



## ORIGINAL ARTICLE

# Long-term Effects of Bilateral Subthalamic Deep Brain Stimulation on Postural Instability and Gait Difficulty in Patients with Parkinson's Disease

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**Objective** The long-term effects of bilateral subthalamic nucleus deep brain stimulation (STN-DBS) on postural instability and gait difficulty (PIGD) in patients with Parkinson's disease (PD) remain unclear. In this study, we aimed to evaluate the long-term effects of STN-DBS surgery on PIGD symptoms in patients with advanced-stage PD.

**Methods** This study included 49 consecutively included patients with PD who underwent bilateral STN-DBS. The Unified Parkinson's Disease Rating Scale (UPDRS) scores and subscores for PIGD were assessed at baseline and at 1, 3, and 5 years post-operatively. The PIGD subscore was divided into PIGD-motor and PIGD-activities of daily living (ADL) scores according to parts III and II of the UPDRS, respectively.

**Results** The PIGD-motor and PIGD-ADL scores at the "medication-off" state improved at 3 and 5 years, respectively. Overall, the UPDRS III and II scores at "medication-off" improved at 5 years. The UPDRS IV score also significantly improved and the levodopa equivalent daily dosage decreased at all follow-ups. Finally, the PIGD-motor score at baseline was able to predict long-term improvement in the PIGD-motor score at the 5-year follow-up.

**Conclusion** The STN-DBS has both short- and long-term effects on PIGD, as well as overall motor function, in patients with advanced PD. The degree of PIGD at the preoperative evaluation can be used to predict long-term outcomes after STN-DBS surgery.

**Key Words** Parkinson disease; Deep brain stimulation; Subthalamic nucleus; Postural instability; Gait difficulty.

High-frequency deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a well-established surgical therapy for patients with advanced Parkinson's disease (PD) and motor complications that cannot be adequately managed with medication.<sup>1</sup> It has been reported that beneficial effects of STN-DBS on the motor symptoms of PD can last for more than 5 years.<sup>2</sup> STN-DBS improves overall motor function in the "medication-off" state and reduces the severity of levodopa-induced dyskinesia. The criteria that clinicians commonly use to select pa-

tients who will likely have a successful outcome after DBS surgery include levodopa-responsive parkinsonian motor symptoms, medically intractable motor fluctuations, and the absence of active cognitive or psychiatric problems.<sup>3</sup> However, the effects of STN-DBS on postural instability and gait difficulty (PIGD) that have been reported in previous studies are inconsistent, even though patients eligible for surgery were included. Some studies have reported that there is little improvement in PIGD after STN-DBS surgery in patients with PD,<sup>4-8</sup> whereas in

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other studies, patients exhibited marked improvement in these symptoms.<sup>9-12</sup> This discrepancy suggests that it is necessary to investigate the factors related to patient outcomes after STN-DBS with regard to PIGD symptoms. Because mobility in the daily life of patients with PD is likely primarily limited by PIGD, the effects of STN-DBS on the mobility of patients with PD needs to be evaluated using measurements that specifically address PIGD to a greater extent than the total Unified Parkinson's Disease Rating Scale (UPDRS) score or scores for parts I-IV.

In our present study, therefore, we investigated the 5-year therapeutic effects of STN-DBS on PIGD and clinical factors of PIGD outcomes after STN-DBS in patients with PD.

## MATERIALS & METHODS

### Participants

We retrospectively reviewed 49 consecutively included patients with PD who underwent bilateral STN-DBS at the Asan Medical Center from 2005 to 2010. All patients with PD underwent DBS surgery according to the institutional guidelines for DBS surgery.<sup>13</sup> All patients showed improvement by more than 30% in the UPDRS III score in a preoperative levodopa test following a supratherapeutic dose based on the levodopa equivalent daily dosage (LEDD). STN-DBS surgery was performed in all patients.<sup>14</sup> All patients underwent STN-DBS on the more severely affected side first, followed by STN-DBS on the contralateral side three months later. Stereotaxic surgery using the Leksell G frame was performed with the patients under local anesthesia after the overnight withdrawal of any anti-Parkinsonian medications. We located the STN using MRI, electrophysiological recordings, and stimulation. Quadripolar electrodes (model 3389, Medtronic Inc., Minneapolis, MN, USA) were implanted and connected to a subcutaneous programmable pulse generator (Solectra TM; Medtronic). All patients underwent brain CT scans postoperatively to detect surgical complications.<sup>14</sup> The electrical parameters (voltage, pulse width, and frequency) and medication dosages were adjusted at every visit. The stimulation frequency and pulse width were set to be 130 Hz and 60  $\mu$ s, respectively. The amplitude of the stimulation voltage and stimulation contacts were adjusted so that there was optimal clinical improvement at each visit.

This study was approved by the institutional Review Board of Asan Medical Center (2014-0332). The board waived the requirement for informed consent from patient because this study was the retrospective and observational study.

### Clinical evaluations

The patients' demographic and clinical characteristics were recorded. The patients were assessed at baseline and postoper-

atively at 1, 3, and 5 years. All patients' clinical symptoms were assessed using the UPDRS during the "medication-off" and "medication-on" states preoperatively and during the "medication-off and stimulation-on" and "medication-on and stimulation-on" states postoperatively. All anti-Parkinsonian medications were discontinued for 12 h to determine UPDRS scores during the "medication-off" condition. The "medication-on" condition was considered the period after patients took 1.5 times their usual dose of levodopa. The specific PIGD-motor subscore was defined as the sum of the subscores for arising from chair (UPDRS part III item 27), posture (UPDRS part III item 28), gait (UPDRS III item 29), and postural instability (UPDRS III item 30). The PIGD-activities of daily living (PIGD-ADL) score was defined as the sum of the subscores for episodes of freezing (UPDRS II item 13), falls (UPDRS II item 14), and walking ability (UPDRS II item 15) during ADL.

### Statistical analyses

The PIGD scores from the same patient were assumed to be correlated and were considered repeated measures. Therefore, a linear mixed model with the Dunnett correction for multiple comparisons was performed to examine the changes in the mean scores for PIGD across time points. A multivariate stepwise regression analysis was performed to predict the long-term effect of STN-DBS on the percent change in the PIGD-motor and ADL scores from baseline to the 5-year follow-up. All data were analyzed using SAS 9.4 (SAS Institute, Cary, NC, USA) with a two-sided test, and the level of statistical significance was set to be  $p < 0.05$ .

## RESULTS

### Baseline characteristics

The mean age of the study subjects at the time of STN-DBS surgery was 59.5 years (range 38-76 years). The mean durations of PD and levodopa treatment at the operation were  $15.9 \pm 4.2$  years and  $10.2 \pm 3.2$  years, respectively (Table 1). All 49 patients were evaluated preoperatively and at 1 year; 37 and 21 patients were evaluated at 3 and 5 years, respectively. Seven patients died within 5 years of the treatment, and 20 patients were evaluated at all four time points. There were no significant differences in any of the clinical characteristics between the patients who completed all the follow-ups and those who were lost to follow-up.

### Clinical outcomes

A linear mixed model for repeated measures showed that the mean PIGD-motor and PIGD-ADL scores in the "medication-off" state improved with time ( $p < 0.0001$ ) (Figure 1).

Both the PIGD-motor and ADL scores in the “medication-off” state showed significant improvement at postoperative 1, 3, and 5 years compared to baseline ( $p < 0.0001$ ,  $p < 0.0001$ , and  $p = 0.0165$ , respectively, for the PIGD-motor score;  $p < 0.0001$ ,  $p < 0.0001$ , and  $p = 0.0004$ , respectively, for the PIGD-ADL score) (Figure 1). The mean PIGD-motor scores in the “medication-on” state worsened with time ( $p = 0.0012$ ) (Figure 1A), whereas the PIGD-ADL scores were comparable at all time points ( $p = 0.1337$ ) (Figure 1B). When the PIGD-motor scores were separated into postural instability (items 27 and 30), gait (item 29), and postural scores (item 28), the postural score in the “medication-on” state appeared to worsen with time, but the other scores did not appear to differ across the follow-ups.

The total UPDRS III and II scores in the “medication-off” state showed significant improvement with time ( $p < 0.0001$ ) (Table 2). However, the UPDRS III and II scores in the “medi-

ation-on” state worsened with time ( $p < 0.0001$ ,  $p = 0.0004$ , respectively) (Table 2). The UPDRS IV scores improved over the follow-up period ( $p < 0.0001$ ). A separate analysis of the dyskinesia part of the UPDRS IV demonstrated that the scores decreased with time ( $p < 0.0001$ ), and the scores at postoperative 5 years were comparable with the baseline scores ( $p = 0.1771$ ) (Table 2). In addition, the LEDD significantly decreased with time postoperatively ( $p < 0.0001$ ) (Table 2).

### Factor related to improvement in PIGD

There were significant correlations between the amount of improvement in the PIGD-motor score at 5 years and that in the PIGD-motor ( $\rho = 0.551$ ,  $p = 0.01$ ) and levodopa responsiveness scores in the UPDRS III ( $\rho = -0.496$ ,  $p = 0.022$ ) at baseline. Improvement in the PIGD motor at 5 years was not correlated with any other variables, including the preoperative UPDRS II and III scores, patient age, disease duration, or changes in the levodopa-equivalent dosage. A multivariable stepwise regression analysis revealed that the preoperative PIGD-motor score remained predictive of the long-term effect of STN-DBS on the PIGD-motor score ( $R^2 = 0.424$ ,  $p = 0.007$ ). The preoperative levodopa responsiveness score in the UPDRS III was excluded from the regression analysis. Improvement in the PIGD-ADL score at 5 years was not significantly correlated with any variable.

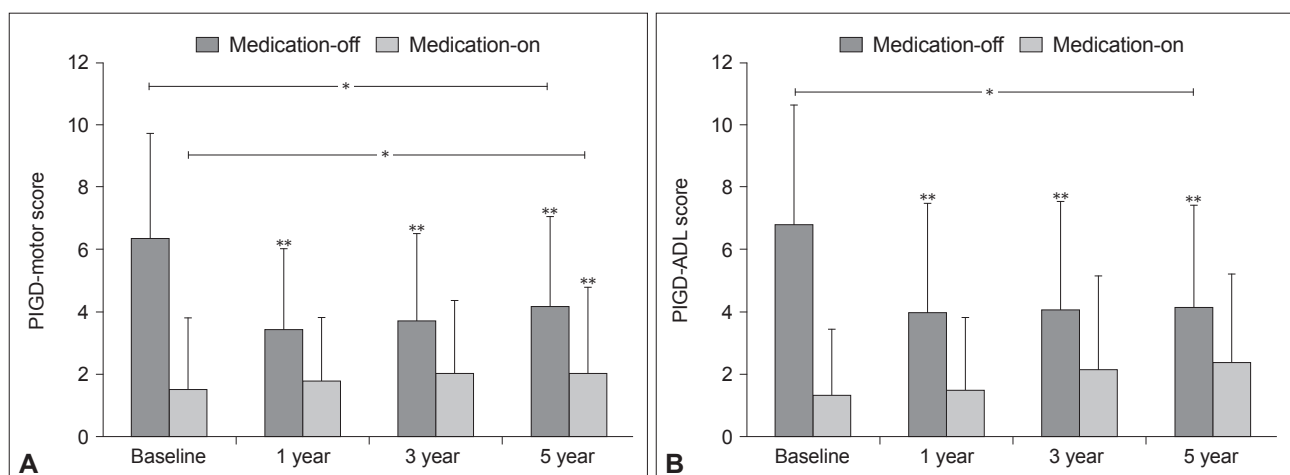
**Table 1.** Baseline demographic characteristics of the patients at the time of surgery

Characteristics	
Male/female, n (%)	18/31 (37/63)
Age (years)	59.5 (38–76)
Age at onset (years)	43.5 (27–63)
Disease duration at operation (years)	15.9 ± 4.2
Levodopa treatment duration at operation (years)	10.2 ± 3.2
Hoehn & Yahr stage	2.3 ± 0.5
K-MMSE	27.1 ± 2.1
LEDD (mg/day)	1181.8 ± 420.8

The results are reported as median (range) or the means ± standard deviations unless otherwise indicated. K-MMSE: Korean version of Mini-Mental Status Examination, LEDD: levodopa equivalent daily dosage.

### DISCUSSION

In this study, we evaluated the long-term effects of STN-DBS on PIGD and clinical factors of PIGD outcomes after STN-



**Figure 1.** Comparison of the postoperative PIGD-motor (A) and PIGD-ADL (B) scores with those recorded at baseline. The PIGD-motor and PIGD-ADL scores in the “medication-off” state significantly improved over the follow-up period and at each follow-up after surgery involving deep brain stimulation of the subthalamic nucleus. The PIGD-motor score worsened, whereas the PIGD-ADL score was comparable in the “medication-on” period over the follow-up period. \* $p < 0.0001$  for the mean equality of the score across the time points, \*\* $p < 0.0001$  for the mean difference in the score from baseline to each of time points using Dunnett’s test for multiple comparisons. ADL: activities of daily living, PIGD: postural instability and gait difficulty.

**Table 2.** Comparison of the motor and activities of daily living scores at each follow-up compared to baseline

	Baseline (n = 49)		1 year (n = 49)		3 years (n = 37)		5 years (n = 21)		p value*
	Mean ± SD	Mean ± SD	p value	Mean ± SD	p value	Mean ± SD	p value		
<b>Medication-off</b>									
UPDRS II	22.49 ± 7.68	13.92 ± 5.97	<0.0010	13.92 ± 7.73	<0.0010	15.10 ± 6.87	0.0050	<0.0001	
UPDRS III	39.70 ± 10.65	21.62 ± 9.81	<0.0010	23.49 ± 10.24	<0.0010	19.43 ± 13.12	<0.0010	<0.0001	
<b>Medication-on</b>									
UPDRS II	5.23 ± 4.49	7.65 ± 4.91	0.0120	7.76 ± 5.19	0.0128	8.57 ± 6.04	0.0010	0.0004	
UPDRS III	11.07 ± 7.63	16.12 ± 9.39	0.0001	14.81 ± 8.05	0.0014	14.90 ± 9.34	0.0002	<0.0001	
UPDRS IV	8.71 ± 3.27	4.08 ± 2.89	<0.0001	2.35 ± 2.02	<0.0001	5.33 ± 3.38	<0.0001	<0.0001	
UPDRS IV-dyskinesia	3.37 ± 2.56	1.63 ± 1.76	<0.0001	1.84 ± 1.83	0.0018	2.52 ± 2.02	0.1771	<0.0001	
LEDD	1181.77 ± 420.82	931.77 ± 418.00	0.0002	897.06 ± 459.88	0.0001	851.79 ± 357.53	0.0009	<0.0001	

All *p*-values were calculated by a linear mixed model using a random intercept model for repeated measures. \**p*-value for the mean equality of the score across the time points. *p*-value for the mean difference in the score from baseline to each of the time points using Dunnett's test for multiple comparisons. UPDRS: Unified Parkinson's Disease Rating Scale, LEDD: levodopa equivalent daily dosage, SD: standard deviation.

DBS in patients with PD. The main findings from this study were as follows: 1) STN-DBS improved the PIGD-motor and ADL scores in the “medication-off” state over 5 years in patients with advanced PD. 2) The PIGD-motor scores at baseline predicted the long-term improvement in the PIGD-motor scores at 5 years after STN-DBS surgery. 3) STN-DBS improved the UPDRS II and III scores in the “medication-off” state over 5 years. 4) The PIGD-motor score in the “medication-on” state worsened over time, along with the UPDRS II and III scores.

These results suggest that STN-DBS may have long-term effects on PIGD symptoms in the “medication-off” state regarding both ADL and motor function. The effects of STN-DBS on PIGD are in line with the long-term improvement observed in the overall motor symptoms and independence in ADL of the patients in the “medication-off” state. A recent meta-analysis showed that bilateral STN-DBS improves gait performance and reduces the severity of freezing of gait (FOG), as measured by item 29 of the UPDRS III (gait) and item 14 of the UPDRS II (freezing when walking), respectively, for as many as 4 years.<sup>15</sup> We used items 27 (arising from chair), 30 (postural instability), 28 (posture) and 29 (gait) from the UPDRS III to assess postural instability. From the UPDRS II, items 13 (falling unrelated to freezing), 14 (freezing when walking), and 15 (walking) were used to calculate the PIGD-ADL score. Improvement in the PIGD-ADL score, as well as the PIGD-motor score, was observed, supporting the hypothesis that STN-DBS is effective in improving mobility in advanced patients with PD. Although the overall motor symptoms and independence in ADL in patients with PD have been evaluated using the UPDRS in most studies, the clinical parameters used to evaluate PIGD symptoms have not been well validated.<sup>16-22</sup> Various clinical and physiological tools have been suggested for measuring PIGD symptoms, including postural instability and

FOG.<sup>23</sup> Moreover, wearable devices that measure patients' motor function, including gait function, have been increasingly utilized in research.<sup>24</sup> However, the lack of standardized clinical assessment tools may result in inconsistent findings regarding the effects of STN-DBS on PIGD symptoms in patients with PD.<sup>23</sup> Although the PIGD-motor and ADL scores extracted from the UPDRS scores have not been validated, it may be worthwhile to evaluate the PIGD symptoms because the PIGD-motor score addresses the severity of gait dysfunction (item 29), posture (item 28), and postural instability (items 27 and 30). Moreover, the PIGD-ADL scores address the frequency at which FOG (item 14), gait difficulty (item 15), and falls (item 13) occur in everyday life. Objective tools for measuring PIGD parameters, such as gait parameters, are lacking, which remains a limitation of this study. Therefore, additional research needs to be conducted to establish a tool that can accurately assess PIGD in patients with PD.

In our study, the PIGD-motor scores at baseline predicted the long-term outcomes of patients, i.e., the PIGD-motor scores at 5 years after STN-DBS surgery. Regarding predictive factors of the effect of STN-DBS on PIGD in patients with PD, the levodopa responsiveness score in the UPDRS III scale at baseline was suggested to be the most significant predictor of gait performance and FOG in a previous meta-analysis study.<sup>15</sup> Another study showed that the preoperative PIGD scores and dosages of medication differed between patients with and without PIGD symptoms that progressed within 8 years after surgery.<sup>11</sup> Because the consensus guidelines for DBS surgery in patients with PD do not specify selection criteria in terms of PIGD,<sup>3</sup> our results may provide useful evidence for the selection of patients for DBS surgery and may aid in planning the long-term treatment of patients with PD who undergo STN-DBS surgery.

In our study, the PIGD-motor scores in the “medication-on”

state worsened over the follow-up period. Worsening of the scores was observed at postoperative 3 and 5 years, whereas no changes were observed at postoperative 1 year. Each item representing postural instability (items 27 and 30), gait (item 29), and posture (item 28) showed that the postural score only worsened with time in the “medication-on” state, whereas the scores for gait and postural instability did not change across the follow-ups. Deficits in posture can be complicated by other factors, including levodopa-induced axial dystonia, and other musculoskeletal problems can possibly affect the postural score. Thus, we suggest that the worsening of the PIGD-motor symptoms in the “medication-on” state can be related to levodopa-induced axial dystonia. The PIGD-ADL score in the “medication-on” state did not change during the follow-up period. The UPDRS III and II scores representing overall motor function worsened in the “medication-on” state after STN-DBS surgery. It is believed that STN-DBS acts on the dopaminergic motor system in a similar manner as dopaminergic medication.<sup>2,25</sup> Accordingly, the additive benefits of dopaminergic medications and STN-DBS surgery have not been expected, and motor function in the “medication-on and stimulation-on” state has not been found to change postoperatively.<sup>2</sup> In the patients in our study, the LEDD decreased by 21%, 24% and 25% at 1, 3 and 5 years, respectively, compared to baseline. The patients in our study had relatively long durations of the disease (mean 15.9 years), so the reduction in the LEDD might affect the PIGD-motor and UPDRS III and II scores more in these patients than in patients who have shorter disease durations.<sup>26</sup> Indeed, the UPDRS IV scores, particularly those concerning dyskinesia, were significantly lower by approximately 50% at all follow-ups than at baseline. This result suggests that the reduction in the LEDD in the patients in our study might not have been sufficient to induce a fully “medication-on” state, resulting in the worsening of the PIGD-motor and UPDRS III and II scores in the “medication-on” state.

Our findings are consistent with the results of previous studies, which reported that bilateral STN-DBS has long-term favorable effects on PIGD or axial symptoms, in addition to long-term beneficial effects on patients’ overall motor symptoms.<sup>9-12,15,27</sup> Contrary to our study, other studies have reported that bilateral STN-DBS improves PIGD or axial levodopa-responsive symptoms for as long as 1 year but that these effects diminish in the long term.<sup>4,5,7,8</sup> Although it is well known that dopaminergic treatment positively affects appendicular parkinsonian symptoms, PIGD has been found to be resistant to dopaminergic medication.<sup>28</sup> In addition to dopaminergic neuronal degeneration, cholinergic neuronal loss in the pedunculopontine nucleus has been suggested to play a major role in PIGD in patients with PD.<sup>29</sup> As PD progresses, neurodegeneration beyond the dopaminergic

neurons becomes prominent, which can explain why levodopa is less effective in reducing PIGD symptoms in advanced-stage PD patients than in early-stage PD patients.<sup>30</sup> The mechanism of STN-DBS involves the dopaminergic motor system,<sup>2</sup> and patients with levodopa-resistant PIGD symptoms may show limited benefits from STN-DBS surgery. All the PD patients in our study showed improvement in the PIGD-motor scores after consuming levodopa in the preoperative examination. Considering the mechanism of action of STN-DBS, the preoperative levodopa responsiveness of PIGD symptoms in our study population can be attributable to the favorable outcomes of STN-DBS surgery in the PD patients in our study. A study with a follow-up period of more than 5 years showed that STN-DBS improves PIGD for 5 years, at which point the effect declines.<sup>10</sup> Follow-up periods of more than 5 years are necessary to determine the outcomes of the patients in our study.

This study has some notable limitations. First, all patients who underwent STN-DBS surgery did not undergo long-term evaluations. Patients who had relatively better mobility were more likely to participate in the evaluation than those with poorer mobility, which may have affected the proportion of favorable outcomes after STN-DBS surgery regarding PIGD that was observed in our study. The lack of differences in the clinical characteristics before surgery between groups who did and did not complete the follow-ups can account for this limitation. Second, PIGD was assessed using only UPDRS subscores. A specific assessment tool for PIGD symptoms and objective gait analysis with a detailed computational program may be necessary for future studies. Last, we did not analyze PIGD symptoms separately according to their levodopa responsiveness; instead, we grouped all symptoms into one parameter using the UPDRS score. Therefore, this study can be considered a preliminary study, and the effects of STN-DBS on levodopa-responsive or nonresponsive PIGD symptoms should be assessed in the future.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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### Author Contributions

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