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Clinical Phenotype Predicts Early Staged Bilateral Deep Brain Stimulation in Parkinson's Disease

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Abstract

Object—While many centers place bilateral DBS systems simultaneously, unilateral STN DBS followed by a staged contralateral procedure has emerged as a treatment option for many patients. However little is known about whether the preoperative phenotype predicts when staged placement of a DBS electrode in the opposite subthalamic nucleus will be required. We aimed to determine whether preoperative clinical phenotype predicts early staged placement of a second subthalamic deep brain stimulation (DBS) electrode in patients who undergo unilateral subthalamic DBS for Parkinson's disease (PD).

Methods—Eighty-two consecutive patients with advanced PD underwent unilateral subthalamic DBS contralateral to the most affected hemibody and had at least 2 years of follow-up. Multivariate logistic regression determined preoperative characteristics that predicted staged placement of a second electrode in the opposite subthalamic nucleus. Preoperative measurements included aspects of the Unified Parkinson Disease Rating Scale (UPDRS), motor asymmetry index, and body weight.

Results—At 2 years follow-up, 28 of the 82 patients (34%) had undergone staged placement of a contralateral electrode while the remainder chose to continue with unilateral stimulation. Statistically significant improvements in UPDRS total and part 3 scores were retained at the end of the 2 year follow-up period in both subsets of patients. Multivariate logistic regression showed

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that the most important predictors for early staged placement of a second subthalamic stimulator were low asymmetry index (odds ratio 13.4; 95% confidence interval 2.8, 64.9), high tremor subscore (OR 7.2; CI 1.5, 35.0), and low body weight (OR 5.5; CI 1.4, 22.3).

Conclusions—This single center study provides evidence that elements of the preoperative PD phenotype predict whether patients will require early staged bilateral subthalamic DBS. These data may aid in the management of patients with advanced PD who undergo subthalamic DBS.

Keywords

deep brain stimulation; predictors; Parkinson's disease

Object

Although bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) is superior to best medical therapy for the management of the motor symptoms of advanced Parkinson's disease (PD), it is associated with a higher incidence of serious adverse events ^{7,37}. While bilateral surgery likely provides greater motor benefit than unilateral surgery, the relative merits of these two surgical approaches have been a matter of debate ^{1,28}. The motor symptoms of PD are asymmetric, and a prior study suggests that the electrode contralateral to the more severely affected hemibody is responsible for most of the motor benefit following staged bilateral subthalamic DBS ²⁸. Additionally, a number of studies have shown significant motor and quality of life benefits following unilateral subthalamic DBS for advanced PD at up to 1 year post-operatively ^{1,3,6,11,31,36}, leading authors to conclude that unilateral DBS followed by a staged bilateral procedure (when needed) is a viable option for many patients ^{1,26}.

Advanced PD patients show heterogeneous phenotypes, including relative degrees of motor asymmetry, tremor, gait dysfunction, dyskinesias, and other symptoms ^{14–16,18,20,22,23,25,32–35}. Despite this, little is known about whether specific phenotypes predict the need for staged placement of a contralateral subthalamic electrode ³². Such knowledge could be valuable to patients and clinicians who seek to maximize motor benefit and minimize potential risks associated with the intervention. Additionally, centers implanting either bilateral or unilateral stimulators might alter their surgical plan in selected patients, taking into account specific motor phenotypes in the context of age, cognitive function, speech and swallowing dysfunction, and other comorbidities. We hypothesized that elements of the preoperative phenotype would predict whether staged bilateral subthalamic DBS occurred within 2 years postoperatively in patients with advanced PD.

Methods

Participants

We evaluated 82 consecutive patients with advanced PD who underwent unilateral subthalamic DBS between March 2004 and December 2008 and were followed for at least 2 years. All patients received unilateral subthalamic DBS contralateral to the most severely affected hemibody and had the option to electively undergo contralateral surgery later if and

when clinically warranted. No patients during that time period underwent initial bilateral subthalamic DBS or pallidal DBS.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Institutional Review Board (IRB) of the University of Alabama at Birmingham. The IRB approved a waiver of consent for collection of these data as part of routine clinical care and quality control.

Surgical Procedure

Electrodes (Model 3387; Medtronic, Minneapolis, MN) were implanted under local anesthesia, guided by magnetic resonance imaging (MRI) frame-based stereotaxy and microelectrode recordings, and all surgical procedures were performed by the same neurosurgeon (BLG). In all cases, post-operative MRI was performed within 24 hours of surgery to verify lead placement and assess for potential surgical complications. Further details of the surgical procedure have been described elsewhere⁴. No formal criteria were established *a priori* for when or whether patients underwent staged placement of the contralateral subthalamic DBS. Rather, the decision to proceed with the second surgery was determined by a real-world clinical risk/benefit assessment based upon patient preference in combination with advice of the treating clinicians. Considerations for the decision included overall quality of life, residual or progressive disability due to motor symptoms, and non-motor symptoms. At the end of the 2 year observation period, we recorded whether or not subjects had undergone staged bilateral subthalamic DBS.

Clinical Outcome Assessment

The Unified Parkinson's Disease Rating Scale (UPDRS) is the standard clinical metric for pre- and post-operative assessment of PD patients⁹. We prospectively measured and recorded preoperative motor function and other baseline characteristics in consecutive patients in a database (Table 1). Tremor subscore was the sum of 'on' medication and 'practically defined off' medication tremor items on UPDRS Parts 2 and 3 (questions 16, 20, and 21). Dyskinesia subscore was the sum of the three dyskinesia items in UPDRS Part 4 (questions 32–34). Asymmetry index was calculated as the absolute difference between the total of the items corresponding to each side of the body divided by the sum of the items for both sides ($(L-R)/(L+R)$)²². Patients in this clinical series had reassessment of total UPDRS scores postoperatively at 3, 6, and 12 months and every 6 months thereafter, as described in our prior report of clinical outcomes of unilateral subthalamic DBS at 12 months follow-up³⁶.

Statistical Analysis

Multivariate logistic regression determined the relationship between the following preoperative predictor variables: UPDRS total score, UPDRS Part 3 "off" total, UPDRS asymmetry index, UPDRS tremor subscore, UPDRS dyskinesia subscore, weight, gender, initial surgery side, and the dichotomous outcome variable of whether staged bilateral subthalamic DBS occurred within 24 months of the initial electrode placement. Cutoff points for the multivariate logistic regression on predictor variables were determined by the

sample mean when normally distributed (UPDRS total, UPDRS part 3 ‘off,’ UPDRS asymmetry index, and body weight) and by empiric clinical criteria (i.e., presence or absence of the trait) when a normal distribution was not present (for the tremor and dyskinesia subscores). Additionally, non-parametric analyses were performed to compare the preoperative UPDRS total score, UPDRS parts 1, 2, 3, and 4, UPDRS tremor subscore, UPDRS dyskinesia subscore, UPDRS asymmetry index, weight, age, and gender between the patients who remained with unilateral stimulation versus those who underwent staged bilateral surgery within two years of the initial procedure.

Results

At 2 years postoperatively, 34% (N = 28) of the patients had undergone staged bilateral subthalamic DBS. Table 1 shows the demographic data for the total sample of patients as well as the non-parametric analyses comparing baseline variables in subjects receiving unilateral or staged bilateral subthalamic DBS within 2 years of follow-up. Adverse events for the total sample of patients is shown in Table 2. Combining the 28 patients who had staged bilateral surgery and the 54 who had unilateral surgery yields a total of 110 subthalamic DBS placements in 82 patients. There were 13 total surgical complications for a rate of 11.8% for the whole study sample. Of the 13 complications, 10 occurred after the first side was placed ($10/82 = 12.2\%$), and 3 occurred after the second side was placed ($3/28 = 10.7\%$). The preoperative phenotypes that were most statistically different between the groups were the asymmetry index (0.5 and 0.3, respectively, $p = 0.0047$) and body weight (86.0 and 72.2 kg, respectively, $p = 0.0076$).

Multivariate logistic regression yielded odds ratios (OR) with 95% confidence intervals for predicting whether staged bilateral subthalamic DBS occurred within two years. The preoperative characteristics most predictive of staged bilateral subthalamic DBS within 2 years of the first surgery were asymmetry index 0.4 (OR 13.4; CI 2.8, 64.9), tremor subscore 8 (OR 7.2; CI 1.5, 35.0), and body weight 80 kilograms (OR 5.5; CI 1.4, 22.3, see Figure 1A). UPDRS total score, UPDRS Part 3 “off,” initial surgery side, gender, and dyskinesia subscore were not significantly predictive of undergoing the staged surgery within 2 years of the initial unilateral procedure. Histograms for each of the potential predictive factors are provided in Figure 1B. Both the unilateral and staged bilateral subthalamic DBS patients showed statistically significant improvements in UPDRS scores at 2 years follow-up (Table 3).

Discussion

Heterogenous phenotypes drive patients with advanced PD toward invasive therapies such as DBS. This single center observational study of 82 consecutive patients who underwent unilateral subthalamic DBS suggests that motor symmetry, high tremor subscore, and low body weight were most predictive of early staged placement of a contralateral subthalamic electrode. Symmetric bilateral motor symptoms were the strongest single predictor for early staged contralateral surgery, indicating conversely that highly asymmetric patients were more likely to remain with unilateral stimulation at 2 years follow-up. This is the most straightforward of our findings as it stands to reason that symmetric symptoms would be

more likely to require bilateral surgery. This finding also agrees with a prior study that pooled results in PD patients who were randomized to either unilateral globus pallidus interna or subthalamic DBS³². Additionally, we show that patients with a high degree of tremor underwent the staged contralateral surgery sooner. This likely reflects the highly visible nature of tremor in some patients and its tendency to be refractory to dopaminergic medications^{8,21}. Though we did not use the independent scale developed by Schiess et al²⁹ to classify patients as being of the tremor-predominant subtype, this scale was derived from UPDRS part 3 much like our method. The clinical relevance of tremor as a predictor is highlighted by the recent research demonstrating that patients with tremor predominant PD have a distinct subtype of PD from those with predominantly postural instability and gait disorder (PIGD) and less tremor^{12,27,30}. Finally, low body weight at the time of the initial surgery was also one of the significant predictors for early staged bilateral subthalamic DBS. This is perhaps the least intuitive of the three predictors, though perhaps there is a correlation between symmetric PD symptoms, and/or high degree of tremor, and weight loss. Regardless of its underlying cause, the clinical importance of low weight as a predictor is supported by the finding that unintended weight loss is a common manifestation of many neurodegenerative diseases⁵. Additionally, we and others have described progressive weight loss associated with PD and weight gain after subthalamic DBS^{14,15,18,20,25,33–35}.

Factors less predictive of early staged bilateral subthalamic DBS warrant further discussion as well. Interestingly, UPDRS total score and UPDRS part 3 “off” scores were not significant predictors for the early staged surgery, arguing that asymmetry and tremor predominance are specific aspects of the motor phenotype that are most strongly associated with early bilateral surgery. Furthermore, severe dyskinesias associated with levodopa frequently necessitate DBS therapy, and in contrast to our findings for tremor, markedly dyskinetic patients did not seek early bilateral surgery and in fact trended towards remaining with unilateral stimulation over the study period. We were somewhat surprised by this finding, particularly considering that expert opinion in the field has generally held that highly dyskinetic patients will require bilateral subthalamic DBS immediately^{16,23}. Importantly, the observed improvement in motor fluctuations and dyskinesias at 2 years follow-up measured by the UPDRS Part 4 argues that patients remained with unilateral stimulation because their dyskinesias were improved by unilateral stimulation. Consistent with this interpretation, prior studies have shown significant improvement in motor fluctuations and activities of daily living following unilateral subthalamic DBS at up to 1 year postoperatively^{6,11,19,24,36}. In another study, subjects reported by questionnaire that they had elected to remain with unilateral stimulation because of symptomatic improvement³². Other aspects of the preoperative phenotype, such as gender and initial side of surgery, were not predictive of early staged surgery, further suggesting that the factors that were significant predictors were not observed by chance alone.

Interestingly, only 38% of these patients elected to have the staged bilateral procedure over the 2 years following their initial surgery. Our finding of significant motor improvement in patients who underwent both unilateral and bilateral subthalamic DBS for PD suggests that many patients with advanced PD retain significant motor improvement following unilateral STN DBS at up to 2 years postoperatively. Considering that motor symptoms of PD are typically asymmetric, responsive to dopaminergic medications, and mildly improved in the

arm ipsilateral to the subthalamic DBS electrode^{11,31}, our current findings suggest that a subset of PD patients who undergo unilateral subthalamic DBS will have sustained improvement in symptoms for years following unilateral surgery. Although prospective, randomized studies comparing unilateral and bilateral stimulation evaluating motor outcomes and potential adverse events are needed, there are several studies suggesting that bilateral subthalamic DBS is associated with decreased verbal fluency and speech dysfunction^{2,10,13}. Additionally, although it has not been studied, it is reasonable to expect shorter surgery times, lower cost, and fewer perioperative complications with placement of one rather than two DBS electrodes, at least with respect to the initial lead placement¹⁷.

This observational study has several strengths and some potential limitations. Selection bias is minimized because this was a consecutive series of patients who underwent unilateral DBS at a single stereotactic target contralateral to the most severely affected hemibody. No patients were offered bilateral DBS or unilateral DBS at another target during the observational period. Additionally, careful characterization allowed detailed analyses of the motor phenotype and assessment of outcomes at 2 years follow-up. Although there were no rigid criteria for when to pursue the second surgery, this is a potential strength of the study in that the decision reflected a real-world clinical decision made by individual patients with the advice of caregivers, based on the multi-faceted aspects of their disease. Though we anticipate that many or most of these patients will eventually require the staged surgery because of the progressive nature of the disease, our data still provide valuable information about the two year postoperative interval. Though our data do not address whether staged surgery will be needed over longer time intervals, they do suggest that many patients derive significant clinical benefit for years after the initial intervention, as manifested by the significant improvements in the global UPDRS, but specifically in the UPDRS part 4 (motor complications). These data in particular argue that significant benefit in dyskinesias and fluctuations is achieved with unilateral stimulation in many patients. These are among the most common clinical symptoms that drive patients to this more invasive therapy. However, since we did not perform a questionnaire asking patients why they did or did not pursue the staged surgery, it does leave open the possibility that some patients chose not to proceed with the staged surgery because of their knowledge and experience with the first surgery. Though the sustained clinical benefit at 2 years in the patients who remained with unilateral DBS argues somewhat against this, follow-up studies would be strengthened by the presence of a questionnaire asking the reasons for pursuing or not pursuing a staged surgery.

Despite the relatively large sample of patients, we cannot exclude the possibility that some of the potential predictors (i.e., UPDRS total and UPDRS part 3 “off”) might reach statistical significance with a larger sample of patients. Indeed, the most extreme total UPDRS scores reflect a trend towards bilateral surgery (Figure 1B). Although it is possible that non-motor features including cognitive decline associated with advanced PD or psychiatric symptoms might also influence whether some patients elected to have the second surgery, the significant predictive factors were still observed despite these potential confounds. The extent to which these and other non-motor aspects of the disease alter clinical decision making in the perioperative period should be addressed more specifically in future studies. Although it is reasonable to suspect fewer perioperative complications from unilateral versus bilateral surgery, our data do not address this issue directly. There are

likely distinct adverse event profiles associated with unilateral electrode placement followed by staged surgery when needed; unilateral followed immediately by a staged procedure; and bilateral simultaneous lead placement in a single initial procedure. The adverse event rates between the first and second surgeries were similar, but the total number of adverse events in our sample is too small to make an adequate comparison between the unilateral and staged bilateral groups. Finally, patient evaluations were not blinded, which might lead to placebo effects or to sources of bias from the rater or the patient when outcome is assessed. Regardless, the observed predictors for early staged subthalamic DBS reflect an important clinical outcome derived from real world clinical decision-making in patients with advanced PD.

In summary, our findings suggest that PD patients with certain preoperative clinical features, including highly symmetric motor symptoms, tremor predominance, and/or low body weight are more likely to require staged contralateral subthalamic DBS surgery sooner than patients without those clinical features. The motor symptoms of PD are typically asymmetric and levodopa-responsive, and we demonstrate that many patients derive significant and enduring improvement in motor function from unilateral subthalamic DBS. Unilateral subthalamic DBS followed by staged placement of a contralateral stimulator (when needed) is a reasonable treatment plan for many patients with PD, particularly those with prominent asymmetry or comorbidities that might increase the risk associated with bilateral surgery. These results may provide useful information for patients and caregivers who are planning to undergo this intervention that can dramatically alter quality of life.

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Figure 1.

Odds Ratios Predicting Likelihood of Having Staged Bilateral DBS Within 24 Months

(A) Logistic regression analyses of preoperative predictors for staged bilateral subthalamic DBS within 2 years of the initial unilateral procedure. (B) Histograms of the preoperative phenotypes, organized by unilateral or bilateral subthalamic DBS at 2 years follow-up.

Table 1

Non-parametric analysis comparing baseline variables in patients receiving unilateral or staged bilateral STN DBS

Variable	All Subjects at Baseline	Unilateral STN DBS		Staged Bilateral STN DBS		p-value
		Mean ± SD	N	Mean ± SD	N	
Age at First Surgery	59.9 ± 9.8	51	60.2 ± 9.5	28	59.3 ± 10.4	0.8421
Weight (kg)	81.5 ± 19.9	48	86.0 ± 18.6	23	72.2 ± 18.8	0.0076*
Total UPDRS	71.3 ± 15.5	53	69.0 ± 14.4	27	75.9 ± 16.7	0.0883
UPDRS Part 1	2.6 ± 1.8	54	2.6 ± 1.6	27	2.7 ± 2.2	0.9273
UPDRS Part 2 'off'	24.3 ± 6.1	54	23.7 ± 5.8	27	25.6 ± 6.6	0.1940
UPDRS Part 2 'on'	8.8 ± 5.1	53	8.6 ± 4.9	27	9.3 ± 5.5	0.5833
UPDRS Part 3 'off'	36.6 ± 10.8	54	34.8 ± 9.8	28	40.0 ± 11.8	0.0645
UPDRS Part 3 'on'	12.7 ± 7.5	53	12.4 ± 6.9	28	13.3 ± 8.5	0.8312
UPDRS Part 4	8.2 ± 2.5	53	8.2 ± 2.5	27	8.2 ± 2.6	0.9632
Tremor Subscore	6.8 ± 6.2	53	5.9 ± 4.9	27	7.4 ± 5.1	0.1770
Dyskinesia Subscore	2.4 ± 2.0	53	2.6 ± 2.1	27	2.0 ± 1.7	0.3420
Asymmetry index	0.4 ± 0.2	53	0.5 ± 0.2	28	0.3 ± 0.2	0.0047*

Table 2

Surgical Adverse Events for First STN DBS Surgery (All Subjects) and Second STN DBS Surgery (Staged Bilateral Subjects Only)

Type of Adverse Event	After first side STN DBS (N=110)	After second side STN DBS (N=28)	Total
Implanted Pulse Generator (IPG) infection	1	1	2
Lead adjustment for scalp erosion	3	0	3
Lead infection	2	1	3
Lead reposition	2	0	2
Lead malfunction	1	1	2
Subdural hematoma	1	0	1
Total	10	3	13

Table 3

Motor Outcomes for Unilateral and Bilateral STN DBS Patients

	Baseline (X$\pm$SD)	24 Month (X$\pm$SD)	p-value
Bilateral (N =28)			
Total UPDRS	75.9 $\pm$ 16.7	61.5 $\pm$ 12.9	0.0007*
Part 1	2.7 $\pm$ 2.2	2.9 $\pm$ 2.3	0.9098
Part 2 OFF	25.6 $\pm$ 6.6	17.2 $\pm$ 3.8	0.0076*
Part 2 ON	9.3 $\pm$ 5.5	9.2 $\pm$ 3.0	0.9645
Part 3 OFF	40.0 $\pm$ 11.8	24.2 $\pm$ 9.8	0.0086*
Part 3 ON	13.3 $\pm$ 8.5	13.7 $\pm$ 8.3	0.5196
Part 4	8.2 $\pm$ 2.6	3.5 $\pm$ 1.7	<0.0001*
Unilateral (N =54)			
Total UPDRS	69.0 $\pm$ 14.4	56.8 $\pm$ 15.5	0.0004*
Part 1	2.6 $\pm$ 1.6	3.3 $\pm$ 2.3	0.4489
Part 2 OFF	23.7 $\pm$ 5.8	20.0 $\pm$ 6.7	0.0325*
Part 2 ON	8.6 $\pm$ 4.9	9.4 $\pm$ 6.4	0.1787
Part 3 OFF	34.8 $\pm$ 9.8	24.4 $\pm$ 8.9	0.0104*
Part 3 ON	12.4 $\pm$ 6.9	12.4 $\pm$ 6.9	0.1250
Part 4	8.2 $\pm$ 2.5	3.8 $\pm$ 1.4	<0.0001*