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Five-Year Outcomes of Bilateral Subthalamic Nucleus Stimulation in Japanese Patients with Parkinson's Disease

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Abstract

Background: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is widely performed for medically refractory Parkinson's disease (PD). Several western studies have examined the long-term outcomes of STN DBS. However, the long-term outcomes in Japanese patients have not been reported. Methods: We studied the long-term outcomes of STN DBS in Japanese patients with PD. Fifty-five consecutive patients treated with bilateral STN DBS were followed for 5 years after surgery. Each patient underwent Unified Parkinson's Disease Rating Scale assessments preoperatively and 1 and 5 years after surgery. Results: Twelve patients (22%) were lost to follow up within 5 years. Among them, 7 died and 5 became bed ridden because of PD deterioration. In the 43 patients followed for 5 years, STN DBS significantly improved motor function. The cardinal motor symptoms of tremor, rigidity, and bradykinesia in medication-on periods were significantly better than baseline 5 years after DBS. However, axial motor symptoms of speech, gait and postural stability gradually deteriorated and significantly worsened 5 years after DBS. Motor complications, including dyskinesia and motor fluctuations, significantly improved after DBS with a marked reduction in dopaminergic medication. These effects were maintained 5 years after DBS. Frequently, persisting adverse effects included apraxia of eyelid opening and dysarthria. Conclusions: STN DBS

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significantly improved motor symptoms in patients with advanced PD. These effects were maintained over 5 years in most patients. However, some showed rapid PD progression even after STN DBS. Other treatments for the axial symptoms and disease progression are needed in long-term PD treatment.

Keywords

Deep Brain Stimulation, Subthalamic Nucleus, Parkinson's Disease, Long-Term Outcome, Adverse Effect

1. Introduction

More than ten years have passed since deep brain stimulation (DBS) was introduced in Japan for the treatment of Parkinson's disease (PD). DBS of the subthalamic nucleus (STN) has been widely performed as a promising treatment option for patients with medically refractory PD [1]. STN DBS is usually indicated for PD patients who suffer from the motor complications of dopaminergic medication such as dyskinesia and motor fluctuation. In general, STN DBS improves motor function in the medication-off state, rather than in the medication-on state. STN DBS also reduces the need for dopaminergic medication and consequently improves dyskinesia and motor fluctuation [2]. There have been several reports from western countries concerning the long-term (more than 5 years) outcomes of STN DBS [3]-[10]. However, the long-term outcomes in Japanese patients have not been reported. In most western studies, early effects of STN DBS were maintained over 5 years, while axial motor symptoms such as speech, gait and postural stability were progressively worsened. In this study, we investigated the 5-year outcomes of STN DBS in Japanese patients with PD.

2. Methods

2.1. Study Design

A single-center, open-label, and prospective study was performed. Patients who underwent bilateral STN DBS from 2004 to 2006 at Nagoya City University Hospital were enrolled. All were followed until 5 years after surgery. Each patient underwent Unified Parkinson's Disease Rating Scale (UPDRS) assessments preoperatively and 1 and 5 years after the surgery. This study was approved by the medical ethics committee of Nagoya City University Graduate School of Medicine.

2.2. Patient Population

We followed 55 consecutive patients (15 males and 40 females) who underwent bilateral STN DBS until 5 years after the surgery. The mean age of the patients at the time of the surgery was 62.5 years (range 41 - 82 years), and the mean duration of the disease was 11.2 years (range 3 - 30 years). All of the patients underwent bilateral STN DBS surgeries in one stage by the same surgeon (A.U.) at Nagoya City University Hospital. STN DBS was indicated in most patients for their significant motor complications, including motor fluctuations and dyskinesia, which were caused by dopaminergic medication.

2.3. Surgery and Adjustment of Stimulation Parameters and Medication

Quadripolar DBS electrodes (model 3389; Medtronic Inc.) were implanted into the STN stereotactically under magnetic resonance imaging guidance with physiological refinement by microelectrode recording. The detailed surgical procedures have been previously reported [11]. The stimulation parameters were adjusted to produce the maximal clinical benefits for cardinal PD symptoms without side effects. Amonopolar electrode setting was preferred unless the stimulation-induced side effects required a more focal bipolar stimulation paradigm. In most cases, the stimulation parameters were 90 μs of pulse width, 130 Hz of pulse rate, and 2 - 3 volts of amplitude. After the surgery, dopaminergic medications were initially reduced by approximately 50% and then further reduced or increased based on the stimulation-induced improvements in the PD symptoms. Later, more detailed medication and stimulation adjustments were performed in the outpatient clinic.

2.4. Clinical Assessments

Each patient underwent a clinical assessment of the UPDRS part III motor score and part IV score preoperatively (medication-on and -off conditions) and then 1 and 5 years after the surgery in the outpatient clinic. The levodopa-equivalent daily dosage (LEDD) calculations were adapted as follows: 100 mg levodopa with a dopa carboxylase inhibitor = 1 mg pergolide = 1.5 mg pramipexole = 9 mg ropinirole = 4 mg cabergoline [12]. Non dopaminergic therapy (anticholinergics and amantadine) was not included in this calculation.

All data are given as means ± standard deviations (SD). Wilcoxon rank sum tests were applied to compare the pre-and post-operative clinical scores. The significance levels were set at $p < 0.05$.

3. Results

3.1. Patients Lost to Follow-Up

Unfortunately, 12 patients (22%) were lost to follow up within 5 years. Among them, 5 patients became bed ridden because of progression of their PD, and they were unable to return to our clinic. All of the bed ridden patients suffered from severe dysphagia and akinesia. The other 7 patients died within 5 years after the surgery. The causes of death were 3 cancer (n = 3), aspiration pneumonia related to PD progression (n = 2), accidental death (n = 1), or sudden death (n = 1).

3.2. Five-Year Outcomes of STN-DBS

The five-year outcomes of the 43 patients with 5-year follow-ups are shown in **Table 1**. The UPDRS III motor scores in the medication-on period were significantly improved 1 year after DBS, but they returned to baseline levels 5 years after DBS. As for each symptom, the cardinal motor symptoms of tremor, rigidity, and bradykinesia in the medication-on period were still significantly better than baseline level 5 years after DBS. However, axial motor symptoms of speech, gait and postural stability gradually deteriorated and were significantly worse 5 years after DBS.

Table 1. Five-year outcome of bilateral STN DBS in 43 patients.

	Pre-DBS	1-year after DBS	p value	5-year after DBS	p value
UPDRS III motor score (total)	19.6 ± 8.4 (med-on)	15.6 ± 6.6 (med-on)	< 0.001	18.4 ± 8.2 (med-on)	0.41
	41.5 ± 12.7 (med-off)				
Tremor (item 20 - 21)	1.0 ± 1.4 (med-on)	0.6 ± 0.9 (med-on)	0.08	0.3 ± 0.8 (med-on)	0.008
	4.6 ± 5.4 (med-off)				
Rigidity (item 22)	4.5 ± 3.0 (med-on)	2.3 ± 2.0 (med-on)	<0.001	1.8 ± 1.8 (med-on)	<0.001
	8.8 ± 3.6 (med-off)				
Bradykinesia (item 23 - 26)	7.8 ± 3.3 (med-on)	6.1 ± 3.3 (med-on)	0.02	5.5 ± 4.1 (med-on)	0.004
	14.0 ± 4.6 (med-off)				
Speech (item 18)	0.9 ± 0.4 (med-on)	0.9 ± 0.4 (med-on)	0.91	1.6 ± 0.7 (med-on)	<0.001
	1.3 ± 0.7 (med-off)				
Gait (item 29)	0.7 ± 0.6 (med-on)	0.9 ± 0.6 (med-on)	0.12	1.8 ± 1.0 (med-on)	< 0.001
	2.3 ± 1.1 (med-off)				
Postural stability (item 30)	1.2 ± 0.6 (med-on)	1.3 ± 0.6 (med-on)	0.6	2.0 ± 0.9 (med-on)	<0.001
	2.1 ± 0.9 (med-off)				
Dyskinesia (item 32 - 35)	2.0 ± 2.0	0.5 ± 0.9	<0.001	0.7 ± 0.8	0.002
Fluctuation (item 36 - 39)	4.0 ± 1.1	0.8 ± 1.4	<0.001	1.2 ± 1.4	<0.001
Medication (LEDD (mg))	600 ± 250	222 ± 174	<0.001	289 ± 171	<0.001

Values are expressed as the means ± the standard deviations. The Wilcoxon signed-rank test was used for comparison between pre- and post-DBS value. UPDRS: Unified Parkinson's Disease Rating Scale Part III; LEDD: levodopa-equivalent daily dosage.

Motor complications, such as dyskinesia and motor fluctuations, of dopaminergic medication were significantly improved after DBS with significant reductions in dopaminergic medication. These effects were still maintained at 5 years after DBS.

3.3. Complications

The complications of STN DBS in this series are summarized in **Table 2**. There was a significant incidence of complications associated with STN DBS. Among the device-related complications, one patient had an infection of implantable pulse generator (IPG) 3 months after the surgery, and two patients had IPG malfunction. They required replacement of the IPG.

As for treatment or stimulation-related complications, transient mood changes, such as hypomania or depression, were sometimes recognized in the early period after surgery. Dysarthria and apraxia of eyelid opening (ALO) were the most frequent permanent sequelae after STN-DBS. The monopolar setting was converted to a bipolar setting for the alleviation of dysarthria. Most patients with ALO were treated with periodic injections of botulinum toxin.

4. Discussion

STN DBS has been shown to be the most promising surgical treatment for patients with medically refractory PD [1]. According to a meta-analysis of early outcomes [2], STN DBS improves UPDRS III motor scores in the medication-off state by 52%. STN DBS also reduces dyskinesia by 69%, the daily off period by 68%, and the need for dopaminergic medication by 56%. Thus, STN DBS provides a second honeymoon to patients suffering from the motor complications of dopaminergic medication. To date, the long-term outcomes of STN DBS have been reported from several centers in western countries, and these have demonstrated that the effects of STN DBS are sustained over time (**Table 3**) [3]-[10].

In this study, we investigated the 5-year outcomes of STN DBS in the Japanese population and demonstrated that STN DBS produced significant improvements in the motor complications in PD and significant reductions in dopaminergic medications over 5 years. These results were mostly consistent with the 5-year outcomes from other centers in western countries (**Table 3**) [3]-[7]. In general, STN DBS improves the motor scores in the medication-off state rather than in the medication-on state. Because we performed the postoperative motor evaluations in our outpatient clinic, we evaluated the motor scores in the medication-on state only. However, the motor fluctuations were significantly improved even 5 years after DBS, which suggested that patients had minimum off periods after DBS. Originally, STN DBS was indicated for patients suffering from motor complications such as fluctuations and dyskinesia. The improvements in these motor complications were maintained over 5 years. Therefore, the aim of STN DBS seemed to be achieved over a long period.

Table 2. Complications of STN DBS in this series.

	Transient	Permanent
# Related to device		
Infection	1	0
IPG malfunction	2	0
# Related to treatment or stimulation		
Hypomania	2	0
Depression	2	0
Impulse control disorder	1	0
Apraxia of eyelid opening	0	8
Dysarthria	0	4
Back pain	0	1
Restless leg syndrome	2	0

Table 3. Five-year outcome of STN DBS in other studies.

Author	Number of patients	Mean age at surgery	Outcome at 5 years (compared with pre-DBS)			
			Motor score	Dyskinesia	Fluctuation	Medication
Krack, *et al*. [3]	49	55	54% imp (med-off) 48% det (med-on)	71% imp	58% imp	63% dec
Schüpbach, *et al*. [4]	37	55	50% imp (med-on) no change (med-on)	59% imp	70% imp	55% dec
Wider, *et al*. [5]	37	65	30% imp (med-off) 26% det (med-on)	85% imp	84% imp	57% dec
Gervais-Bernard, *et al*. [6]	23	55	55% imp (med-off) 11% imp (med-on)	NA	NA	57% dec
Moro, *et al*. [7]	35	60	45% imp (med-off) 7% det (med-on)	83% imp	NA	30% dec
Our series	43	60	NA (med-off) 6% imp (med-on)	65% imp	70% imp	52% dec

Imp: improvement; det: deterioration; dec: decrease; NA: not available.

We also demonstrated that the improvements in cardinal motor symptoms of tremor, rigidity and bradykinesia were maintained. However, axial motor symptoms of speech, gait and postural stability were gradually deteriorated over 5 years. Progressive worsening of the axial symptoms has also been mentioned in other studies [3] [5] [8]-[10]. These axial symptoms are also resistant to dopaminergic medication. The symptoms of gait disturbance or postural instability seem to be mediated by nondopaminergic mechanisms.STN DBS substantially improves only the dopamine-mediated motor symptoms. Therefore, the aggravation of axial symptoms reflects the progression of PD itself.

There have been a few reports on the long-term outcomes of STN DBS for more than 5 years [8]-[10]. Zibetti et al. have reported the 9-year outcome of STN DBS [9]. They demonstrated a persistent effect on cardinal motor symptoms. However, the activity of daily living worsened considerably because of progressive axial symptoms and cognitive decline. Other studies have shown similar results [8]-[10].

In this study, 22% of the patients (12 of 55 patients) dropped out from the 5-year follow up. Seven patients died within 5 years after the DBS. Two deaths were related to the progression of PD (aspiration pneumonia), and 5 deaths were not related to PD. Besides, 5 patients were not followed due to the deterioration of PD. The initial outcomes after STN DBS were all favorable in these patients. Also in other studies from western countries, a significant number of patients were lost to follow up within 5 years (**Table 4**) [3]-[7]. There is a significant incidence of patients who die within 5 years after DBS or who are unable to return to follow up. Most of these cases seem to be related to the progression of PD. The speed of the clinical progression of PD varies in each patient. In patients with rapid progression, the subsequent disease progression after the temporary relief by STN DBS also seems to be rapid. Therefore, STN DBS seems to be more beneficial for patients with a slow progression of the disease. Considering these facts, the actual global long-term outcome of STN DBS may be much worse than expected.

It is controversial whether STN DBS contributes to improvements in the survival of patients with PD. Ngoga et al. have demonstrated that patients undergoing STN DBS have significantly longer survivals than those who are managed only by medication. STN DBS markedly reduces the death rate that is related to respiratory complications, such as pneumonia [13]. However, Lilleeng *et al*. have demonstrated no significant difference in the long-term mortalities between the STN DBS group and the control group [14].

DBS devices need to be surgically implanted to introduce this treatment. Therefore we should pay attention to surgery-related complications. Intracranial hemorrhage (ICH) and device infection are typical surgery-related complications [15]. ICH is caused by insertion of the electrode into the brain. Although no ICHs occurred in this

Table 4. Loss of follow-up cases in other studies.

Author	Original No. of patients	Final No. of patients	Reason of loss of follow-up within 5 years
Krack, *et al*. [3]	49	42	3 death (unknown details), 4 unable to return (2 lived overseas, 2 personal reason)
Schüpbach, *et al*. [4]	37	30	6 death (2 progression of PD, 1 suicide, 1 CVD, 2 sudden death) 1 unable to return due to moving
Wider, *et al*. [5]	50	37	13 death (3 suicide, 7 infectious disease, 2 pulmonary embolism, 1 myocardial infarction)
Gervais-Bernard, *et al*. [6]	42	23	5 death (1 suicide, 5 other disease), 14 unable to return (unknown details)
Moro, *et al*. [7]	68	35	24 death (unknown details), 5 unable to return (unknown details)
Our series	55	43	7 death, 5 unable to return due to progression of PD

series, the general incidence of ICH in DBS surgery is 1% - 3%. Infection is the most probable device-related complication of DBS. The reported incidence of device infection varies from 0.4% to 10%. In general, infected DBS systems should be removed, and reimplantation is required after treatment with antibiotics. Dysarthria and ALO were the most frequent permanent complications after STN DBS. Stimulation-induced dysarthria is caused by excessive stimulation to the pyramidal tract that is located lateral to the STN. In such cases, altering stimulation to a bipolar setting is effective. Besides, dysarthria may be a problem of verbal fluency that is caused by STN DBS [16]. The mechanism of ALO is not well understood. ALO is not treated by adjusting stimulation parameters. However, most patients are successfully treated by injections of botulinum toxin.

5. Conclusion

STN DBS significantly improved cardinal motor symptoms rather than axial motor symptoms in patients with advanced PD. STN DBS also improved the motor complications from dopaminergic medications and provided a second honeymoon for patients. These effects were maintained over 5 years in most patients. However, some patients showed a rapid progression of PD even after STN DBS. The establishment of other treatment strategies that are geared towards the axial symptoms and disease progression is the next step in determining the long-term treatment of patients with PD.

Conflict of Interest

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