, age at onset, age at surgery and disease duration (table 1).

Three years after implant, the 'ICB' group had improved on the UPDRS motor score by 42.8% ($p=0.028$) and had decreased the DAA dose by 60.8% ($p=0.012$). There was a trend towards a reduction of levodopa ($p=0.093$), but no differences for amantadine or MAOIs doses.

At 3-year follow-up, the 'No-ICB' group had improved on the UPDRS motor score by 57.5% ($p=0.001$) and had decreased levodopa by 47.7% ($p=0.001$); there were no changes for DAA, amantadine or MAOIs doses. Between-group comparison showed no difference at the end of follow-up regarding levodopa, DAA, amantadine, MAOIs, UPDRS motor score or TEED (table 1).

Eleven (84.6%) of the 13 patients with preimplant ICBs had fully remitted their behavioural symptoms, on average 6 months (range 2–8 months) postsurgery and were symptom free at 3 years. However, one patient had a transient relapse (compulsive gambling) 2 years after surgery that lasted for 6 months. Two of the 13 patients with preimplant ICBs were symptomatic 3 years after surgery: baseline hypersexuality had resolved in both, but compulsive eating had developed. None of the 43 patients in the 'No-ICB' group had ICBs at the end of follow-up; however, six of them (14%) developed *de novo* ICBs after surgery (see online figure 1). These symptoms were transient; their onset was on average 16 months after surgery and lasted for an average of 15 months.

Contact location was verified in all patients after implant. The stimulating contact was always located in the posterolateral and middle-dorsal portion of STN. The location of electrodes and the calculated volume of tissue activated are shown for patients who developed *de novo* ICBs after implant (see online figure 2).

DISCUSSION

We carried out a longitudinal evaluation of ICBs for 3 years after STN DBS in a cohort of 56 patients with PD. The main result is a complete resolution in most patients who had baseline ICBs, in keeping with earlier studies.^{5 6 8} We also observed the onset of *de novo* ICBs in a minority of patients who had no baseline ICBs, starting about 1 year after surgery. These transient phenomena may explain some inconsistencies of earlier studies showing the occurrence of new ICBs 1 year after implant.^{8 12}

We confirm a strong association between DAA dosages and ICB occurrence.¹³ In the present series, 'ICB' patients took 36% higher DAA doses at baseline compared with the 'No-ICB' group. A 60.8% decrease of DAA doses was associated with ICB improvement after implant, whereas levodopa, amantadine and MAOIs remained unchanged. Three years after implant both groups were comparable for any antiparkinsonian medication and ICBs had almost disappeared. This supports the importance of an appropriate reduction of DAA in patients with ICBs who receive STN DBS.^{4 6} Such reduction should be carefully

Figure 1 Frequency of specific impulse control behaviours at baseline and during the 3-year follow-up.

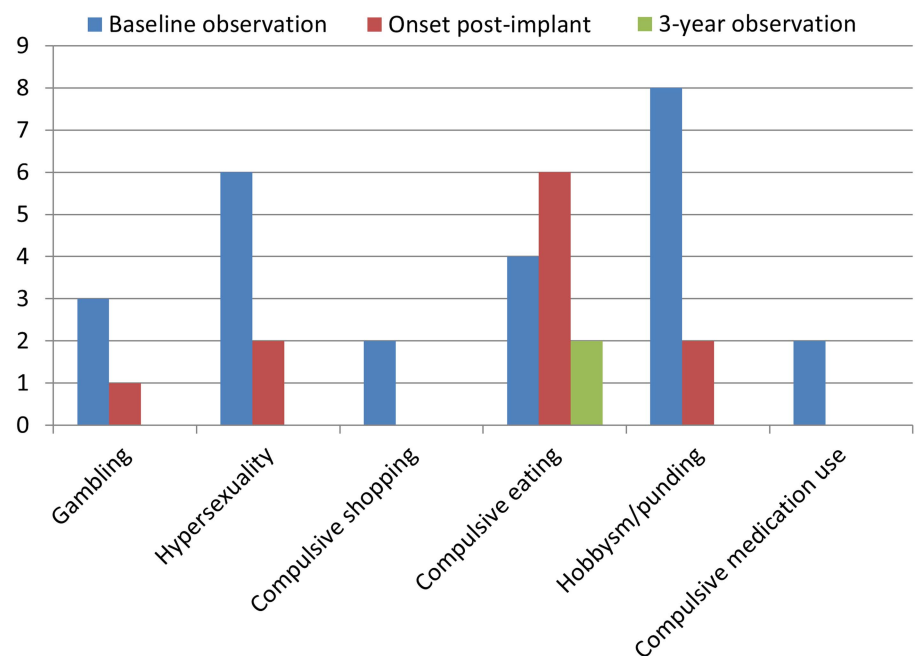


Table 1 Demographic and clinical characteristics of patients with and without ICBs before and after STN DBS

	ICB	No-ICB
Number	13	43
Gender (female/male)	4/9	17/28
Age at PD onset	40.9 (±7.8)	44.9 (±7.5)
Age at surgery	52.9 (±6.3)	56.3 (±7.3)
Disease duration at surgery	12 (±4.6)	11.3 (±4.1)
UPDRS motor score at baseline (practically defined off condition)	39.6 (±17.1)	45 (±16.6)
UPDRS motor score at 3-year follow-up (practically defined off condition and stimulation turned on)	25.3 (±14.2)*	19.7 (11.4)*
Levodopa (LEDD mg) before surgery	838.2 (±689.2)	837.4 (±494.2)
Levodopa (LEDD mg) at 3-year follow-up	508.8 (±401.2)†	437.6 (±381.1)*
DAA (LEDD mg) before surgery	473.1 (±276.6)‡	232.9 (±188.6)
DAA (LEDD mg) at 3-year follow-up	185.4 (±156.7)*	210.3 (±188.6)
Amantadine (LEDD mg) before surgery	69.2 (±126.7)	23.3 (±63.9)
Amantadine (LEDD mg) at 3-year follow-up	46.2 (±87.7)	38.4 (±83)
MAOIs (LEDD mg) before surgery	19.2 (±38.4)	23.3 (±63.9)
MAOIs (LEDD mg) at 3-year follow-up	23.1 (±43.9)	28.9 (±101.9)
Total LEDD before surgery	1399.7 (±677)	1114.5 (±529.1)
Total LEDD at 3-year follow-up	763.4 (±449.1)*	715.1 (±432)*
TEED (μJ)	180 (±67.1)	221 (±83.3)

Continuous variables are expressed as mean (±SD), dichotomous variables as ratio. The within-participants comparisons were made by Wilcoxon signed rank test. The between-participants comparisons were made by Mann-Whitney test for quantitative data and by χ^2 test for categorical data.

*Significant difference in within-participants confrontation.

†Trend towards a difference in within-participants confrontation.

‡Significant differences in between-participants confrontation.

DAA, dopamine agonist; DBS, deep brain stimulation; ICB, impulse control behaviours; LEDD, levodopa-equivalent daily dose; MAOIs, monoamine oxidase inhibitors; PD, Parkinson's disease; STN, subthalamic nucleus; TEED, total electrical energy delivered; UPDRS, Unified PD rating scale.

managed, as behavioural complications (eg, apathy, depression or DAA withdrawal syndrome) may occur.¹⁴

We also observed new ICB cases after STN DBS despite a substantial decrease of DAA doses, a finding in keeping with recent studies reporting that de novo ICBs can happen after implant.^{5 12 15}

The reason why ICBs may occur in some patients after surgery remains unclear, indicating that DAA may not be the unique factor involved in ICB pathophysiology after STN implants.¹⁶

Compulsive eating was the most frequent behavioural phenomenon observed after STN DBS and the only remaining symptom at the end of follow-up: four patients without previous ICBs had transient compulsive eating after implant and two, who recovered from baseline hypersexuality, developed persistent compulsive eating. Whether this is a specific behaviour related to STN DBS is a matter of interest, which could explain the long-standing observation that weight gain occurs in many patients who receive STN implants.¹⁷ In keeping with this, a recent longitudinal study showed an increase of compulsive eating 1 year after STN DBS.⁵

The present study confirms and expands previous observations showing that ICBs significantly improve after STN DBS⁵⁻⁷ and also that de novo cases can arise.^{12 15 16} Taking the present and earlier studies into account it may be concluded that decrease or withdrawal of DAA medication has a pivotal role on such ICB improvement. In addition, since some patients may

develop de novo ICBs despite a reduction or withdrawal of DAA medication, factors related to implant are also likely to play a causative role. We did not find relevant variations in sub-nuclear targeting and observed that compulsive eating may represent a specific behavioural complication after STN DBS.

Current evidence suggests that occurrence of ICBs does not provide a primary treatment indication for DBS surgery.¹⁶ In cases where surgery is performed the time course of ICBs occurrence after surgery needs to be taken into account, as long-term plasticity may influence the functioning of STN and related basal ganglia structures.

Contributors PA and SP were involved in analysis and interpretation and manuscript writing. ID, FF, LMR and AF took part in acquisition of data. EMJF was involved in study concept and design. AA took part in critical revision of the manuscript for important intellectual content and study supervision.

Funding Italian Ministry of Health and Italian Ministry of University and Research (ordinary research) to AA.

Competing interests LR received research support from Medtronic and EMJF received honoraria from serving on the scientific advisory board of Boehringer-Ingelheim and TEVA pharmaceuticals. AA serves as Editor of *Frontiers in Movement Disorders* and Associate Editor of the *European Journal of Neurology*. He receives royalties from the publication of the book *Hyperkinetic Movement Disorders: Differential Diagnosis and Treatment* and received honoraria from Merz, Ipsen and TEVA pharmaceuticals.

Ethics approval Carlo Besta Institute ethical committee.

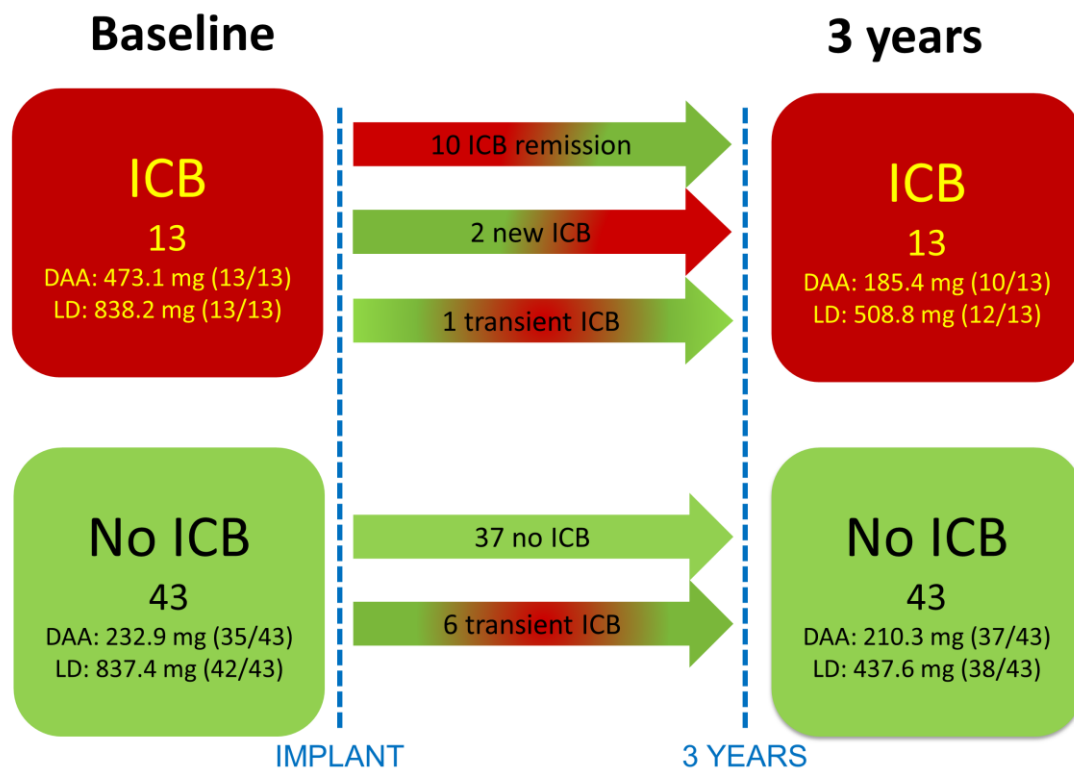
Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Figures

Comparison of the "ICB" and "No-ICB"s groups at baseline and through the 3-year follow-up period. The average dose of levodopa and dopamine agonists is reported (with the number of patients taking each drug class shown in brackets). Abbreviations: LD, levodopa; DA, dopamine agonists.



Reconstruction of electrode positioning and volume of tissue activated in six patients who developed de novo ICBs after implant. In an anterior view of the brain stem the STN (blue), the substantia nigra (fuchsia) and the red nucleus (pink) are individually reconstructed in 3D. The electrode location and the volume of tissue activated are superimposed to the anatomical landmarks (images generated by the Optivise DBS Care Management Software). Lead1 refers to the right electrode, Lead2 to the left one.

