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Low-frequency Subthalamic Stimulation in Parkinson's Disease: Long-term Outcome and Predictors

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ABSTRACT

Background: Parkinson's disease patients undergoing subthalamic nucleus deep brain stimulation (STN DBS) at standard frequency (>100 Hz) often develop gait impairment, postural instability and speech difficulties. Low frequency stimulation (<100 Hz, LFS) can improve such axial symptoms, but there are concerns that improvement may be transient.
Objective: To identify long-term outcome and predictors of low-frequency subthalamic stimulation in Parkinson's disease.
Methods: Through a chart review we identified 85 out of 324 STN DBS patients who received a trial of LFS and describe their characteristics and outcome predictors.
Results: Patients were switched to LFS (<100 Hz) 3.8 ± 3.3 years after surgery. Most patients (64%) attained a subjective improvement of gait, speech or balance for 2.0 ± 1.9 years. Motor scores improved within the first year after the stimulation change and showed a slower progression over time when compared to patients switched back to high frequency stimulation. UPDRS III axial score on medication before surgery and the y-axis coordinate of the active contact were independent predictors of LFS retention.
Conclusions: This report provides evidence that the use of LFS yields an enduring benefit in a considerable percentage of patients who develop axial motor symptoms during conventional stimulation.

Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-recognized treatment for motor fluctuations and appendicular motor symptoms in patients with advanced Parkinson's disease (PD) [1]. Unfortunately, over time many DBS patients develop axial motor symptoms, such as gait impairment, postural instability and speech difficulties poorly responsive to pharmacological therapy and conventional high frequency stimulation (HFS, >100 Hz) [2]. Recently, an increasing number of reports have explored the use of low frequency stimulation (LFS, <100 Hz) to improve axial symptoms including freezing of gait [3–7], postural control [8], dysarthria [9], swallowing function [10], and also bradykinesia [11]. However, these reports only addressed the short-term effects, and the initial promising results were limited either by the transient clinical benefits or worsening of appendicular symptoms [5,12].

In order to clarify the long-term effects and outcome predictors of LFS in STN DBS patients, we conducted a systematic chart review of all PD patients who underwent such treatment at Toronto Western Hospital from 1999 to 2014, having failed HFS due to occurrence of troublesome axial symptoms at variable time points after surgery.

Patients and methods

With the approval of the local institutional Research Ethics Board, a systematic chart review was conducted by searching the

Abbreviations: DBS, deep brain stimulation; HFS, high frequency stimulation; LFS, low frequency stimulation; PD, Parkinson's disease; STN, subthalamic nucleus; UPDRS, unified Parkinson's disease rating scale.

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electronic database of DBS patients. Out of the 324 STN DBS patients, we identified 85 subjects who received LFS (Table 1). All but two patients had bilateral STN stimulation, three patients received a staged procedure and one had undergone a previous unilateral pallidotomy. Twenty-nine patients had taken part in a previous study [6]. Seven patients were excluded from further analysis (six had a very short LFS trial < 2 days and one received LFS on one side only).

The unified Parkinson's disease rating scale (UPDRS) [13] at different time points pre and post DBS was used as outcome measure.

Demographical and clinical data were collected as well as the reasons for trying LFS, which were categorized as being related to speech, balance or gait issues or combinations thereof. Different time points were identified for each patient: the date of surgery, the date of switching from HFS to LFS, the date of switching back to conventional HFS for those patients who stopped LFS, and the date of last follow-up visit available for patients with LFS still ongoing at the time of study.

The total motor score, the axial (items speech, arising from a chair, posture, gait and stability) and tremor sub-scores of the UPDRS-III were recorded; in addition, single UPDRS-III item scores for speech, gait, stability plus single UPDRS part II (activities of daily living) item scores for speech, falls, freezing of gait and walking were also taken into account. The UPDRS was assessed at baseline (preoperatively) and postoperatively at 6 months, according to the core assessment program for surgical interventional therapies (CAPSIT) in PD protocol [14]. Before surgery, patients were evaluated after an overnight withdrawal of dopaminergic medications and after an acute levodopa challenge using 150% of the morning medication dose. Postoperatively, patients were assessed in 4 conditions: off medication/on stimulation, off medication/off stimulation, on medication/off stimulation, and on medication/on stimulation, with the same dose of levodopa used in the preoperative challenge. As an index of the stimulation induced benefit, a ratio between levodopa and stimulation response was calculated for each patient according to the formula: (UPDRS III pre-op med OFF – med ON)/(UPDRS III post-op Med OFF Stim OFF – UPDRS III med OFF Stim ON). UPDRS III data were also collected from assessments done routinely during follow-up evaluations (with stimulation and ongoing medication).

Pharmacological therapy converted into levodopa equivalent daily dose (LEDD) [15], stimulation parameters as well as the active contact/s in use were noted for each time point. All patients underwent post-operative imaging and gross electrode misplacement was excluded. For the calculation of active electrode coordinates, we imported both the pre and post-operative images into the stealth planning station (Medtronic Inc., Minneapolis, MN). The pre and post-operative images were fused using the pointmerge and automerge protocols available within the FrameLink planning software (version 5, Medtronic Inc., Minneapolis, MN). The calculated fusion error was always kept below 1 mm. Finally, the fused images were visually inspected to ensure good fusion accuracy. Once satisfactory fusion was achieved, the images were reformatted and aligned to the anterior commissure (AC) – posterior commissure (PC) line. The software automatically corrects variations in the pitch, yaw and roll of the frame. The electrode artifact from Medtronic 3387 (Medtronic Inc., Minneapolis, MN) was reliably identified in the 52 patients with available neuroimaging data [16,17]. We determined the coordinates of the center of the electrode on a T1 volumetric scan similarly to other published reports [17,18]. Briefly, we calculated the frame coordinates of both the tip and the entry point of the implanted electrode. For consistency, we defined the 'tip' of the electrode as the first clear oval artifact seen on axial volumetric T1 sequences. We refer to the 'entry point' as the center of the electrode artifact at the entry of the electrode at the cortical surface. If the trajectory was curved, the most proximal point at the straight electrode trajectory was chosen as the 'entry point'. We calculated the coordinates of the contacts using three parametric equations based on the known dimensions of the Medtronic 3387 electrode. The x coordinate of the active contact was also calculated from the wall of the third ventricle. The x and y coordinates of the electrodes were then normalized for plotting on the Schaltenbrand and Wahren atlas. The y coordinate was normalized to the AC–PC length. For the x-axis, we chose the distance of the active electrode from the ventricle wall, assuming that it represents the normalized x-coordinate.

Statistical analysis

Continuous variables were tabulated as mean and standard deviation and discontinuous variables as median and interquartile range (IQR 25th–75th percentile). The impact of the switch from HFS to LFS on UPDRS scores was analyzed with Wilcoxon rank sum test, after checking for normal distribution of data with the Shapiro–Wilk test. UPDRS III total score, axial sub-score and single items for speech, gait and stability were analyzed in the entire group of patients receiving LFS and separately in two groups based on the time of reassessment (within 1 year or later).

Time to LFS failure was evaluated by means of the Kaplan–Meier survival curve. The clinical characteristics of patients who maintained LFS were compared with those of patients who stopped LFS using the Mann–Whitney or chi square tests for continuous or categorical values, respectively. Factors related to retention of LFS were assessed using logistic regression analysis in which 'to retain' or 'not to retain' LFS was the explanatory variable, as well as multivariate models with forced entry and backward and forward selection of variables with $P = 0.05$ and $P = 0.10$, respectively, for each strategy. Independent variables included all pre- and post-operative characteristics that were significantly different in patients retaining LFS compared to patients switching back to HFS.

In patients with ongoing LFS and a follow-up of more than 1 year, the UPDRS III data were plotted against time of assessment in order to evaluate the disease progression under different frequencies of stimulation. All *P*-values reported are two-tailed, considering 0.05 as statistical threshold. Statistical analyses were performed with SPSS Statistics 21.0 for Mac.

Results

Patients were switched to LFS after a mean of 3.8 ± 3.3 years of continuous HFS; reported reason for switching was the variable combination of impairment of gait, balance or speech in 60, 42 and 40 patients, respectively. The stimulation frequency was reduced from a median value (IQR 25th–75th percentile) of 130 (130–185) to 80 (80–100) Hz ($P < 0.001$), and the voltage was increased from a median value of 3.3 (2.7–3.6) to 3.75 (3.2–4.0) volts ($P < 0.001$).

Effects of LFS

Twenty-eight patients (36%) stopped LFS and were switched back to HFS after a mean period of 3.4 ± 6.5 months (Fig. 1A). The most common reported reason was the worsening of appendicular signs (14 patients), the lack of clinical benefit (11 patients) or further worsening of axial signs (3 patients).

By contrast, 50 patients (64%) had LFS still ongoing at the last follow up visit after a mean period of 2.0 ± 1.9 years and reported an improvement of gait (33 patients), speech (20 patients) and balance (10 patients). No significant changes in UPDRS measures were found when comparing LFS with HFS in the entire group of 50 patients (Table 2). Analyzing separately the group of 23 patients with ongoing LFS reassessed within the first year (0.5 ± 0.3 years), there was an improvement of UPDRS III total score (from