

Predictive Factors of Antiparkinsonian Drug Reduction after Subthalamic Stimulation for Parkinson's Disease

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Abstract

Subthalamic nucleus deep brain stimulation (STN-DBS) improves motor symptoms in individuals with advanced Parkinson's disease (PD) and enables physicians to reduce doses of antiparkinsonian drugs. We investigated possible predictive factors for the successful reduction of antiparkinsonian drug dosage after STN-DBS. We evaluated 33 PD patients who underwent bilateral STN-DBS. We assessed rates of reduction of the levodopa-equivalent daily dose (LEDD) and levodopa daily dose (LDD) by comparing drug doses before vs. 6-months post-surgery. We used correlation coefficients to measure the strength of the relationships between LEDD and LDD reduction rates and preoperative factors including age, disease duration, preoperative LEDD and LDD, unified Parkinson's Disease Rating Scale part-II and -III, levodopa response rate, Mini-Mental State Examination score, dyskinesia score, Hamilton Rating Scale for depression, and the number of non-motor symptoms. The average LEDD and LDD reduction rates were 61.0% and 70.4%, respectively. Of the variables assessed, only the number of psychiatric/cognitive symptoms was significantly correlated with the LEDD reduction rate. No other preoperative factors were correlated with the LEDD or LDD reduction rate. A wide range of preoperative psychiatric and cognitive symptoms may predict the successful reduction of antiparkinsonian drugs after STN-DBS.

Key words: subthalamic nucleus, deep brain stimulation, antiparkinsonian drug, non-motor symptom, Parkinson's disease

Introduction

Globus pallidus internus deep brain stimulation (GPi-DBS) and subthalamic nucleus deep brain stimulation (STN-DBS) have been established as effective surgical treatments for motor fluctuations in individuals with advanced Parkinson's disease (PD).^{1–4} STN-DBS dramatically alleviates cardinal motor symptoms and reduces “wearing-off” and dyskinesia.^{5–7} Unlike GPi-DBS, STN-DBS enables further reduction of antiparkinsonian drugs after surgery.^{8–10}

This reduction in drug dosage plays a major role in ameliorating dyskinesia.⁹ DBS therapy can replace part of the levodopa action during “on-time”.¹¹

Globus pallidus internus deep brain stimulation has a direct antidyskinetic effect that is independent of reductions in antiparkinsonian drug dosage. In contrast, STN-DBS allows the reduction of antiparkinsonian drug dose with no adverse effects on motor function, although it may exacerbate dyskinesia. Amelioration of dyskinesia following STN-DBS is dependent on the reduction of antiparkinsonian drug dosage.¹² Long-term administration of high-dose antiparkinsonian drugs can cause various neuropsychiatric side effects.^{13–15} Therefore, another important objective of STN-DBS, in addition to alleviating motor symptoms during “off-times,” is the reduction

Received February 21, 2019; Accepted May 7, 2019

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of antiparkinsonian drug dosage. In this study, we investigated the preoperative factors that enable successful reduction of antiparkinsonian drug dose after STN-DBS by comparing them in terms of the rate of drug reduction.

Materials and Methods

We included 33 consecutive patients with advanced idiopathic PD (16 men and 17 women) who underwent bilateral STN-DBS at Kaizuka Hospital between August 2010 and July 2012. All patients were assessed before and after surgery, and gave written informed consent for the collection and publication of their data. All experimental procedures were approved by the Ethics Committee of the hospital. We evaluated all patients by comparing the rate of reduction of the levodopa-equivalent daily dose (LEDD) and levodopa daily dose (LDD) before and 6 months after surgery. After surgery, patients temporarily continued to take the preoperative dosages of their antiparkinsonian drugs. These dosages were then reduced while the DBS parameters were repeatedly adjusted with the goal of identifying a combination of dose and stimulation parameters that provided the greatest improvement in motor function with the fewest side effects. The medication dosage had stabilized after 6 months in most patients, so this was chosen as the post-surgery evaluation point. The LEDD was calculated according to the conversion formula proposed by Tomlinson et al.¹⁶⁾ Patients completed the unified Parkinson's Disease Rating Scale (UPDRS) with the activity of daily living score (UPDRS part-II) and motor score (UPDRS part-III). The preoperative factors were age, disease duration, preoperative LEDD and LDD, UPDRS part-II and -III, levodopa response rate (UPDRS part-II and -III), Mini-Mental State Examination (MMSE) score, number of non-motor symptoms (NMSs), Hamilton Rating Scale for Depression (HAM-D) score, and dyskinesia score. We multiplied the scores for items 32 (duration) and 33 (disability) from the UPDRS part-IV to obtain a total dyskinesia score. We used correlation coefficients and regression analysis to measure the strengths of the relationships between LEDD or LDD reduction rates and the preoperative factors. *P*-values <0.05 were considered significant. We interpreted the size of correlation coefficients as follows: $0.0 \leq |r| < 0.2$: very weak correlation; $0.2 \leq |r| < 0.4$: weak correlation; $0.4 \leq |r| < 0.7$: moderately strong correlation; and $0.7 \leq |r| \leq 1.0$: strong correlation. Data analysis was performed using SPSS version 21.0.J (IBM Corp., Armonk, NY, USA). As per Witjas et al.,¹⁷⁾ we administered an online questionnaire that asked the patients about 54 NMSs in three categories (26 dysautonomic, 21 psychiatric/cognitive, and seven

sensory symptoms). We attempted to include as many NMSs as possible. We made some modifications to adapt the questionnaire to the Japanese language. In consideration of patient comfort, the questionnaire was completed during "on-time" (on-drug condition preoperatively, and on-stimulation and on-drug conditions at 6–12 months after surgery). Initial postoperative DBS programming was performed using unipolar stimulation in all patients. The stimulation parameters were re-evaluated and adjusted as required during hospital visits. When we observed symptoms such as dysarthria or tetanic muscle contraction that appeared to be caused by current diffusion into neighboring fibers or nuclei, bipolar stimulation was introduced to focus the current.

Results

The mean age of the patients was 62.6 years and the mean age at disease onset was 50.7 years. The mean disease duration was 11.9 years. After surgery, we found significant improvements in UPDRS part-II scores during "off-time" ($P < 0.01$), and a significant reduction in LEDD ($P < 0.01$) and LDD ($P < 0.01$). There were insufficient data to analyze the postoperative UPDRS part-III, HAM-D, and dyskinesia scores. The average reduction rates of LEDD and LDD were 61.0% and 70.4% respectively. Table 1 summarizes the patient profiles and

Table 1 Summary of patient profiles and surgical outcomes after STN-DBS

Male:Female	16:17		
Age (years)	62.6 ± 10.9		
Disease onset (years)	50.7 ± 11.5		
Disease duration (years)	11.9 ± 7.2		
Characteristics	Preope	Postope	<i>P</i> -value
UPDRS part-II (on)	6.1 ± 5.7	4.2 ± 4.3	0.14
UPDRS part-II (off)	19.2 ± 7.1	8.7 ± 6.4	<0.01
UPDRS part-III (on)	13.5 ± 8.9	NR	NR
UPDRS part-III (off)	30.0 ± 11.7	NR	NR
LEDD (mg/day)	803.8 ± 254.2	313.6 ± 236.8	<0.01
LDD (mg/day)	513.6 ± 194.9	151.5 ± 116.2	<0.01
MMSE	26.6 ± 3.1	27.3 ± 2.9	0.34
HAM-D	7.7 ± 4.0	NR	NR
Dyskinesia score	2.2 ± 2.9	NR	NR

HAM-D: Hamilton Rating Scale for depression, LDD: levodopa daily dose, LEDD: levodopa-equivalent daily dose, MMSE: Mini-Mental State Examination, NR: not rated, UPDRS: Unified Parkinson's Disease Rating Scale.

Table 2 Correlation coefficients and *P*-values for regression analysis between preoperative factors and reduction rates of LEDD and LDD

	Preoperative value	Reduction rate of LEDD		Reduction rate of LDD	
	Average \pm SD	<i>R</i>	<i>P</i> -value	<i>R</i>	<i>P</i> -value
Age	62.6 \pm 10.9	-0.057	0.753	-0.070	0.698
Disease duration	11.9 \pm 7.2	-0.261	0.142	-0.310	0.079
UPDRS part-II	19.2 \pm 7.1	-0.197	0.271	-0.043	0.811
UPDRS part-III	30.0 \pm 11.7	0.043	0.811	0.182	0.312
Preoperative LDD	513.6 \pm 195.0	0.084	0.643	0.224	0.210
Preoperative LEDD	803.8 \pm 254.2	0.034	0.852	0.154	0.393
Levodopa response rate of UPDRS part-II	69.5 \pm 23.4	0.095	0.600	0.057	0.753
Levodopa response rate of UPDRS part-III	52.0 \pm 26.7	0.192	0.284	0.013	0.944
MMSE	26.6 \pm 4.1	-0.133	0.459	-0.128	0.478
No. of dysautonomic symptoms	9.9 \pm 4.0	0.248	0.164	0.023	0.897
No. of psychiatric/cognitive symptoms	6.8 \pm 4.5	0.346	0.049*	0.225	0.208
No. of sensory symptoms	1.9 \pm 1.5	0.120	0.504	0.099	0.583
HAM-D	7.7 \pm 4.0	0.270	0.180	0.100	0.620
Dyskinesia score	2.2 \pm 2.9	-0.120	0.560	-0.010	0.980

**P* < 0.05. HAM-D: Hamilton Rating Scale for Depression, LDD: levodopa daily dose, LEDD: levodopa-equivalent daily dose, MMSE: Mini-Mental State Examination, *R*: correlation coefficient, UPDRS: Unified Parkinson's Disease Rating Scale.

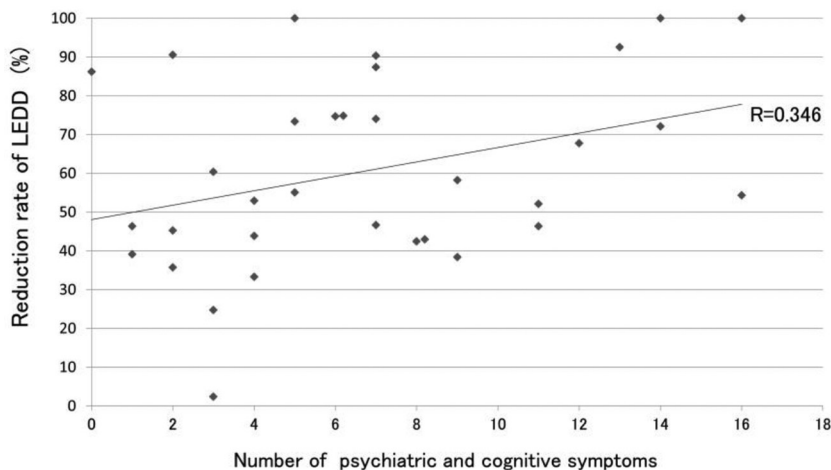


Fig. 1 Scatter plot showing a significant correlation between levodopa-equivalent daily dose (LEDD) reduction rate and number of psychiatric/cognitive symptoms. *R*: correlation coefficient.

surgical outcomes. Table 2 shows the correlation coefficients and *P*-values for the regression analysis comparing the rate of LEDD or LDD reduction and preoperative factors. Only the number of psychiatric/cognitive symptoms significantly correlated with the LEDD reduction rate (*P* = 0.049) (Fig. 1). Age, preoperative LDD and LEDD, UPDRS part-II and -III scores, the levodopa response rate as measured by the UPDRS part-II and -III, MMSE scores, and dyskinesia scores were not correlated with LEDD or LDD reduction rates. We have

omitted the postoperative data for these variables in Table 2 because the purpose of this study was to detect preoperative factors that could predict successful reductions in drug dosage. Disease duration, preoperative LDD, and the number of psychiatric/cognitive symptoms showed weak, non-significant correlations with the reduction rate of LDD. Further, disease duration, the number of dysautonomic symptoms, and HAM-D scores showed weak, non-significant correlations with the reduction rate of LEDD.

Discussion

Subthalamic nucleus deep brain stimulation can ameliorate dyskinesia, enable reduced doses of dopaminergic medication, and increase “on-time” in PD patients.^{5–7} A meta-analysis by Kleiner-Fisman et al.¹⁸ that was based on a review of 37 cohorts of patients quantified a 55.9% reduction in the average LEDD following surgery. Merola et al.¹⁹ examined long-term outcomes in STN-DBS patients. They reported that the average LEDD decreased from 1120 to 510 mg (54%) following surgery, while Ortega-Cubero et al.²⁰ showed a 59.6% reduction. According to Zibetti et al.,²¹ antiparkinsonian therapy was reduced and simplified after STN-DBS in 67 patients. Further, more patients were able to transit to either levodopa or dopamine agonist monotherapy, and fewer patients relied on a combination of both, with an average LEDD reduction rate of approximately 60% at 1 and 3 years after surgery. The average LEDD reduction rate in our study was 61.0%, which is similar to that reported in previous studies. We compared preoperative LEDD and LDD with those 6 months after surgery because the patients had reached a stable state by this time point.

The impact of decreasing doses of antiparkinsonian drugs after STN-DBS on postoperative psychiatric/cognitive decline is controversial.^{22–27} In general, doses of antiparkinsonian drugs can be reduced following STN-DBS with no adverse effects on motor function, although dyskinesia may be exacerbated. The reduction of dyskinesia following STN-DBS is mainly dependent on the reduction of antiparkinsonian drugs.¹² With regards to the relationships among preoperative drugs, disease duration, and psychiatric/cognitive symptoms, Williams et al.²⁸ indicated that STN-DBS patients (who were slightly younger, had a longer disease duration, and were taking more levodopa at baseline compared with the PD sample) may be at increased risk of cognitive decline. Dafsari et al.²⁹ showed no correlation between postoperative LEDD reduction and improvement in NMSs such as altered perception and hallucinations, although STN-DBS might improve hallucinations in PD patients.^{15,29,30} In contrast, a meta-analysis by Stowe et al.³¹ found that improvements in a range of NMSs (including hallucinations, cardiovascular, gastrointestinal, and sleep and fatigue symptoms) were associated with LEDD reduction. Most of these studies assumed the “cause and effect” hypothesis that drug reduction ameliorates NMSs; however, these two factors may both be induced by STN-DBS. A search in PubMed in 2018 revealed no additional studies that investigated factors that could predict the successful reduction of antiparkinsonian drugs after STN-DBS.

There are several possible explanations for our finding that only the number of psychiatric/cognitive symptoms was correlated with the LEDD reduction rate. The preoperative number of psychiatric/cognitive symptoms was not correlated with preoperative LEDD, but was inversely correlated with postoperative LEDD. This may be explained by the finding that patients with more psychiatric/cognitive symptoms preoperatively showed a greater LEDD (or dopaminergic agonist dose) reduction postoperatively. Moreover, lower doses of postoperative antiparkinsonian drugs, but not higher doses of preoperative drugs, are associated with high LEDD reduction rates. It is possible that prior to surgery, PD patients with many psychiatric/cognitive symptoms take higher doses of antiparkinsonian drugs than those required to effectively manage their motor symptoms, such that the doses are reduced to an optimal level after STN-DBS. Thus, our findings may indicate that patients with more preoperative psychiatric symptoms are more likely to have a greater postoperative reduction in LEDD.

The anti-dyskinetic effect of DBS occurs through a reduction in dopaminergic medication and also by direct dyskinesia suppression.³² GPi-DBS has a strong direct dyskinesia suppression effect, even in the absence of a significant change in drug dosage.³³ Katayama et al.³⁴ showed that stimulation in the area above the STN caused effects similar to thalamic or pallidal DBS and inhibited peak-dose dyskinesia. Because STN-DBS suppresses dyskinesia mostly through the subsequent reduction of antiparkinsonian drugs, it is important to determine whether preoperative dyskinesia severity can predict the degree to which antiparkinsonian drug dosages can be reduced postoperatively. However, in our study, we found that dyskinesia scores were not correlated with LEDD or LDD reduction rates. Therefore, we assume that the direct dyskinesia suppression effect of STN-DBS may have affected these correlation results.

We cannot be fully confident that the preoperative number of psychiatric/cognitive symptoms can predict antiparkinsonian drug reduction because the *P*-value was close to 0.05 (*P* = 0.049). Further studies with larger patient samples are needed to produce clearer results. At present, we cannot predict the degree to which antiparkinsonian drugs can be reduced following successful STN-DBS in individual patients. However, such information would be useful for patients who are considering surgical interventions and may choose to undergo STN-DBS to reduce the dosage of antiparkinsonian drugs. Thus, further investigation is needed.

Levodopa-equivalent daily dose reduction mainly serves to minimize levodopa-induced motor (and

occasionally non-motor) fluctuations. However, it may not be easy to reduce doses of antiparkinsonian drugs in individual patients if they have psychological symptoms. Levodopa may be preferentially reduced in individuals with dopamine dysregulation syndrome. However, in patients with hallucinations, care must be taken when reducing dopamine agonists to avoid dopamine agonist withdrawal syndrome. Levodopa doses may be maintained if the reduction of dopamine agonist doses cannot be compensated by DBS because of fatigue, anhedonia, or loss of activity. In cases where DBS cannot replace levodopa treatment, the additional use of long-acting dopamine agonists is an important consideration. The titration of medical treatment for post-DBS patients requires knowledge and skills in the fields of pharmacology, physiology, and neuroanatomy, and there are considerable cross-regional differences in the roles that neurologists play in DBS management. In this study, optimal medical treatment for post-DBS patients was provided by specialists (YM) skilled in both medical therapy and surgical intervention, instead of by general neurologists in our center. Indeed, the types of healthcare professionals caring for DBS patients (for instance, neurologists vs. neurosurgeons) may modulate the patient outcome. This may be a topic for future research.

Conclusion

Preoperative factors such as age, disease duration, preoperative LDD and LEDD, UPDRS part-II and -III scores, levodopa response rate (UPDRS part-II and -III), MMSE score, number of NMSs (except psychiatric/cognitive symptoms), HAM-D score, and dyskinesia severity do not appear to predict changes in antiparkinsonian drug dosage after STN-DBS. Patients with a wide range of preoperative psychiatric/cognitive symptoms are more likely to experience successful reduction in antiparkinsonian drug dosage after STN-DBS.

Acknowledgments

We thank Rachel Baron, PhD, and Sydney Koke, MFA, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Conflicts of Interest Disclosure

All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

No work resembling the enclosed article has been published or is being submitted for publication elsewhere.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sector.

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