

# Predictive Factors for Long-term Outcome of Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease

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## Abstract

Despite the recognition of the usefulness of subthalamic nucleus deep brain stimulation (STN-DBS) for the treatment of Parkinson's disease (PD), preoperative predictive factors for the long-term outcome of STN-DBS are not sufficiently established. We performed this study to determine such predictive factors. The subjects were 66 patients who were classified into two groups on the basis of their activities of daily living (ADL) evaluated five years after the STN-DBS surgery: 33 patients were assigned to the independent ADL group (group I) and the remaining 33 patients to the dependent ADL group (group D). Group I patients showed a Schwab and England (S&E) scale score of more than 70 during the off-period, indicating that these patients can maintain their independent ADL all the time. Group D patients showed a score of 70 or lower during the off-period, indicating that these patients cannot maintain their independent ADL for an entire day. We studied the differences in the preoperative state between these two groups. Statistically significant differences were noted in PD onset age, age at surgery, preoperative unified Parkinson's disease rating scale (UPDRS) part I score, part II score, total subscore for axial symptoms in part III, mini-mental state examination (MMSE) score and S&E score. Multiple logistic regression analysis showed that the significant independent variables related to long-term independent ADL were the age at surgery, MMSE score and preoperative S&E scale score during the off-period. The PD onset age, age at surgery, preoperative high-level ADL, cognitive function, and axial symptoms are important predictive factors for the long-term outcome of STN-DBS.

Key words: predictive factor, deep brain stimulation, subthalamic nucleus, Parkinson's disease, onset age

## Introduction

Subthalamic nucleus deep brain stimulation (STN-DBS) is one of the important treatment choices for Parkinson's disease (PD). More than 20 years have passed since the first use of STN-DBS for the treatment of PD; since then, recent studies have disclosed its usefulness not only in the short term but also in the long term after the surgery.<sup>1–3)</sup> On the other hand, it is also evident that there are some patients who did not sufficiently benefit from STN-DBS in the long term. Axial motor symptoms and cognitive decline may occur in the long term after the surgery and highly affect the long-term outcome.<sup>1)</sup> A positive relationship of L-dopa responsivity with the short-term outcome of STN-DBS was reported.<sup>4)</sup> However, it was also reported that such a relationship was not applicable to the long-term outcome of STN-DBS.<sup>5)</sup>

Thus, the preoperative clinical historical factors and symptomatic findings related to the long-term outcome are as yet unclarified. We believe that it is important to predict the long-term outcome of STN-DBS preoperatively. The aim of this study was to clarify the preoperative clinical features of PD patients that may predict the beneficial long-term outcome of STN-DBS.

## Patients and Methods

### Subjects

We designed a retrospective, single-center, observational study. The subjects were 66 patients who underwent surgery for electrode implantation for STN-DBS in our institute. The PD symptoms of all the patients were responsive to L-dopa and the patients did not have severe psychiatric symptoms nor cognitive decline preoperatively. These patients satisfied the criteria for operative indication in terms

of cognitive function evaluated by mini-mental state examination (MMSE score: >24p).

The surgery for STN-DBS was performed by the same neurosurgeon using the same procedure for all these patients who were then followed up for more than 5 years after the surgery. These patients underwent the programming of stimulation parameters also in our institute throughout all of their postoperative follow-up period. Their scores of Unified Parkinson's Disease Rating Scale (UPDRS) and other neuropsychological data, including Hamilton depression scale (HDS) and MMSE scores, were collected from the preoperative state to more than five years after the surgery.

### Patient classification

These patients were classified into two groups the basis of their Schwab and England (S&E) scale score at the time of the fifth-year evaluation after the surgery: the group who can maintain their independent activities of daily living (group I) and the group who are dependent on others for their activities of daily living (ADL) (group D). Thirty-three patients were assigned to group I and the remaining 33 patients to group D. The patients in group I showed a S&E scale score of more than 70 when their PD symptoms were most severe, indicating that these patients can maintain their independent ADL for an entire day. In contrast, the patients in group D showed an S&E scale score of 70 or lower when their PD symptoms were most severe, indicating that these patients cannot maintain their independent ADL all day.

### Surgical procedure and stimulation parameters

All the patients underwent bilateral STN-DBS in one stage in our institute. Quadripolar DBS electrodes leads (Activa 3387; Medtronic, Minneapolis, MN) were implanted into the bilateral STN regions under magnetic resonance imaging (MRI) guidance with physiological confirmation using the multitrack microelectrode recording. After the implantation of the DBS device, programming of stimulation parameters was started. The initial parameters were established by monopolar stimulation of the motor component of STN with high-frequency of square wave pulses for a short duration. Constant-voltage stimulation intensity was gradually increased in association with the patient's symptoms that were mainly L-dopa-responsive. We changed from monopolar to bipolar stimulation parameters when stimulation adverse effects appeared.

### Clinical evaluation and statistical analysis

We studied the differences in preoperative clinical background features and medications between groups I and D including onset age, preoperative disease

duration, age at surgery, preoperative levodopa equivalent dose (LED), and L-dopa dose. We also studied the differences in neurological and psychological states including the scores of UPDRS, HDS, MMSE, and S&E scale. These evaluations were performed by a neurologist and a physical therapist who did not belong to our neuromodulation team. Regarding UPDRS part III (motor exam), we studied the differences in total subscores for tremor (items 20 and 21), rigidity (item 22), bradykinesia (items 23–26 and 31) and axial symptoms (items 18, 27–30) between groups I and D.

The statistical package SPSS Statistics was used for data analyses. The Mann-Whitney *U*-test was used for the nonparametric comparison of onset age, preoperative disease duration, age at surgery, and UPDRS, HDS, and MMSE scores between groups D and I. Unpaired Student's *t*-test was used for the parametric comparison of LED and L-dopa dose because of the continuity and normal distribution of these data. Differences were considered significant when the *P*-value was less than 0.05. In addition, multiple logistic regression analysis was carried out when factors were regarded as statistically significant by single regression analysis. On the basis of the results of this analysis, we identified independent predictive variables significantly associated with long-term independent ADL after the surgery for STN-DBS.

### Ethical issues

All the patients provided their written informed consent to undergo the surgery for DBS lead and device implantation. Study approval was obtained from institutional review board of the Nihon University Itabashi Hospital and conformed to the principles outlined in the Declaration of Helsinki.

## Results

There were no serious surgical complications such as intracranial hemorrhage, infection, and device malfunctions. These patients also did not develop serious psychiatric symptoms and cognitive decline except for a brief episode of delirium noted immediately after the surgery.

Table 1 shows the preoperative background characteristics and medications of groups I and D. Statistically significant differences were noted in onset age ( $P = 0.041$ ) and age at surgery ( $P = 0.002$ ). The age at surgery was significantly younger in group I than in group D. There was no significant difference in preoperative disease duration between groups I and D ( $P = 0.24$ ). Preoperative LED and L-dopa dose were not significantly different between groups I and D (LED,  $P = 0.16$ ; L-dopa dose;  $P = 0.37$ ).

Table 2 shows the preoperative UPDRS scores of groups I and D. The total score of UPDRS during the off-period was significantly lower in group I ( $P = 0.035$ ). The UPDRS Part I score was also significantly lower in group I ( $P = 0.016$ ), and the UPDRS part II scores during both the on- and off-periods were significantly lower in group I (on-period,  $P = 0.029$ ; off-period,  $P = 0.005$ ). There were no significant differences in the scores of parts III and IV. Differences in the total subscores for tremor, rigidity, bradykinesia and axial symptoms of UPDRS part III are shown in Table 3. Significant differences were noted in the total subscore for axial symptoms (items 18, 27, 28, 29 and 30) during the off-period ( $P = 0.002$ ).

The preoperative HDS score of group I was not statistically significantly different from that of group D (Table 4). The MMSE score was significantly different between groups I and D ( $P < 0.001$ ) (Table 4). That of group I was significantly higher than that of group D. The S&E scale scores during both the on- and off-periods were significantly higher in group I (on-period,  $P = 0.005$ ; off-period,  $P < 0.001$ ) (Table 4).

The results of multiple logistic regression analysis are summarized in Table 5. The significant independent

**Table 1 Preoperative background characteristics and medications of groups I and D**

	Group I	Group D	<i>P</i> value
Onset age (years)	48.3 ± 8.0	52.2 ± 9.5	0.041*
Disease duration (years)	10.4 ± 4.3	12.3 ± 6.2	0.24
Age at surgery (years)	58.7 ± 6.7	64.5 ± 7.9	0.002*
LED (mg)	606.8 ± 278.5	729.3 ± 345.6	0.16
L-dopa dose (mg)	437.9 ± 212.3	500.3 ± 243.4	0.37

\*Statistically significant. LED: levodopa-equivalent dose.

**Table 2 Preoperative UPDRS scores of groups I and D**

UPDRS		Group I	Group D	<i>P</i> value
Total	on	31.1 ± 13.8	36.8 ± 13.6	0.11
	off	59.5 ± 17.5	69.5 ± 18.7	0.035*
Part I		1.4 ± 1.7	2.3 ± 1.7	0.016*
Part II	on	5.7 ± 5.7	8.5 ± 6.0	0.029*
	off	17.5 ± 7.7	22.8 ± 7.7	0.005*
Part III	on	16.3 ± 10.6	18.4 ± 9.1	0.24
	off	32.8 ± 9.6	36.8 ± 10.7	0.21
Part IV	on	7.8 ± 3.5	7.8 ± 4.1	0.89
	off	7.8 ± 3.6	7.6 ± 4.2	0.77

\*Statistically significant. UPDRS: Unified Parkinson's Disease Rating Scale.

**Table 3 Selected UPDRS III subscores and results of Mann-Whitney *U*-test of difference between groups I and D**

Symptoms and related subscores		Mann-Whitney <i>U</i>	<i>Z</i>	<i>P</i> value
Tremor (items 20 and 21)	on	512.5	-0.477	0.633
	off	510.5	-0.441	0.659
Rigidity (item 22)	on	491.5	-0.686	0.493
	off	471	-0.958	0.338
Bradykinesia (items 23, 24, 25, 26 and 31)	on	404.5	-1.802	0.072
	off	453.5	-1.172	0.241
Axial symptoms (items 18, 27, 28, 29 and 30)	on	417	-1.651	0.099
	off	299	-3.165	0.002*

\*Statistically significant, UPDRS: Unified Parkinson's Disease Rating Scale.

**Table 4 Preoperative HDS, MMSE, and S&E scores of groups I and D**

	Group I	Group D	<i>P</i> value	
HDS	10.0 ± 7.7	12.5 ± 7.8	0.14	
MMSE	28.8 ± 1.9	26.5 ± 3.3	<0.001*	
S&E scale	on	86.7 ± 12.2	77.9 ± 13.6	0.005*
	off	59.4 ± 19.8	39.4 ± 21.1	<0.001*

\*Statistically significant. HDS: Hamilton depression scale, MMSE: mini-mental state examination, S&E: Schwab & England.

variables related to long-term independent ADL were the age at surgery [odds ratio = 1.251 (95% CI: 1.068 – 1.466),  $P = 0.006$ ], MMSE score [odds ratio = 0.755 (95% CI: 0.593 – 0.961),  $P = 0.022$ ] and preoperative S&E score during the off-period [odds ratio = 0.94 (95% CI: 0.899 – 0.983),  $P = 0.007$ ].

## Discussion

It is important to predict the beneficial effects of an interventional therapeutic measure before the procedure. L-dopa responsiveness has been regarded as the established predictive factor for the STN-DBS outcome.<sup>4)</sup> However, it cannot sufficiently predict the long-term outcome of STN-DBS.<sup>5)</sup> Although many studies of the predictive factors for the outcome of STN-DBS have been carried out, almost all of them were a follow-up for a few years.

We studied the differences in clinical characteristics between the patients found to be independent and those found to be dependent five years after the surgery for STN-DBS. The results of our study demonstrated that the patients with younger onset of PD and younger at the time of surgery were

**Table 5** Results of multiple logistic regression analysis

Independent variable	Partial regression coefficient	Significance probability	Odds ratio	95% CI	
				Lower limit	Upper limit
Onset age (year-old)	-0.036	0.578	0.965	0.851	1.094
Age at surgery (year-old)	0.221	0.008	1.247	1.061	1.467
Preoperative UPDRS total off	-0.07	0.203	0.933	0.838	1.038
Preoperative UPDRS part I	0.105	0.672	1.11	0.684	1.804
Preoperative UPDRS part II on	-0.022	0.811	0.978	0.818	1.17
Preoperative UPDRS part II off	0.173	0.128	1.189	0.951	1.485
MMSE	-0.283	0.022	0.754	0.592	0.96
Preoperative S&E on	-0.004	0.894	0.996	0.935	1.06
Preoperative S&E off	-0.061	0.012	0.941	0.898	0.987
Axial Symptoms off	0.029	0.872	1.03	0.721	1.471

CI: confidence interval, S&E: Schwab & England.

expected to have the long-term beneficial outcome of STN-DBS. Preoperatively, better cognitive and motor functions were also significant factors for predicting the beneficial long-term outcome of STN-DBS. Regarding the motor functions, axial symptoms during the off-periods were an important predictive factor. Furthermore, the preoperative S&E scale scores during both the on- and off-periods were significantly higher in the independent patients. Additional multiple logistic regression analysis demonstrated that the age at surgery, MMSE score and preoperative S&E scale score during the off-period were the independent variables significantly related to the 5 year long-term beneficial outcome of STN-DBS.

There are some previous studies suggesting the significant relationship between the patient age at surgery and the outcome of STN-DBS. Ory-Magne et al.<sup>6)</sup> highlighted the effect of ageing on the outcome of STN-DBS. Their study of 45 patients followed up for 24 months showed a significant negative correlation between the age at surgery and the improvement of Parkinson's disease questionnaire (PDQ 39) scores. In addition, according to their study, the appearance of apathy and depression after STN-DBS positively correlated with the age at surgery.<sup>6)</sup> A study of 39 patients followed up for 12 months by Jaggi et al.<sup>7)</sup> showed that the significant predictive variables for outcome were age at surgery, preoperative percent change in UPDRS part III score from the off- to on-period, and disease duration. Although our results coincided with their results concerning the age at surgery, the onset age of PD disagreed with their results. Onset age might have an effect as a confounding factor.

On the other hand, there are some previous studies suggesting the importance of disease duration as a predictive factor; however, our results demonstrated that disease duration was not significant. Multiple logistic regression analysis by Umemura et al.<sup>8)</sup> indicated that the significant independent variables related to early deterioration of axial symptoms were the rapidly progressive short duration of the disease and advanced age at surgery. In addition, one report mentioned that the patients who showed postoperative improvement of the psychiatric symptoms after STN-DBS had a significantly shorter disease duration than the patients who showed postoperative behavioral deterioration with similar preoperative prevalence and severity of behavioral problems.<sup>9)</sup> Moreover, long disease duration and poor preoperative speech intelligibility are reported as predictive factors for deterioration of speech intelligibility after STN-DBS.<sup>10)</sup>

Some studies revealed preoperative cognitive function as an additional important predictive factor for the outcome, as similarly shown in our study. Tsai et al.<sup>11)</sup> studied the prognostic factors in their 36 patients who underwent bilateral STN-DBS with a mean follow-up examination period of 31.3 months. According to their study, the prognostic factors for better long-term outcome of STN-DBS for PD patients were good cognitive function and tremor dominance, and those for the poor outcome of STN-DBS were older age and nondopaminergic-responsive axial disability. The follow-up period of their study was shorter than ours. However, our main results may lend support to their study. It is worth emphasizing the importance of tremor dominance and axial symptoms.



There are some additional studies of predictive factors from another viewpoint. The presence of the microlesion effect in the early postoperative period indicated a positive correlation with the improvement degree after STN-DBS.<sup>12)</sup> Similarly, it was reported that the presence of transient disabling dyskinesia in PD patients immediately after STN-DBS was a predictor of good outcome.<sup>13)</sup> Conversely, preoperative severe dyskinesia may predict postoperative apathy in the acute phase.<sup>14)</sup> Furthermore, an increase in lateral ventricle volume was reported as a predictive factor for poor improvement of motor function after STN-DBS.<sup>15)</sup> Some recent studies showed the association of specific genes as predictive factors for the beneficial outcome of STN-DBS.<sup>16,17)</sup>

As mentioned above, many studies of the predictive factors for the outcome of STN-DBS have already been reported. Unfortunately, the majority of those studies showed the results based on a relatively short-term follow-up after the surgery. Therefore, the predictive factors for the long-term outcome are still unestablished. The significance of our study was to determine the long-term predictive factors for STN-DBS outcome focusing on the preoperative characteristics of the patients.

We consider that the results of our study suggest three important factors with clinical usefulness. Firstly, patients tend to show decrease in MMSE score preoperatively; thus, STN-DBS should be introduced carefully and informed consent considering the long-term outcome should be obtained prior to STN-DBS. Secondly, a better long-term STN-DBS outcome may be obtained if STN-DBS is introduced when the PD symptoms are not yet severe. Thirdly, patients with the early-onset type of PD may show a better response to STN-DBS in the long term. Genetic factors may also underlie such a response.

Some of our results are in line with the findings of the EARLYSTIM study.<sup>18)</sup> The findings of our study about the disease duration did not concur with that study. However, the essential point suggested by both studies is that a better outcome will be expected by introducing STN-DBS before PD has advanced, which may be linked to neural plasticity. On the other hand, we should consider countermeasures regarding the preoperative decrease in MMSE score from an aspect different from the timing of surgery. Cognitive decline was assumed to appear depending on the background of genetic factors. Genetic evaluation may be useful for predicting the outcome of STN-DBS.

This study has several limitations. Firstly, there may be selection bias because our retrospective study included only patients who were followed up for

5 years. Therefore, there were some patients who dropped out of our study. Furthermore, despite the absence of a significant difference in disease duration before the surgery, the preoperative scores of some items of the UPDRS and S&E scale of group I were significantly better than those of group D. Such findings suggest that the patients in group I had the benign type of PD compared with the patients in group D. Unfortunately, it was difficult to confirm this presumption from the results of our study. Unavoidably, there was a certain degree of selection bias in these points. Secondly, in this study, we did not sufficiently investigate the effects of psychiatric symptoms. We investigated depression only using HDS. The criteria of our institute for surgical indication exclude the patients who have advanced psychiatric problems. Originally, psychiatric symptoms should be differentiated between those induced by drugs and those caused by the disease itself, because such a difference is assumed to affect the outcome of STN-DBS. To resolve the above-mentioned limitations of our study, randomized prospective studies with long-term follow-up are required.

## Conclusions

Younger age at surgery, preoperative high-level cognitive function and preoperative high S&E scale score during the off-period were the independent important predictive factors for the beneficial long-term outcome of STN-DBS. In addition, younger onset age of PD, good preoperative UPDRS part I and II scores, and good UPDRS part III scores of axial symptoms seem to be useful predictive factors for the beneficial long-term outcome of STN-DBS.

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## Conflicts of Interest Disclosure

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