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Musculoskeletal problems need more attention in deep brain stimulation for Parkinson's disease

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Abstract

Background and Objectives: This study aimed to examine factors of poor outcome by analyzing the outcomes of bilateral subthalamic deep brain stimulation in Parkinson's disease after 3 years. *Methods:* We assumed that patients who could not manage independent life in their best stimulation-on/medication-on condition after a defined period might not have been a good surgical candidate. A poor outcome is defined as a failure to maintain functional independence at three years during a stimulation-on/medication-on state. *Results:* A total of 84 patients underwent bilateral subthalamic deep brain stimulation and all were followed up for 3 years. We excluded one patient who had intracranial hemorrhage. Twenty-one patients of the 83 patients could not keep up independent life even during their best condition for the following reasons: freezing in 15 patients, dementia in 5, depression in 3, musculoskeletal problems in 7, and cancer in one patient.
Conclusions: Many patients could not keep up independent life during their best condition as early as three years after deep brain stimulation. Musculoskeletal problems were one major cause of disabilities, as were freezing and dementia. We emphasize that musculoskeletal problems need more attention in the preoperative screening of deep brain stimulation candidates and during the follow up.

INTRODUCTION

The success of deep brain stimulation (DBS) depends not only on accurate placement of electrodes by neurosurgeons, but also on selection of suitable candidates and on postoperative adjustment of stimulation parameters and medications by neurologists. Okun *et al*. reviewed 41 referral patients who complained of suboptimal results from DBS surgery, and they reported that there were problems related to patient selection for approximately half (20) of those patients. Their results emphasize the need for careful patient selection.[1]

Although data on referral patients with DBS failure have been analyzed, there are no studies examining patient selection and DBS outcome at an individual medical center. In order to evaluate the performance of a center, three separate phases of presurgical candidate selection, surgical accuracy and postoperative management need to be explored. Surgical accuracy can be examined by postoperative imaging which we do on a routine basis.[2] Performance of the neurologists in adjusting stimulation parameter and medication is difficult to measure unless all patients are referred to and managed by other independent groups.

We assumed that the patients can achieve the best condition during the optimally adjusted DBS-on/medication-on state, and that the poor performance in activities of daily life at the best condition suggests that the disease is advanced. If this progression of condition could have been predicted at the time of screening, the patient might not have been considered a good candidate to begin with. Thus we may be able to examine the performance in screening patients by analyzing their best DBS-on/medication-on condition after a certain period of DBS. In the cases of misplaced electrodes, DBS-on/medication-off condition will be poor; however, medication is expected to improve the poor DBS-on condition up to the best achievable state during DBS-on/medication-on condition. Thus this method of measuring the

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performance of a center in selecting candidates by analyzing their DBS-on/medication-on condition may circumvent the problem of surgical accuracy.

Here, we examined our performance in screening candidates by analyzing the outcomes of DBS in their best condition after 3 years. More importantly we wanted to examine factors which contributed to the poor functioning of the patients even when they were in their best condition. We speculated that patients who could not manage independent life under so-called "best" conditions (i.e., DBS-on/medication-on) and after a defined period (three years) might not have been a suitable surgical candidates. Thus those factors will be useful in considering surgical candidates.

METHODS

All pre-surgical evaluations and all postoperative management are provided by neurologists under a prospective protocol since 2005 at our Movement Disorder Center, Seoul National University Hospital.[3] Patients are selected after extended outpatient follow-up and observation in a specialized monitoring unit.[3] Evaluations are based on Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr stage (H&Y), Schwab and England Activities of Daily Living (SEADL), as well as on neuropsychiatric examination results, including Mini-Mental State Examination (MMSE) and Beck Depression Inventory (BDI) questionnaires.

Evaluations are performed before surgery, at 6 and 12 months after surgery, and yearly thereafter. A poor outcome is defined as a failure, for any reason, to maintain functional independence (SEADL ≤ 70) at three years during a DBS-on/medication-on state. The Institutional Review Board of Seoul National University Hospital approved this study.

RESULTS

A total of 84 patients with Parkinson's disease (PD) underwent bilateral subthalamic nucleus (STN) DBS between March, 2005 and July, 2008. All patients had a follow-up period of more than three years or until death. We excluded one patient from the study because he had intracranial hemorrhage resulting in hemiplegia. Twenty-one of the 83 patients did not keep up independent life after STN DBS for the following reasons: gait disturbance due to freezing in 15 patients (including one multisystem atrophy and one SCA17[4]), cognitive decline in 5 patients, depression and apathy in 3 patients (including one suicide), musculoskeletal problems in 7 patients, and cancer in one patient (Table 1).

Most patients in poor outcome group had relatively good arm motor function, but lost the range of mobility that is required for independent daily activities. In addition, they wanted and/or needed someone to accompany them due to a fear of falling in patients with gait disturbance due to freezing and due to pain in patients with musculoskeletal problems. Indeed, gait freezing resulted in falls, fractures, shoulder dislocations, and further limiting patients' of daily activities.

The patients in the poor outcome group were older than those in the good outcome group (62.0 ± 6.2 vs. 57.9 ± 8.7 years, respectively, p = 0.034), had a later average onset age (52.5 ± 7.8 vs. 47.4 ± 10.4 years, respectively, p = 0.038), a significantly poorer MMSE score (25.1 ± 4.2 vs. 27.4 ± 2.1, respectively, p = 0.018), higher UPDRS part III rating (28.1 ± 14.7 vs. 17.5 ± 10.4, respectively, p = 0.002), and lower change of UPDRS part III between medication-on and off (38.5 ± 20.7 vs. 56.2 ± 18.4 %, respectively, p = 0.001). In addition, there were significant differences between the poor-outcome and good-outcome group on the preoperative medication-on state in gait (1.2 ± 0.9 vs. 0.7 ± 0.5, respectively, p = 0.005) and postural stability (1.3 ± 0.9 vs. 0.8 ± 0.8, respectively, p = 0.031) and in H&Y stage (2.6 ± 0.6 vs 2.2 ± 0.6, respectively, p = 0.019) (Table 2). In the preoperative medication-off state, there were no significant differences between the poor-outcome and good-outcome groups in disease duration at operation, BDI score, UPDRS part III score, gait, postural stability, and H&Y stage.

DISCUSSION

Even after following our center's pre-surgical screening protocol, we were not able to screen out patients who would not keep up independent life during their best condition as early as three years after DBS. As in the previous reports, common causes of disabilities in post DBS state were freezing and dementia.[5,6] A major finding in this study was that musculoskeletal problems were important contributing causes of disabilities. Musculoskeletal problems coexisted in one patient with freezing and cognitive problems, which must have contributed to falls resulting in fractures. It is now well appreciated that osteoporosis is frequent in PD[7,8], which would have further contributed to fractures even from minor falls. It

Table 1: Patients in poor outcome group in subthalamic deep brain stimulation

Patients	Freezing	Dementia and apathy	Depression	Musculoskeletal	Cancer	Suboptimally placed electrodes
1	+		+	+ (L-spine compression fracture) ‡		R: Dorsomedial
2	+					
3		+				L: Anterior ventrolateral
4		+	+			R: Dorsomedial
5	+	+		+ (L-spine compression fracture) ‡		
6	+	+				R: Dorsomedial, L: Dorsomedial
7	+				+ (Ovarian cancer)	L: Dorsomedial
8	+			+ (Femur fracture)		L: Posterior dorsomedial
9	+			+ (L-spine compression fracture) ‡		
10	+ (SCA17) *					
11	+					
12	+			+ (L-spine compression fracture) ‡		R: Dorsomedial
13	+					
14	+					
15	+ (MSA) †					L: Ventrolateral
16	+			+ (Shoulder dislocation)		
17		+				R: Dorsomedial
18				+ (Osteoarthritis on knees) ‡		
19	+					
20	+					
21			+ (Suicide)			

* Patient 10 in the present report correspond to Case 7 in reference 4. This patient later proved to be *SCA17*.[4]
† Patient 15 later developed severe autonomic dysfunction, and is believed to be multiple system atrophy.
‡ Patient 1, 5, 9 and 12 had back pain in preoperative state. Their back pain was aggravated later and L-spine compression fracture was diagnosed. Patient 18 had pain on both knees in preoperative state. The gait was interfered with by the knee pain.
SCA17, spinocerebellar ataxia type 17; MSA, multiple system atrophy; R: electrode on right side; L: electrode on left side.
( ): detailed description.

Table 2: Preoperative clinical characteristics of poor and good outcome groups

	Poor outcome group (N=21)	Good outcome group (N=62)	*P* value
Onset age	52.5 ± 7.8	47.4 ± 10.4	0.038*
Age at DBS operation	62.0 ± 6.2	57.9 ± 8.7	0.034*
Duration of disease, years	9.5 ± 3.7	10.5 ± 5.5	0.979
Sex (M:F)	9 : 12	30 : 32	0.801
LEDD, mg	962.5 ± 376.9	954.4 ± 485.6	0.582
MMSE	25.1 ± 4.2	27.4 ± 2.1	0.018*
BDI	23.0 ± 12.7	18.1 ± 9.7	0.108
Total UPDRS part III score, medication-on	28.1 ± 14.7	17.5 ± 10.4	0.002*
Total UPDRS part III score, medication-off	44.8 ± 15.9	38.8 ± 14.6	0.173
Change of UPDRS part III score between medication-off and on (%)	38.5 ± 20.7	56.2 ± 18.4	0.001*
Gait, medication-on	1.2 ± 0.9	0.7 ± 0.5	0.005*
Gait, medication-off	2.1 ± 1.0	1.8 ± 1.0	0.272
Instability, medication-on	1.3 ± 0.9	0.8 ± 0.8	0.031*
Instability, medication-off	2.0 ± 1.0	1.6 ± 1.0	0.050
Dyskinesia duration score	1.5 ± 0.7	1.5 ± 1.0	0.684
Dyskinesia disability score	3.0 ± 1.1	2.1 ± 1.4	0.010*
H&Y, medication-on	2.6 ± 0.6	2.2 ± 0.6	0.019*
H&Y, medication-off	3.4 ± 0.9	3.1 ± 0.9	0.128

LEDD, Total daily levodopa equivalent dose; MMSE, Mini-mental State Examination; BDI, Beck Depression Inventory; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr stage.
* P<0.05

was also shown that shoulder problems are very common in PD.[9] However, no previous studies took note of the importance of musculoskeletal problems in DBS. Therefore, it will be important to carefully screen musculoskeletal problems in surgical candidates and to take measures to prevent fractures or other musculoskeletal problems. Therefore, it will be important to carefully screen musculoskeletal problems in surgical candidates and to take measures to prevent fractures such as fall precaution. Promoting bone and joint health will need to be further emphasized in the management of PD. One patient died because of unsuspected ovarian cancer, emphasizing that careful screening of general medical conditions is also warranted, particularly in a geriatric population.

The patients in the poor selection group were older in onset age (52.5 ± 7.8 vs. 47.8 ± 10.4, respectively, p=0.038) and at operation (62.0 ± 6.2 vs. 57.9 ± 8.7, p=0.034) than those in the good selection group and had significantly poorer MMSE scores (25.1 ± 4.2 vs. 27.4 ± 2.1, p=0.018), higher UPDRS part III rating (28.1 ± 14.7 vs. 17.5 ± 10.4, p = 0.002), as well as significant differences in gait (1.2 ± 0.9 vs. 0.7 ± 0.5, p = 0.005), postural stability (1.3 ± 0.9 vs. 0.8 ± 0.8, p = 0.031) and H&Y stage (2.6 ± 0.6 vs 2.2 ± 0.6, p = 0.019) in the preoperative medication-on state (Table 2). There was no difference between two groups in disease duration at operation, BDI, UPDRS part III, gait, postural stability and H&Y stage in the preoperative medication-off state.

That poor-outcome group did relatively well during the initial two years of follow-up, but outcome status was poor at three years (Table 3). The data suggest that DBS over an extended period may not result in a good outcome.

Therefore, DBS should be considered in more advanced stage PD patients, especially the elderly,

Table 3: Motor benefits of poor and good outcome groups

	Poor outcome group					Good outcome group				
	Preop (N= 21)	**Postop 6M (N=20)**	**Postop 1Y (N=19)**	**Postop 2Y (N=14)**	**Postop 3Y (N=12)**	**Preop (N=62)**	**Postop 6M (N=60)**	**Postop 1Y (N=59)**	**Postop 2Y (N=56)**	**Postop 3Y (N=54)**
Total UPDRS part III score, medication-on	28.1 ± 14.7	22.3 ± 9.0	22.0 ± 9.3	21.9 ± 8.7	31.8 ± 9.1	17.5 ± 10.4	14.0 ± 7.9	14.8 ± 8.0	14.5 ± 7.4	14.9 ± 8.0
Total UPDRS part III score, medication-off	44.8 ± 15.9	31.2 ± 10.0	27.3 ± 9.1	27.1 ± 10.9	35.5 ± 10.9	38.8 ± 14.6	19.6 ± 10.9	18.8 ± 9.1	19.6 ± 10.6	20.1 ± 8.7
Change of UPDRS part III medication-off and on (%)	38.5 ± 20.7	31.3 ± 21.3	17.9 ± 4.1	24.6 ± 9.5	15.8 ± 8.4	56.2 ± 18.4	29.5 ± 21.8	21.2 ± 30.6	29.0 ± 23.4	34.7 ± 25.3
Dyskinesia duration score	1.5 ± 0.7	0.6 ± 0.8	0.6 ± 1.0	0.5 ± 0.8	0.5 ± 0.9	1.5 ± 1.0	0.2 ± 0.6	0.2 ± 0.4	0.3 ± 0.5	0.2 ± 0.5
Dyskinesia disability score	3.0 ± 1.1	1.0 ± 1.3	1.3 ± 1.6	0.9 ± 1.3	0.5 ± 1.2	2.1 ± 1.4	0.4 ± 1.0	0.4 ± 1.0	0.6 ± 1.1	0.3 ± 0.9
Duration score, medication off	1.6 ± 1.0				0.9 ± 1.1	1.8 ± 0.8				0.7 ± 0.9

Y, year; Preop, preoperative; Postop, postoperative; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr stage.

with the understanding that the functional benefit may not be maintained over an extended period. However, it should be emphasized again that these poor outcome group achieved reduction of dyskinesia and off symptoms, and improvement in quality of life.

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JYY participated in the design of the study and the statistical analysis and drafted the manuscript. BSJ conceived study design and methodology, drafted and reviewed the manuscript and supervised all work. HJK conceived study design and methodology, and reviewed the paper. YEK conceived methodology, and reviewed the paper. JYL conceived methodology, and reviewed the paper. SHP conceived study design and methodology, reviewed the paper and supervised all work. All authors read and approved the final version of manuscript.

DISCLOSURE

Conflict of interests: BSJ has received funding for travel from Norvartis Korea and has received research support as PI from Norvartis, Boehringer Ingelheim, the Korea Health 21 R&D project, Ministry of Health & Welfare, Republic of Korea (A101273), ABRC (Advanced Biometric Research Center), KOSEF (Korean Science and Engineering Foundation), Seoul National University Hospital, the Mr. Chung Suk-Gyoo and Sinyang Cultural Foundation, and the Song Foundation.

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