Predictors of effective bilateral subthalamic nucleus stimulation for PD

CHARLES, David, et al.


PMID : 12297584
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Abstract—To identify factors predictive of effective bilateral subthalamic nucleus (STN) stimulation for PD with severe motor complications, pre- and postoperative Unified PD Rating Scale (UPDRS) scores were analyzed in a series of 54 patients who received bilateral STN stimulation. Younger age and levodopa responsiveness predict a favorable response to bilateral STN stimulation. For individual PD symptoms, those that improve with a suprathreshold dose levodopa challenge are likely to improve with stimulation.

P.D. Charles, MD; N. Van Blercom, MD; P. Krack, MD; S.L. Lee, MD, PhD; J. Xie, MD; G. Besson, MD; A.-L. Benabid, MD, PhD; and P. Pollak, MD

Bilateral deep brain stimulation (DBS) to the subthalamic nucleus (STN) is proving to be a safe and effective treatment for patients with PD, especially those with advanced disease.1–3 It remains unclear, however, which preoperative factors are most predictive of a beneficial response. To identify clinical characteristics of the candidate who may receive the greatest benefit and aid in the prediction of the expected degree of improvement, we present a univariate and multivariate analysis of 54 patients with PD treated with bilateral STN stimulation to determine the preoperative indicators of clinical outcome.

Methods. Patients. During a 5-year period, 56 consecutive PD patients, 29 men and 27 women, with a mean age 56.0 ± 7.7 years at the time of surgery received bilateral STN stimulator implantation. Selection criteria were 1) clinically diagnosed idiopathic PD; 2) disabling motor fluctuations despite all drug strategies; 3) good general health; 4) brain MRI within normal range; and 5) no severe dementia (Mini-Mental State Examination score > 24).2,4 Mean illness duration at the time of surgery was 15.7 ± 4.9 years. All patients were treated with levodopa and a peripheral decarboxylase inhibitor (average preoperative daily levodopa dose 1,102 ± 576 mg). Two patients were not available for the 3-month assessment. One patient suffered a severe frontal hematoma at the time of surgery, and the other patient, living far away, reported great benefit from the therapy but refused to return for formal assessment. This investigation was approved by the hospital ethics committee at the University of Grenoble, Grenoble, France.

Clinical Evaluation. Patients were evaluated preoperatively and 3 months postoperatively. Analysis in the immediate postoperative period was not performed because of the transient, lesion-like, postsurgical effect. Three months postoperatively, most patients demonstrated a chronic, stable condition that was sustained for up to 3 years and required little electrical adjustment.2

All patients were assessed using the complete Unified PD Rating Scale (UPDRS) after a suprathreshold dose levodopa challenge.5 A motor scale, UPDRS part III (UPDRS-III), was assessed preoperatively in both off- and on-drug states. Postoperatively, the UPDRS-III was performed in four conditions: 1) off-drug/off-stimulation; 2) off-drug/on-stimulation; 3) on-drug/off-stimulation; and 4) on-drug/on-stimulation. The remaining parts of the UPDRS were also rated.2 For the levodopa challenge, patients received dispersible Madopar (Hoffmann-La Roche, Ltd., Basel, Switzerland) in the morning after an overnight fast. The dose was calculated as 120% of the regular morning levodopa dose plus additional levodopa equivalent to the dopamine agonist dose that would usually have been taken in the morning.6

Surgery. The STN was targeted using five parallel microelectrodes that allowed the mapping of the region by microrecording and stimulation. The implanted stimulating electrode (DBS-3387 or DBS-3389, Medtronic, Minneapolis, MN) replaced the best of the five microelectrodes

References

according to the following criteria: 1) neuronal activity characteristic of STN; 2) improvement in motor symptoms; and 3) no adverse effect with the level of stimulation that improves parkinsonism. Confirmation of STN placement by this method has been validated by MRI. Each electrode was then connected to a pulse generator (Itrel II, Medtronic) placed subcutaneously in the subclavicular area. The pulse generator is programmable by telemetry to allow the adjustment of the different variables of stimulation. After surgery, voltage was progressively increased (0.1 to 3.6 V). High-frequency stimulation (130 to 185 Hz) with a pulse width of 60 μs was delivered in a unipolar or bipolar fashion depending on efficacy and side effects.

Data Analysis. Preoperative response to levodopa was calculated as the difference in UPDRS-III off and on drug:

\[
\text{Improvement-from-levodopa} = \text{Preoperative UPDRS-III off-drug} - \text{Preoperative UPDRS-III on-drug}.
\]

Because the off-drug/off-stimulation condition did not contribute substantially to the motor score (not shown), postoperative response to stimulation was calculated as:

\[
\text{Improvement-from-stimulation} = \text{Preoperative UPDRS-III off-drug} - \text{Postoperative UPDRS-III off-drug/on-stimulation}.
\]

A series of parkinsonian symptoms were individually analyzed: akinesia (UPDRS-III items 23 to 26; 0 to 32); tremor (UPDRS-III items 20 and 21; 0 to 28); rigidity (UPDRS-III item 22; 0 to 20); postural instability gait disorder composite score (UPDRS-II items 13 to 15, UPDRS-III items 29 and 30; 0 to 20); gait (UPDRS-III item 30; 0 to 4); pull test (UPDRS-III item 29; 0 to 4); and speech (UPDRS-III item 18; 0 to 4). Hoehn and Yahr and Schwab and England global ratings were similarly analyzed.

A univariate analysis (Spearman’s nonparametric rank correlation; SPSS Inc., Chicago, IL) was performed for age and levodopa responsiveness. Multiple regression analysis (Statview 5.0, SAS Institute Inc., Cary, NC) was performed on the improvement of the individual scores produced by levodopa. All analyses were performed with n = 54 and, where appropriate, a p value of < 0.05 was considered significant.

Results. Univariate analysis demonstrated that improvement from levodopa, as measured by change in the UPDRS-III score, correlated positively with postoperative improvement from stimulation \((r = 0.58, p < 0.00001; \text{figure 1})\), the \(R^2\) value indicating that this factor accounts for 32% of the postoperative improvement. Age correlated negatively with postoperative improvement from stimulation \((r = 0.41, p < 0.01; \text{figure 2})\).

A preoperative levodopa response in an individual symptom correlated with a postoperative stimulation response for that same symptom: akinesia \((r = 0.46, p < 0.001)\); tremor \((r = 0.84, p < 0.001)\); rigidity \((r = 0.69, p < 0.001)\); composite score for postural instability gait disorder \((r = 0.65, p < 0.001)\); gait \((r = 0.48, p < 0.001)\); and pull test \((r = 0.65, p < 0.001)\). Improvement from levodopa in the Hoehn and Yahr and Schwab and England global
ratings was predictive of a similar improvement from stimulation in the same rating (Hoehn and Yahr \( r = 0.60, p < 0.001 \)) and Schwab and England \( r = 0.79, p < 0.001 \)).

To predict the postoperative improvement from preoperative levodopa response, we performed multiple regression analysis and obtained the following formula after discarding factors with low predictive power.

Predicted postoperative improvement relative to preoperative UPDRS-III off score = 38 – age \( \times 0.36 \) + duration of illness \( \times 0.33 \) + rigidity response to levodopa \( \times 1.3 \) + pull test response to levodopa \( \times 3.9 \) – freezing response to levodopa \( \times 2.4 \)

This was simplified by retaining only the three most powerful factors.

Predicted postoperative improvement relative to preoperative UPDRS-III off score = 34 – age \( \times 0.29 \) + rigidity response to levodopa \( \times 1.3 \) + pull test response to levodopa \( \times 3.8 \)

**Discussion.** We have identified age and preoperative levodopa responsiveness as key predictors of outcome for bilateral STN stimulation for advanced PD; this is consistent with current understanding that young-onset PD patients have a more isolated dopaminergic lesion.\(^7,8\) Although the selection criteria are biased toward younger patients with good levodopa responsiveness, the ranges of age and levodopa responsiveness were great in this study. Multivariate analysis identified levodopa responsiveness of rigidity, pull test performance, and to a lesser extent, illness duration and levodopa responsiveness of gait freezing as additional predictive factors. Rigidity may be a strong predictor based on its influence as the primary symptom guiding optimum lead placement. Other signs, if assessed intraoperatively, might also predict outcome. The pull test may be a strong predictor based on its ability to identify patients with minimal lesions outside the dopaminergic nigrostriatal system.

Bilateral STN DBS can provide major benefit to patients with advanced PD, but given the difficulty, cost, and risk, only those with a clear benefit-to-risk ratio should be considered. Although this study was nonrandomized and nonblinded, its findings should help identify candidates who may receive the greatest benefit and help predict the degree of expected improvement. Future prospective studies should help confirm or clarify these findings.

**Acknowledgment**

The authors thank Dan Byrne, MS, for biostatistical analysis.

**References**

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Neurology 2002;59:932-934
DOI 10.1212/WNL.59.6.932

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