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ORIGINAL ARTICLE

Development of Clinical Milestones in Parkinson's Disease After Bilateral Subthalamic Deep Brain Stimulation

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ABSTRACT

Objective Deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's disease (PD) patients does not halt disease progression, as these patients will progress and develop disabling non-levodopa responsive symptoms. These features may act as milestones that represent the overall functionality of patients after DBS. The objective of this study was to investigate the development of clinical milestones in advanced PD patients who underwent bilateral STN-DBS.

Methods The study evaluated PD patients who underwent STN-DBS at baseline up to their last follow-up using the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr scale. The symptoms of hallucinations, dysarthria, dysphagia, frequent falls, difficulty walking, cognitive impairment and the loss of autonomy were chosen as the clinical milestones.

Results A total of 106 patients with a mean age of 47.21 ± 10.52 years at disease onset, a mean age of 58.72 ± 8.74 years at surgery and a mean disease duration of 11.51 ± 4.4 years before surgery were included. Initial improvement of motor symptoms was seen after the surgery with the appearance of clinical milestones over time. Using the moderately disabling criteria, 81 patients (76.41%) developed at least one clinical milestone, while 48 patients (45.28%) developed a milestone when using the severely disabling criteria.

Conclusion STN-DBS has a limited effect on axial and nonmotor symptoms of the PD patients, in contrast to the effect on motor symptoms. These symptoms may serve as clinical milestones that can convey the status of PD patients and its impact on the patients and their caregivers. Therefore, advanced PD patients, even those treated with bilateral STN-DBS, will still require assistance and cannot live independently in the long run.

Keywords Clinical milestones; Deep brain stimulation; Parkinson disease; Subthalamic nucleus.

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is effective in the treatment of patients with advanced Parkinson's disease (PD), improving both motor PD symptoms and levodopa-induced motor complications, despite the use of optimal oral medication.[1] With the improvement of both motor and some nonmotor symptoms after STN-DBS, it is possible to reduce the dopaminergic medication load.[2] Studies have shown long-term sustained stimulation-induced improvements; how-

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ever, some initial benefits subside due to underlying disease progression with the onset of levodopa-resistant symptoms and worsening of axial and nonmotor symptoms.[1,3]

One of the most comprehensive studies about long-term disease progression in PD patients is the Sydney Multicentre Study, where newly diagnosed PD patients were followed-up for 20 years.[4] In the 20-year survivors, dementia was present in 83%, falls in 87%, freezing in 81%, urinary incontinence in 71%, moderate dysarthria in 81%, choking in 48%, and hallucinations in 74%, and 48% lived in a nursing home.[4] In a study of 23 PD patients who underwent STN-DBS with a median PD duration of 18 years before surgery and median PD duration of 30 years at the last follow-up, 61% developed dementia, 52% were unable to talk, 35% were unable to swallow, 52% were unable to walk, 61% had psychosis, 65% had urinary incontinence, and 52% experienced a loss of autonomy.[5] These studies show that PD patients, with or without STN-DBS, will continue to progress and develop disabling non-levodopa responsive symptoms that severely affect their quality of life (QoL). The development of these clinical disease features may act as milestones that represent the overall functionality of patients after deep brain stimulation (DBS). The objective of this study was to investigate the development of clinical milestones in advanced PD patients who underwent bilateral STN-DBS in our center from 2005–2009.

MATERIALS & METHODS

Participants

PD patients in our movement disorder center who underwent DBS have been evaluated since March 7, 2005, according to a previously described prospective protocol.[6] The current study was a retrospective analysis of a prospectively collected dataset. We reviewed 118 PD patients who underwent bilateral STN-DBS surgery before December 31, 2009. Patients were excluded if they 1) had previous brain surgery, 2) had DBS removal, or 3) had less than 2 years of follow-up. The study protocol was approved by the SNUH Institutional Review Board and conformed to the principles of the Declaration of Helsinki (IRB#2009-044-1155). Patient consent was not required due to the retrospective nature of the study.

Neurosurgical procedure

All patients underwent STN-DBS implantation as previously described.[7] The stimulation settings and medications were adjusted individually to maintain the optimal clinical condition.

Clinical evaluation

The current study evaluated the patients at baseline up to their last follow-up, which referred to data obtained at the last recorded admission at the movement disorders center ward. The patients were evaluated in their best condition with both medication and stimulation in the on state or during the on-stimulation state only if the patient was not taking any anti-parkinsonian medication at the time of evaluation.

The parkinsonian states of the patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) and the modified Hoehn and Yahr (H&Y) stages. The levodopa equivalent daily dosage (LEDD) of all medications at baseline was calculated, and the baseline cognitive status was assessed using the Korean version of the Mini-Mental State Examination (K-MMSE).

The following symptoms were chosen as the clinical milestones: 1) hallucination, 2) dysarthria, 3) dysphagia, 4) frequent falls, 5) difficulty walking, 6) cognitive impairment, and 7) loss of autonomy. Two sets of criteria were used to describe the occurrence of milestones: moderately disabling criteria and severely disabling criteria (Table 1).

The clinical milestones chosen for this study were previously described physical, medication-related and cognitive/psychiatric symptoms, which greatly affect the QoL of PD patients.[8-10] Since the benefit of STN-DBS in controlling motor symptoms is already well established, we focused more on the axial and nonmotor symptoms that are not effectively addressed by DBS and chose them as the key clinical milestones. The chosen symptoms,

Table 1. Occurrence of clinical milestones defined using the two sets of criteria

Clinical milestone	Criteria	Score	
		Moderately disabling	Severely disabling
Hallucination	UPDRS item 2 (thought disorder)	> 3	4
Dysarthria	UPDRS item 5 (speech)	> 3	4
Dysphagia	UPDRS item 7 (swallowing)	> 3	4
Frequent falling	UPDRS item 13 (falling) OR UPDRS item 14 (freezing when walking)	> 3	4
Difficulty in walking	UPDRS item 15 (walking)	> 3	4
Cognitive impairment	UPDRS item 1 (mentation)	> 3	4
Loss of autonomy	Modified Hoehn and Yahr	> 4	5

UPDRS, Unified Parkinson's Disease Rating Scale.

such as hallucinations, speech and swallowing difficulties, mobility and cognitive impairment, are irreversible once present. Even if some of these symptoms are present prior to surgery, they persist postoperatively, making them good indicators of a patient's QoL.

Data analysis

Descriptive analysis was used in this study. The values are expressed as the mean ± standard deviaion, unless otherwise specified. Survival analysis, including Kaplan–Meier (KM) graphs and log rank analyses, was used to evaluate milestone development over time. The analysis was performed in all PD patients and separately for males and females. The level of significance was set at $p < 0.05$. All statistical analyses were performed with SPSS 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Demographic data

A total of 106 patients (45 males and 61 females) were included in this study. The demographic data and clinical characteristics are shown in Table 2. The mean age at disease onset was 47.21 ± 10.52 years, and the mean disease duration before surgery was 11.51 ± 4.4 years. Clinical assessments at baseline and after DBS surgery showed improvements of the UPDRS scores and reductions in the LEDD postoperatively. However, the initial improvements progressively worsened in the subsequent follow-ups with a concomitant increase in the LEDD (Supplementary Table 1 in the online-only Data Supplement). The mean follow-up duration after surgery was 8.90 ± 3.31 years, and the mean disease duration at the last follow-up was 21.75 ± 5.64 years.

Table 2. Demographic data and baseline clinical characteristics

Characteristics	Value
Number of PD patients	106
Sex	
Male	45 (42.45)
Female	61 (57.55)
Age at disease onset (yr)	47.21 ± 10.52
Age at surgery (yr)	58.72 ± 8.74
Disease duration (before DBS, yr)	11.51 ± 4.94
Disease duration (last follow-up, yr)	21.75 ± 5.64
Baseline LEDD (mg/day)	1,035.84 ± 516.80
Baseline UPDRS	
Part 3 score (Med ON)	20.08 ± 11.59
Baseline UPDRS	
Total score (Med ON)	31.40 ± 15.71
Baseline H&Y score (Med ON)	2.33 ± 0.57
Baseline MMSE score	27.0 ± 2.53

Values are presented as number (%) or mean ± standard deviation. PD, Parkinson's disease; DBS, deep brain stimulation; LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr; MMSE, Mini-Mental State Examination.

Clinical milestones

Using the moderately disabling criteria, 81 out of the 106 patients (76.41%) developed at least one clinical milestone after STN-DBS, while 48 patients (45.28%) developed a milestone in the severely disabling criteria (Figure 1A). Before the surgery, 19 patients and 11 patients already had a clinical milestone according to the moderately and severely disabling criteria, respectively (Supplementary Tables 2 and 3 in the online-only Data Supplement). Using both criteria, the most frequent clinical milestone reported was frequent falls (Table 3).

Hallucinations

Using the moderately disabling criteria, two patients reported hallucinations at baseline. Over time, eight more patients developed persistent hallucinations. In total, 10 PD patients (9.43%) had hallucinations at their last follow-up. Using the severely disabling criteria, one patient had hallucinations at baseline, and only two more developed hallucinations over time, resulting in a total of three PD patients (2.83%) with hallucinations at their last follow-up.

Dysarthria

At baseline, four patients met the slurring of speech criterion in the moderately disabling criteria. Thirty-five additional patients were reported to have slurring of speech over time, with a total of 39 PD patients (36.79%) with dysarthria at their last follow-up. Using the severely disabling criteria, only two patients reported slurring of speech at baseline, and 11 more patients developed slurring of speech over time. A total of 13 PD patients (12.26%) reported developing dysarthria (Figure 1B).

Dysphagia

One patient reported difficulty swallowing at baseline when the moderately disabling criteria were used. Over time, 15 more patients developed difficulty swallowing, with a total of 16 PD patients (15.09%) having dysphagia at their last follow-up. However, when the severely disabling criteria were used, no patients had difficulty swallowing at their last follow-up.

Frequent falls

At baseline, fourteen PD patients reported frequent falls in the moderately disabling criteria. In the subsequent follow-ups, 43 more patients reported frequent falls. In total, 57 patients (53.77%) developed frequent falls. Using the severely disabling criteria,

nine patients had frequent falls at baseline, and 31 patients subsequently developed frequent falls over time. Overall, a total of 40 patients (37.74%) developed frequent falls using the severely disabling criteria.

Difficulty walking

Using the moderately disabling criteria, six patients had difficulty walking at baseline, and over time, 32 more patients developed difficulty walking. At their last follow-up, a total of 38 PD patients (35.85%) required assistance while walking. Using the severely disabling criteria, all patients could walk independently at baseline. However, at their last follow-up, five patients (4.72%) subsequently had difficulty walking (Figure 1C).

Cognitive impairment

At baseline, none of the patients showed signs of cognitive impairment, but two patients (1.89%) developed cognitive impairment over time when using the moderately disabling criteria; in contrast, when using the severely disabling criteria, none of the patients developed cognitive impairment.

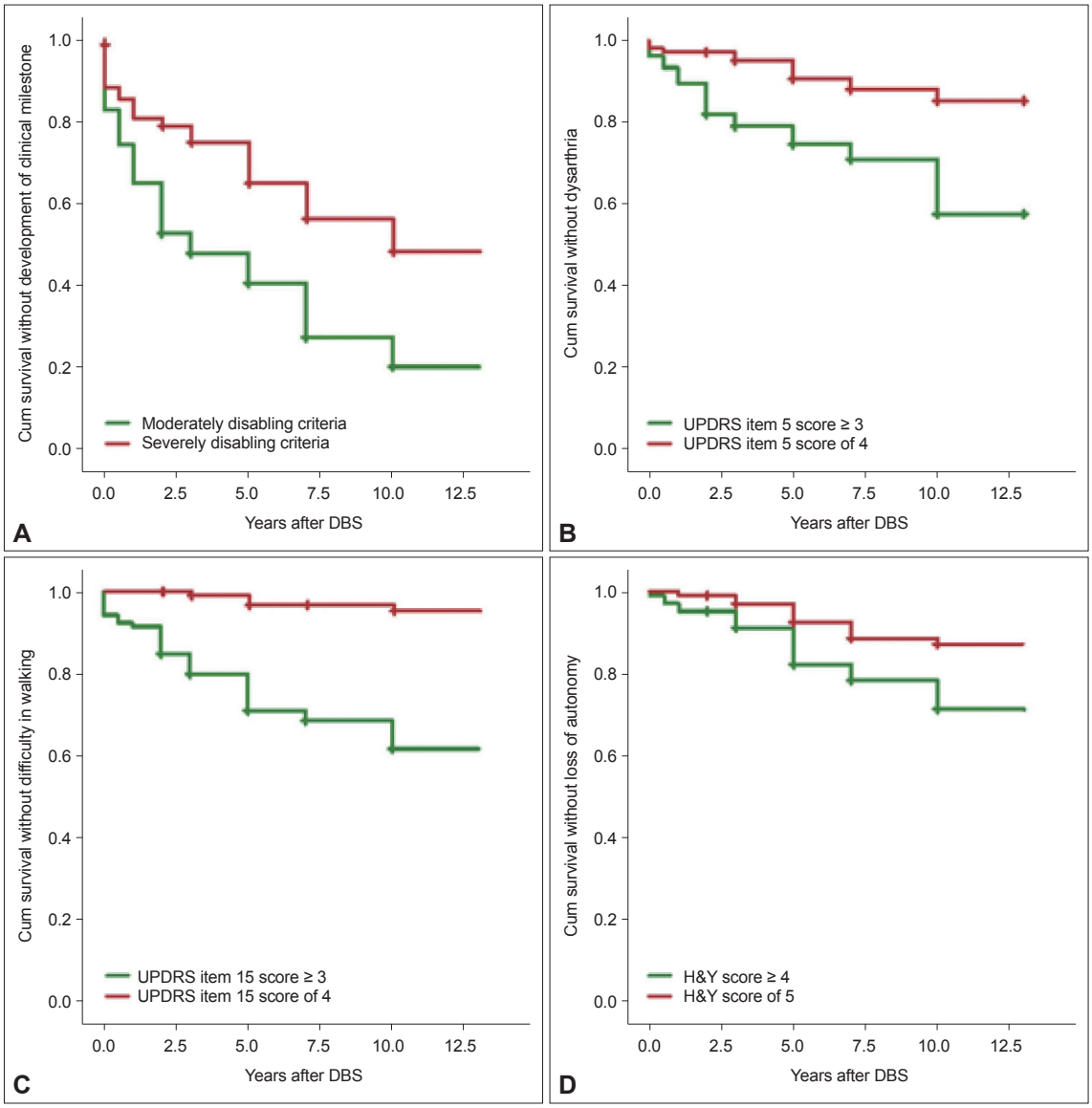

Figure 1. Kaplan–Meier survival plots of the clinical milestones in the 106 Parkinson's disease patients treated with DBS of the subthalamic nucleus before surgery (time 0) up to their last follow-up. The follow-ups were performed at 6 months and 1, 2, 3, 5, 7, 10, and 13 years after the surgery. Only 17 patients reached the 13-year follow-up. The two sets of criteria used are shown in these graphs: the moderately disabling criteria (green) and severely disabling criteria (red). Seventeen patients were lost to follow-up during the observation period. A: Survival without the development of clinical milestones. B: Survival without the development of dysarthria. C: Survival without the development of difficulty walking. D: Survival without the loss of autonomy. DBS, deep brain stimulation; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr.

Table 3. Key clinical milestones in Parkinson's disease patients treated with deep brain STN-DBS

	Disabling criteria (*n* = 106)	
	Moderately	Severely
Developed at least 1 milestone	81 (76.41)	48 (45.28)
Clinical milestones		
Hallucinations	10 (9.43)	3 (2.83)
Dysarthria*	39 (36.79)	13 (12.26)
Dysphagia*	16 (15.09)	0 (0)
Frequent falls	57 (53.77)	40 (37.74)
Difficulty walking	38 (35.85)	5 (4.72)
Cognitive impairment	2 (1.89)	0 (0)
Loss of autonomy	26 (24.53)	12 (11.32)

Values are presented as number of patients and percentage (%). Using the moderately disabling criteria, 81 of the 106 patients (76.41%) developed at least one clinical milestone after deep brain stimulation of the subthalamic nucleus (STN-DBS), while 48 patients (45.28%) developed a milestone using the severely disabling criteria. In both criteria, the most frequent clinical milestone reported was frequent falls. *significant difference between sexes.

Loss of autonomy

One patient had severe disability at baseline when the moderately disabling criteria were used. An additional 25 patients subsequently developed loss of autonomy over time, resulting in a total of 26 patients (24.53%) reporting loss of autonomy. Using the severely disabling criteria, all patients were independent at baseline. At their last follow-up, 12 patients (11.32%) had an H&Y score of 5, which indicates requiring a wheelchair or being bedridden (Figure 1D).

Sex differences

There were significant differences between sex and the development of dysarthria and dysphagia over time, with more males developing these symptoms than females. There were no significant differences found for the other milestones (Supplementary Table 4 in the online-only Data Supplement).

Mortality

Forty-two patients (39.62%) died after their last follow-up, but more than 75% of the patients survived to at least 10 years of follow-up after DBS surgery (Figure 2A). Half of the patients also reached a disease duration of 30 years and were still alive at the age of 75 (Figure 2C). Of the 42 reported deaths, the worsening of symptoms and pneumonia were reported as the most common causes of death in our patients (Table 4).

DISCUSSION

In our study, we analyzed a prospectively collected dataset of 106 PD patients who underwent bilateral STN-DBS from 2005 to 2009. After the surgery, all the patients had significant improvement in their motor disability, with a concomitant decrease in the use of dopaminergic medications. However, in the subsequent follow-ups, the patients' motor status slowly deteriorated. Medication dose was also slowly increased to compensate for the worsening status of the patients. However, even with medication adjustments, the natural course of the disease occurs, affecting the QoL of patients. Most of the patients developed some of the major clinical milestones, such as hallucinations, dysarthria, dysphagia, frequent falls, difficulty walking, cognitive impairment, and loss of autonomy, which also contributed to the functional capacity of the patients.

After a postoperative follow-up of 10 years or more, 64 of the 106 patients were still alive, and all had active DBS electrodes. DBS was deemed to still be efficacious for their motor symptoms but not for their axial and nonmotor symptoms, which are usually poorly responsive or non-levodopa responsive. These symptoms often lead to impairments in the patients' activities of daily living and may result in functional dependency for some. Our results are comparable with those of previous reports showing that patients will progressively develop disabling non-levodopa responsive symptoms even after undergoing DBS.[5,11]

In a previous report, the authors used very stringent criteria to identify the presence of key clinical milestones in patients.[5] Since the importance of the patients' QoL has been emphasized several times in this study, we believe that using more lenient criteria would better reflect the impact of these milestones on the patients and their caregivers. In this study, two sets of criteria were chosen with two different sets of cutoff values. The first set is the severely disabling criteria, which are more stringent and use the highest scores possible for both the UPDRS and H&Y scales. The second set is the moderately disabling criteria, which are more lenient than the first set of criteria. As expected, more patients developed the milestones using the moderately disabling criteria than when using the severely disabling criteria, which was also shown as a clear separation between the KM curves of the two sets of data (Figure 1). Our results emphasized that using more lenient criteria for identifying key clinical milestones demonstrates a better picture of patients' QoL. Even if the symptoms are not severe, they can still affect a patient's functional capacity and can be burdensome for both patients and their caregivers.

Comparing our results with those from a previously published study,[5] the incidence was lower for all clinical milestones: hallucinations (9.43% vs. 60.87%), dysarthria (36.79% vs. 52.17%), dysphagia (15.09% vs. 34.78%), difficulty walking (35.85% vs. 52.17%), cognitive impairment (1.89% vs. 60.87%) and loss of autonomy (24.53% vs. 52.17%). A possible reason for these differences is that their sample population only included 23 patients. Another reason is that we used different criteria for each

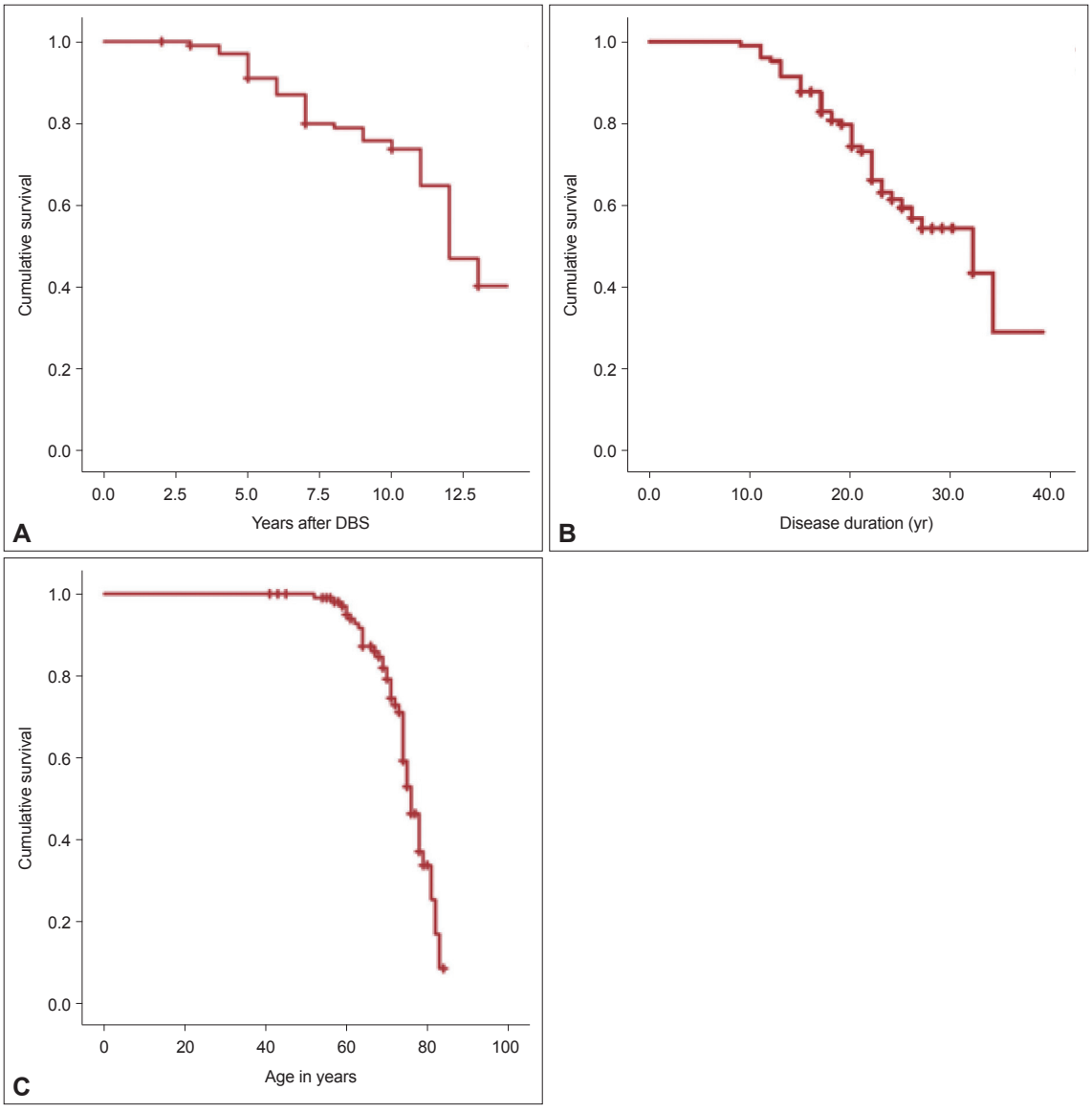

Figure 2. Kaplan–Meier survival plots of the 106 PD patients treated with STN-DBS according to the follow-up period after STN-DBS surgery (A), disease duration (B), and age (C). PD, Parkinson's disease; STN-DBS, deep brain stimulation of the subthalamic nucleus.

milestone. However, both studies emphasized that the presence of these milestones greatly affects the QoL of patients.

In this study, less than 10% of the patients developed hallucinations over the observation period, which is inconsistent with previous reports wherein a higher percentage of PD patients developed hallucinations and psychosis whether they underwent DBS[5] or not.[4,12] A possible explanation for this is that we only included patients who had persistent hallucinations and excluded those who had transitory hallucinations. We also did not exclude patients taking antipsychotic medications, which may have addressed their hallucinations.

For cognitive impairment, only two patients (1.89%) developed the symptom using the moderately disabling criteria, and none developed it using the severely disabling criteria. Our result goes against those of previous reports wherein a high percentage of medically treated[4,12,13] or DBS-treated[1,5,14] PD patients developed dementia over time. Neuropsychiatric assessments, scales and interviews would aid in accurately detecting cognitive impairment in these patients. Item 1 of the UPDRS (mentation), the K-MMSE and other neuropsychological battery tests were performed preoperatively to assess a patient's overall cognitive function. Postoperatively, we did not perform full neuropsychological tests for all patients and only performed the UPDRS item 1, the K-MMSE and interviews. We opted to adhere to the UPDRS mentation score to avoid heterogeneity with the results. However, we report that this is one limitation of the study, since Item

Table 4. Postoperative outcomes of Parkinson's disease patients after their last follow-up

Patient outcome	Result
Survival	64 (60.38)
Death	42 (39.62)
Worsening of symptoms	14
Pneumonia	14
Sepsis	2
Unknown cause	7
Other causes	5

Values are presented as number (%) or number only.

1 of the UPDRS is not specific and the data gathered may be underrepresented.

Our study showed that none of the patients developed severe dysphagia or cognitive impairment (UPDRS items 1 and 7, score of 4) over time, which is not consistent with previous reports.[5,11] We think that our data may be underrepresented because some of the patients may have died prior to developing the milestones. We can also say that those who did not develop severe dysphagia and cognitive impairment survived longer than those who did develop these symptoms.

Our findings are inconsistent with previous reports highlighting that clinical milestones will emerge after a PD diagnosis, either in sequence[12] or not,[5] and before death; seven out of the 42 patients who died in our study did not develop a single milestone and those who did develop a milestone did not develop all the milestones. Three of these patients had less than 6 years of follow-up, and we can assume that these patients did not have the chance to develop any milestones. On the other hand, our results support the concept of PD as a complex, multifactorial disease with clinical variability per individual;[15] hence, we do not expect all PD patients to develop the same symptoms. However, if clinical milestones are present, we can still use them as determinants of a patient's QoL.

Data from the current study showed a lower mortality compared to previously reported data.[16-19] This may be explained by several factors. First, there is an increasing life expectancy because of advancements in the field of medicine, with better treatments being readily accessible, leading to longer disease duration. Second, the overall mortality rate in South Korea is lower than that in other countries. Third, there might be selection bias in our study population since not all PD patients were eligible for DBS treatment. Fourth, the demographic data of our patients were different from those of patients in a previous study,[19] wherein there were more women and a lower mean age at surgery. We can assume that our data on mortality might not be representative of the entire PD patient population.

This study has several limitations. First, 17 of the 106 PD patients (16.0%) were lost to follow-up; therefore, some of the valuable clinical data were also lost. Second, we did not report on the other medications, such as anti-psychotics, used by the patients, which may affect the appearance of some milestones. Third, the 13-year follow-up period was chosen arbitrarily. This was the longest follow-up available during data collection because DBS was only started in our center in 2005. A previously published study had 15 years of follow-up, but it only had a small number of patients compared to ours. Fourth, the correlation between the development of the clinical milestones and the QoL of the patients would have emphasized the importance of the nonmotor and axial symptoms; however, this was not evaluated in this study. Last, the results cannot be directly applied to the general population of PD patients; there might be a possible selection bias since there was no control group with which to compare the results.

In conclusion, our findings suggest that STN-DBS has a limited effect on axial and nonmotor symptoms of PD in contrast to the effect on motor symptoms. These symptoms may serve as clinical milestones that can convey the status of PD patients and its impact on the patients and their caregivers. Therefore, advanced PD patients, even those treated with bilateral STN-DBS, will still require assistance and cannot live independently in the long run.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.21106.

Conflicts of Interest

The authors have no financial conflicts of interest.

Funding Statement

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Author Contributions

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Supplementary Table 1. Clinical variables of Parkinson's disease patients with deep brain stimulation of the subthalamic nucleus from baseline up to 13-years post-operative follow-up

Clinical variables	Before surgery	6 Months	1 Year	2 Years	3 Years	5 Years	7 Years	10 Years	13 Years*
LEDD (mg/day)	1,035.84 ± 516.80	393.99 ± 305.83	431.16 ± 350.07	472.64 ± 356.07	537.75 ± 411.53	667.05 ± 483.66	651.59 ± 427.17	614.06 ± 363.75	508.01 ± 280.78
UPDRS part 1 score	1.93 ± 2.12	2.33 ± 2.16	2.64 ± 2.42	2.51 ± 2.00	2.72 ± 2.54	3.22 ± 2.23	2.84 ± 2.27	3.47 ± 2.9	2.69 ± 2.46
UPDRS part 2 score	9.45 ± 7.31	9.2 ± 5.83	10.28 ± 6.91	10.39 ± 6.92	11.36 ± 7.49	15.55 ± 8.80	13.73 ± 7.07	17.27 ± 9.45	13.15 ± 10.25
UPDRS part 3 score	20.08 ± 11.59	15.15 ± 8.73	15.93 ± 8.85	15.91 ± 8.17	20.10 ± 11.02	23.81 ± 12.36	24.04 ± 11.18	27.17 ± 13.86	27.35 ± 10.69
Dyskinesia duration (hr)	4.52 ± 3.79	0.88 ± 2.01	0.87 ± 2.07	1.02 ± 2.80	1.15 ± 2.35	1.13 ± 2.72	1.13 ± 2.29	1.13 ± 3.19	1.06 ± 1.85
Off duration (hr)	6.30 ± 3.51	3.42 ± 3.71	3.55 ± 3.76	3.28 ± 3.63	3.57 ± 3.75	4.21 ± 4.15	4.49 ± 4.11	4.94 ± 4.44	6.6 ± 5.22
UPDRS total score	31.40 ± 15.71	26.82 ± 13.47	28.63 ± 14.53	29.06 ± 13.76	34.20 ± 17.81	42.54 ± 19.84	40.75 ± 16.22	48.11 ± 22.11	43.04 ± 18.71
H&Y score	2.33 ± 0.57	2.31 ± 0.62	2.34 ± 0.67	2.43 ± 0.53	2.58 ± 0.72	2.94 ± 0.87	2.73 ± 0.85	2.72 ± 0.72	2.81 ± 0.95

Data are presented as mean ± standard deviation. *17 patients reached 13-years post-operative follow-up during the study period and were included in the data set. LEDD, levodopa equivalent daily dose; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr.

Supplementary Table 2. Clinical milestones (moderately disabling) in Parkinson's disease patients with deep brain stimulation of the subthalamic nucleus from baseline up to 13-years post-operative follow-up

Clinical milestone	Before surgery	6 Months	1 Year	2 Years	3 Years	5 Years	7 Years	10 Years	13 Years*	Total
Hallucination	2	0	2	1	1	1	2	1	0	10
Dysarthria	4	3	4	8	3	4	3	10	0	39
Dysphagia	1	1	1	2	3	4	1	2	1	16
Frequent falling	14	5	3	5	5	10	11	3	1	57
Difficulty in walking	6	2	1	7	5	8	2	5	2	38
Cognitive impairment	0	1	0	1	0	0	0	0	0	2
Loss of autonomy	1	2	2	0	4	8	4	4	1	26

*17 patients reached 13-years post-operative follow-up during the study period and were included in the data set.

Supplementary Table 3. Clinical milestones (severely disabling) in Parkinson's disease patients with deep brain stimulation of the subthalamic nucleus from baseline up to 13-years post-operative follow-up

Clinical milestone	Before surgery	6 Months	1 Year	2 Years	3 Years	5 Years	7 Years	10 Years	13 Years*	Total
Hallucination	1	0	0	0	1	0	1	0	0	3
Dysarthria	2	1	0	0	2	4	2	2	0	13
Dysphagia	0	0	0	0	0	0	0	0	0	0
Frequent falling	9	3	4	2	3	9	4	5	1	40
Difficulty in walking	0	0	0	0	1	2	0	1	1	5
Cognitive impairment	0	1	0	1	0	0	0	0	0	0
Loss of autonomy	0	0	1	0	2	4	3	1	1	12

*17 patients reached 13-years post-operative follow-up during the study period and were included in the data set.

Supplementary Table 4. Log rank comparison of development of clinical milestones between sexes

Clinical milestone	Chi-square	Significance
Cognitive impairment	0.051	0.821
Hallucinations	0.331	0.565
Dysarthria	4.442	0.035
Dysphagia	5.136	0.023
Frequent falling	0.888	0.346
Difficulty in walking	1.584	0.208
Loss of autonomy	0.310	0.578
Milestone development	0.039	0.844
Death		
Years post DBS	0.044	0.834
Disease duration	0.172	0.679
Age in years	0.230	0.631

DBS, deep brain stimulation.