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Effect of deep brain stimulation of the subthalamic nucleus on non-motor fluctuations in Parkinson's disease: Two-year' follow-up

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ABSTRACT

Background: Deep brain stimulation of the subthalamic nucleus (STN-DBS) reduces motor fluctuations in Parkinson's disease (PD) but its effect on non-motor fluctuations (NMF) is not well known. In this study we assess the efficacy of STN-DBS on NMF two years after surgery.
Methods: Autonomic, cognitive, psychiatric and sensory NMF in 20 patients were evaluated using a questionnaire designed to assess the frequency and severity of the NMF preoperatively and after two years of follow-up. The UPDRS scale was used for assessing the motor state.
Results: Compared with the preoperative situation, STN-DBS at 2 years of follow-up was associated with a significant reduction in the number and severity of autonomic and psychiatric NMF in the "off" state (without medication), and in the severity of sensory NMF, which were not observed in the "on" state (with medication). A cross-sectional analysis at the two-year time-point of the four possible motor conditions (combining medication and stimulation) showed a reduction in the total number of NMF and in the severity of autonomic and sensory NMF after switching on the stimulation in the "on" state. Improvement of the UPDRS-motor score was correlated with a reduction in the severity but not in the frequency of NMF. A worsening of motor function after suppressing stimulation in the "off" state was not paralleled by a worsening of NMF.
Conclusion: After two years of follow-up, STN-DBS in the "off" medication was associated with a reduction in the frequency and severity of NMF. These results will need to be confirmed in controlled studies.

1. Introduction

Non-motor fluctuations (NMF) in patients with Parkinson's disease (PD) are non-motor symptoms (dysautonomic, cognitive, psychiatric and sensory/pain) [1] that vary according to dopaminergic treatment in a manner similar to motor fluctuations (MF). Their prevalence in patients with MF varies between 17 and 100% [2,3], conveying a greater disability than MF in almost one-third of patients [3]. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) induces long-term improvement of PD motor features and MF [4]. In addition, DBS-STN has been shown to be efficient in reducing pain [5–8] and other non-motor symptoms associated with PD [9,10], as well as reducing the number of NMF one year postoperatively [11]. As is the case for MF, not only the presence but also the severity of NMF is an important consideration; however despite their clinical relevance, a lack of validated instruments to assess these aspects of NMF has limited the study of how they are affected by STN-DBS. The aim of the present study, therefore, was to assess the efficacy of STN-DBS in attenuating the number and severity of NMF in a group of patients followed for 2 years after electrode implantation. For this purpose, we have used a structured questionnaire based on previous studies [2,3,11,12] that enables analysis of the presence and severity of the most frequent and disabling forms of NMF.

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2. Methods

2.1. Patients

Consecutive patients with PD [13] treated between May-2006 and January-2010 and in whom bilateral STN-DBS was indicated were considered for the study. Only patients with NMF according to a specific questionnaire (Appendix A) were included. Patients with severe depression (Geriatric depression scale score (GDS) >20) or cognitively impaired (mini-mental state examination (MMSE) score <26) were excluded. The local Ethics Committee for Medical Research at the Clinica Universidad de Navarra approved the study and all patients provided their written informed consent. The surgical procedure used was the one routinely carried out by our group [14].

2.2. Study protocol

Evaluations were conducted preoperatively, after surgery but prior to the commencement of programmed electrical stimulation (4–7 days after electrode implantation) if medically possible, and postoperatively every 6 months up to a minimum of 18 months of follow-up.

Assessments were undertaken preoperatively after 12 h without antiparkinsonian medication ("off" medication state) and under the effect of medication ("on" medication state) after a dose of levodopa equal to 150% of the usual first morning dose. Postoperatively, assessments were made in the "off" medication state without stimulation ("off med-off stim"), in the "off" medication state with stimulation ("off med-on stim"), in the "on" medication state without stimulation ("on med-off stim"), and in the "on" medication state with stimulation ("on med-on stim"). Evaluations were undertaken over the course of one morning in the order described. Controlled release dopaminergic drugs were not taken in the 24 h prior to evaluations. "Off" and "on" stimulation conditions were assessed 1 h after turning the stimulator off or on, respectively.

Evaluations were performed in an open fashion by a neurologist specialized in movement disorders (MCR). Motor features were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) III and IV and the Hoehn and Yahr scale. Due to the lack of a validated instrument to asses NMF, a questionnaire and scale were developed that took into account the most frequent and disabling NMF previously reported [2,3,11,12] (Appendix A). The questionnaire contained 25 items across 4 categories to assess autonomic, psychiatric, cognitive and sensory symptoms. Each item was scored from 0 to 3 (0 = absence; 1 = mild; 2 = moderate; 3 = severe) (total range 0–75). Thus, in addition to the presence of NMF, symptom severity was also scored. Activities of daily living were assessed using the UPDRS-II scale. The Global Assessment scale was used to determine the degree of impairment in the following manner: 0 = no functional disability, 1 = mild disability (1–24%); 2 = moderate disability (25–49%); 3 = marked disability (50–74%); 4 = severe disability (75–100%).

The primary outcome of this study was the effect of STN-DBS on the number and severity of NMF after a minimum of 18 months postoperative follow-up compared with baseline values.

2.3. Statistics

The normality of the distribution of variables and variance homogeneity were tested using the Shapiro–Wilk's and Levene's tests, respectively. For parametric comparisons, the Wilks' lambda test was employed, and the Student's *t*-test for paired samples used for post hoc analysis. The Friedman test was applied for non-parametric analysis with the Wilcoxon rank sum test for post hoc comparison when the asymmetry coefficient was less than 1. If asymmetry was higher than 1 a sign test was used instead. Pure discrete counting variables were compared using the χ^2-test. The level of significance was 5%, with Bonferroni correction in the case of multiple testing. All *p*-values are two-sided and all analyses were carried out using SPSS 15.0 software for Windows (SPSS Inc., Chicago, Illinois, USA).

3. Results

Twenty patients were enrolled in the study. Three patients dropped out during the follow-up because of heart surgery ($n = 1$), incorrect placement of one electrode that required further surgery 4 months later ($n = 1$), and withdrawal because of family problems that precluded follow-up evaluations ($n = 1$). The mean follow-up time was 25.8 ± 6.8 (range 18–40) months (18–24 months ($n = 4$), 24 months ($n = 6$), more than 24 months ($n = 7$)). Patient characteristics are summarized in Supplementary table 1.

In the "off" medication state (without dopaminergic drugs), and in comparison with preoperative scores, STN-DBS significantly improved ($p < 0.001$) the UPDRS-III, IV and II scores by 45.76%, 73.8% and 44.1%, respectively, at the 2-year follow-up (Supplementary table 1). The levodopa equivalent daily dose (LEDD) was reduced by 59.6% ($p < 0.0001$). Monopolar stimulation was applied to 25 nuclei (73.5%), while bipolar stimulation was used in the remaining patients to avoid side-effects (i.e. internal capsule stimulation, dysarthria, etc.) and for better motor control ($n = 8$).

3.1. Frequency and severity of NMF at the two-year follow-up with respect to the preoperative state

3.1.1. Findings when patients were not under the effect of antiparkinsonian medication ("off" medication condition)

After two years of STN-DBS, we observed a significant improvement both in the total number (Wilks' lambda test, $p = 0.02$) (Table 1) and severity (Wilk's lambda test, $p = 0.04$) (Table 2) of NMF with respect to the preoperative state. This improvement was also observed at each evaluation point throughout the study (Table 1) (Student's *t*-test for post hoc analysis corrected for multiple testing, $p < 0.05$). Postoperative evaluations to assess if the benefit diminished over time revealed no difference (Wilks' lambda test, $p > 0.05$) in either the number or severity of the total or each subtype of NMF.

The benefit of subthalamic stimulation for two years was consistently observed in relation to autonomic and psychiatric symptoms, which were the most frequent and severe at baseline (Tables 1 and 2 and Supplementary table 2). Although the reduction of the number of sensory NMF was only significant at the 6-month time-point after surgery (Table 1), their severity was significantly reduced through until the last evaluation. Moreover, the reduction in severity was greater for the sensory (73.1%) than the psychiatric (58.3%) and autonomic (53.7%) NMF (Table 2). No benefit was observed in relation to cognitive NMF, which remained practically unaffected compared with preoperative measurements (Tables 1 and 2 and Supplementary table 2).

The most common NMF prior to surgery were autonomic, psychiatric and sensory (Supplementary table 2). Dry mouth, fatigue, anxiety, sadness, urinary urgency, shyness and paresthesias were

Table 1
Number of NMF per patient observed under the effect of stimulation of the STN in the "off" medication state (without antiparkinsonian medication) at each evaluation with respect to baseline.

	Preoperative ($n = 17$)	Post-surgery before starting stimulation ($n = 12$)		6 months ($n = 11$)		12 months ($n = 9$)		24 months ($n = 17$)	
			p-value		*p*-value		*p*-value		*p*-value
Total NMF	9.38 ± 3.48 (4–19)	4.08 ± 2.64 (0–9)	0.004	4.00 ± 2.72 (1–9)	0.004	3.75 ± 2.96 (0–10)	0.032	4.93 ± 3.67 (1–13)	0.008
Autonomic NMF	3.88 ± 1.67 (1–8)	1.83 ± 1.19 (0–3)	0.048	1.36 ± 0.92 (0–3)	0.016	1.22 ± 1.20 (0–3)	0.032	2.00 ± 1.62 (0–6)	0.008
Psychiatric NMF	3.06 ± 1.06 (1–5)	1.25 ± 1.36 (0–4)	0.032	1.18 ± 1.33 (0–4)	0.048	1 ± 2[a] (0–2)	0.016	1.64 ± 1.34 (0–4)	0.044
Cognitive NMF	0 ± 1 (0–2)[a]	0 ± 0 (0–3)[a]	n.s.	0 ± 2 (0–3)[a]	n.s.	0.78 ± 0.97 (0–3)	n.s.	1 ± 1(0–2)[a]	n.s.
Sensory SNM	1 ± 2 (0–5)[a]	0 ± 1 (0–3)[a]	0.032	0 ± 2 (0–2)[a]	0.016	0.50 ± 1 (0–2)[a]	n.s.	0.86 ± 1.03 (0–3)	n.s.

Data are given as mean ± SD (range) and the Student's *t*-test was used for post hoc analysis.
n.s. not significant. Level of significance was 5% taking into account the need for Bonferroni correction for multiple testing.
[a] Data are presented as median ± interquartile range (range) and the Wilcoxon rank sum test has been used for post hoc analysis.