Determination of Parkinson Disease Laterality After Deep Brain Stimulation Using ^{123}I FP-CIT SPECT

Hye Ran Park, MD, PhD, Seunggyun Ha, MD, PhD,†‡ Dong Soo Lee, MD, PhD,‡§ Hyung-Jun Im, MD, PhD,§ and Sun Ha Paek, MD, PhD||¶*

Introduction: Symptom laterality is one of the main characteristics of Parkinson disease (PD) and reported to be associated with motor and nonmotor symptom severity and prognosis. This study aimed to evaluate the changes of laterality after deep brain stimulation (DBS) and the association between dopamine transporter SPECT using ^{123}I FP-CIT (DAT SPECT) and symptom laterality in PD before and after DBS.

Methods: Nineteen patients with PD who received bilateral subthalamic nucleus DBS were enrolled. The clinical scores including Unified Parkinson Disease Rating Scale (UPDRS) and Hoehn and Yahr were evaluated at baseline, 6 months, and 1 year after DBS. Also, the patients underwent DAT SPECT before and 6 months and 1 year after DBS. Symptom and DAT laterality indices were determined based on the UPDRS part 3 and DAT SPECT, respectively. The association between DAT and symptom laterality was assessed at baseline and 6 months and 1 year after DBS.

Results: At baseline, 11, 6, and 2 among 19 patients had left-side–dominant, right-side–dominant, and symmetric motor symptom, respectively. Among 19 patients, there were 10 patients who showed changed symptom laterality within 1 year after DBS. The agreement between symptom laterality and DAT laterality was good to excellent at baseline and 6 months and 1 year after DBS (weighted $\kappa = 0.742$, 0.736, and 0.813). Furthermore, symptom and DAT laterality indices showed significant correlation at baseline ($r = 0.542$, $P = 0.02$), 6 months ($r = 0.579$, $P = 0.01$), and 1 year after DBS ($r = 0.689$, $P = 0.02$). Symptom laterality could be determined by DAT laterality index with areas under curve of 0.833 ($P = 0.045$), 0.982 ($P < 0.001$), and 1.000 ($P < 0.001$) at baseline and 6 and 12 months after DBS, respectively.

Conclusions: The symptom laterality could be altered after DBS and was well correlated with laterality evaluated by DAT SPECT. An objective evaluation of laterality using DAT SPECT would be helpful for the management of patients with PD especially for adjusting the DBS programming for fine balancing of the asymmetric symptom after DBS. The large-scale study is warranted for validation of this result.

Key Words: deep brain stimulation, dopamine transporter, laterality, Parkinson disease, SPECT

(*Clin Nucl Med* 2020;00: 00–00)

Parkinson disease (PD) is a neurodegenerative disorder that affects predominately dopaminergic neurons in substantia nigra.[1] Parkinson disease is characterized by a unilateral onset and persisting asymmetry of motor symptoms. The laterality of motor symptom has been reported to have associations with motor and nonmotor symptoms and prognosis.[2–5] The laterality of PD patients is clinically determined by Unified Parkinson Disease Rating Scale (UPDRS) motor score and could be evaluated by neuroimaging techniques including magnetoencephalography, MRI, and dopamine transporter (DAT) imaging by SPECT or PET.[6–8]

Deep brain stimulation (DBS) is a neurosurgical procedure that includes implantation of electrodes to produce chronic electrical stimulation at specific brain regions.[9] Deep brain stimulation had shown efficacy in the alleviation of symptoms in advanced PD.[10] In a recent randomized clinical trial of patients with relatively early PD, the DBS group showed better quality of life and motor function than medication-only group in 2-year follow-up.[11] Also in a pilot trial, early DBS group showed a slower progression of rest tremor than the medication-only group, which was assessed in off-medication and off-stimulation state.[12] Furthermore, DBS provides the opportunity to modify stimulation parameters in each hemisphere separately in contrast to medication, which is a huge advantage of DBS in managing lateralized motor symptom.[13] While unilateral DBS can be applied to highly asymmetric patients,[14] the baseline laterality is an important factor for the effectiveness and decision-making process between unilateral and bilateral DBS.[15] Also, Ehm et al[16] reported that 7 of 8 PD patients with highly asymmetrical symptoms who underwent unilateral DBS showed aggravation of the ipsilateral symptom after the initial surgery while the motor benefit in the contralateral symptom remained. Four of them underwent a second surgery about 5 years after the initial surgery.[16] In addition, the DBS programming is a time-consuming task, and the patients suffer during the period. Once the DBS lead is placed on the target using standard surgical techniques, DBS programming begins within a week. The initial DBS programming setting usually takes 3 to 6 months, and the patients should visit the hospital almost

Received for publication July 22, 2019; revision accepted December 3, 2019.
From the *Department of Neurosurgery, Soonchunhyang University Seoul Hospital; †Division of Nuclear Medicine, Department of Radiology, Seoul St Mary's Hospital, The Catholic University of Korea; ‡Department of Nuclear Medicine, Seoul National University College of Medicine; §Graduate School of Convergence Science and Technology, Seoul National University; ||Department of Neurosurgery, Clinical Research Institute, Seoul National University Hospital; and ¶Hypoxia/Ischemia Disease Institute, Seoul National University College of Medicine, Seoul, Republic of Korea.
Conflicts of interest and sources of funding: This study was supported by the Korea Healthcare Technology R&D Project (grant HI11C21100200, HI18C0886), funded by the Ministry of Health & Welfare, Republic of Korea; the Industrial Strategic Technology Development Program (grant 10050154, Business Model Development for Personalized Medicine Based on Integrated Genome and Clinical Information) funded by the Ministry of Trade, Industry & Energy (MI, Korea); the Original Technology Research Program for Brain Science through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (grant 2015M3C7A1028926, 2017M3C7A1044367); the Original Technology Research Program for Brain Science through the NRF funded by the Ministry of Education, Science and Technology (2017M3C7A1047392); Basic Science Research Program through the NRF funded by the Ministry of Education (NRF-2017R1D1A1B03035556); and Soonchunhyang University research fund. This work was also supported by the Research Resettlement Fund for the new faculty of Seoul National University. None declared to all authors.
Authors' Contributions: S.H.P., H.-J.I., and D.S.L. conceptualized the study. H.R.P. and S.H. did the statistical analysis. H.R.P. and H.-J.I. wrote the manuscript. H.-J.I. and H.R.P. revised the manuscript.
Correspondence to: Hyung-Jun Im, MD, PhD, Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Gwanak-ro 1, Gwanak-gu, Seoul 08826, Korea. E-mail: iiihjjj@gmail.com; or Sun Ha Paek, MD, PhD, Department of Neurosurgery, Seoul National University Hospital, 28 Yongon-Dong, Jongno-Gu, Seoul 110-744, Korea. E-mail: paeksh@snu.ac.kr.
Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.nuclearmed.com).

ISSN: 0363-9762/20/0000–0000
DOI: 10.1097/RLU.0000000000002955

every month during this period. In addition, the parameters should be adjusted at intervals of 6 to 12 months afterward.[17–19] In this regard, dynamic and objective evaluation of laterality could be important information for managing asymmetric motor symptoms of PD before and after DBS. However, the impact of bilateral DBS on symptom laterality and the role of neuroimaging on it have not been well evaluated.

Herein, we evaluated the dynamic change of the symptom laterality after bilateral DBS and the role of DAT SPECT in the assessment of the symptom laterality before and after DBS. We hypothesized that the symptom laterality can be changed after the bilateral DBS and DAT SPECT can reflect the alteration of the symptom laterality after DBS.

METHODS

Patients

Nineteen patients with PD were enrolled in the study (Fig. S1, Supplemental Digital Content 1, http://links.lww.com/CNM/A231). The patients underwent bilateral subthalamic nucleus (STN) DBS. The patients underwent DAT SPECT before DBS and 6 and 12 months after DBS. Also at the same time point, clinical evaluation was performed including UPDRS, Hoehn and Yahr (H&Y) score, and levodopa equivalent daily dose (LEDD). The retrospective study using the Seoul National University Hospital cohort was approved by the institutional review board of our institute, and informed consent was waived because of the retrospective design. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Surgery

Bilateral simultaneous STN DBS implantations were done in all patients as previously described.[20] In brief, the STN was located by stereotactic target planning with MRI using SurgiPlan software and electrophysiological monitoring (microrecording and electric stimulation). The electrode for stimulation was inserted at the precisely localized STN. An implantable pulse generator was implanted in the subclavicular area, and the electrode was connected to the generator under general anesthesia.

UPDRS Score

Clinical evaluation was performed according to the previously described movement disorder center protocol.[21] Preoperative evaluations were done for 3 days while the patients were admitted to the movement disorder center. Motor tasks of the patients were videotaped, and UPDRS and H&Y stage were evaluated on-medication and off-medication. In the motor UPDRS score, half point was allowed. The LEDD was also calculated. Postoperative evaluation was carried out at 6 and 12 months after the surgery. The postoperative motor UPDRS scores were checked in both on- and off-medication states with the on- and off-stimulation. Off-stimulation values were obtained at least 30 minutes after the switching off of the stimulator. Motor symptoms were assessed using the revised Movement Disorder Society UPDRS part 3 (UPDRS-III) at baseline and 6 and 12 months after DBS. Symptom laterality index was calculated by the absolute difference of the left- and right-sided motor score (left − right) in UPDRS-III during off-medication and off-stimulation, and symptom laterality was determined as left dominant when the index is positive, right dominant when the index is negative, and symmetric when the index is zero. Deep brain stimulation parameters were adjusted according to the clinical symptom (Table S1, Supplemental Digital Content 2, http://links.lww.com/CNM/A232).

DAT SPECT and Analysis

SPECT images were acquired by a dedicated triple-head gamma camera (TRIONIX Triad XLT 3; Trionix Research Laboratory, Inc, Twinsburg, Ohio) with Fan-Beam collimator. Patients were intravenously injected 185 MBq (range, 170–200 MBq) of ^{123}I FP-CIT. The baseline DAT SPECT was performed at median of 5 days before the DBS. The follow-up DAT SPECT scans were obtained at median of 26 and 55 days after the clinical tests were done 6 and 12 months after DBS, respectively. Dopamine transporter SPECT was performed in on-medication state at baseline and in on-medication and on-stimulation state at post-DBS. Three hours after the injection, images were acquired with the image parameters of 40 step-and-shoot for 45 seconds per each step. Images were reconstructed as follows: (1) 128 × 128 matrices, (2) filtered back projection, (3) Butterworth filter with high cut frequency of 0.4 and roll-off degree of 5.0, and (4) Chang's method for attenuation correction. Spatial normalization was performed in Statistical Parametric Mapping (SPM8; University College of London, London, UK) using an in-house template with Montreal Neurological Institute space. Mean uptakes of both caudoputamen (CP) and occipital cortex were measured using volume of interest (VOI) from the Korean Structural Statistical Probabilistic Anatomical Map.[22] Specific binding values of both CPs were calculated using the occipital cortex as reference tissue.[23,24] Specific binding value of CP was calculated as follows: [(mean counts of the CP VOI − mean counts of occipital cortex VOI)/(mean counts of the occipital cortex VOI)].[23] Dopamine transporter laterality index was calculated as left CP-specific binding value / right CP-specific binding value. FP-CIT laterality was determined as left dominant when the index is greater than 1 and as right dominant when the index is lower than 1.

Statistical Analysis

Nonparametric tests were used for the analysis because of the small number of subjects. Spearman test was performed to show the correlation between the 2 measurements. Receiver operating characteristic analysis was done to evaluate the performance of DAT laterality index to determine symptom laterality of the patients. The optimized cutoff was determined based on the Youden index. Weighted κ value was used to demonstrate the agreement between the 2 classifications. All statistical analyses were performed using

TABLE 1. Patients Characteristics

Baseline Characteristics	Value
Age, mean (range), y	57 (41–68)
Sex, n (%)	
Male	10 (53)
Female	9 (47)
Duration of symptom, mean (range), y	11.5 (6–23)
Duration of levodopa, mean (range), y	11.2 (5–23)
UPDRS total, mean (range)	Mx On: 33.7 (0–72) Mx Off: 71.6 (37–126)
H&Y, mean (range)	Mx On: 2.43 (0–3) Mx Off: 2.97 (1.5–5)
LEDD, mean (range), mg/d	1449 (465–2075)

Mx Off indicates off-medication; Mx On, on-medication.

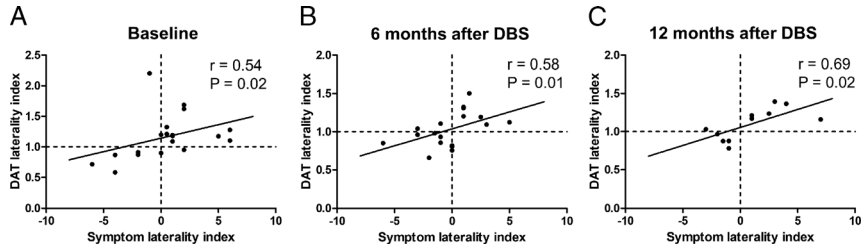

FIGURE 1. Correlation between DAT and symptom laterality at baseline (**A**) and 6 and 12 months after DBS (**B**, **C**). Of note, symptom laterality index was calculated off-medication and off-stimulation.

SPSS software (SPSS Inc, Chicago, Ill). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics of the Patients

The patient characteristics are summarized in Table 1. Mean age of the patients was 57 years. The duration of motor symptom ranged from 6 to 23 years (mean, 11.5 years). Fourteen patients started levodopa treatment at the same year of motor symptom onset. Whereas 3 patients started levodopa treatment 1 year after the symptom onset, 1 patient started 2 years after the symptom onset. The mean UPDRS total and H&Y scores were 33.7 and 2.43 on-medication and 71.6 and 2.97 off-medication, respectively. The mean specific binding value of both CPs ranging from 0.14 to 3.50 (mean, 1.21) was well correlated with duration of symptom onset and the length of levodopa usage (Fig. S2, Supplemental Digital Content 3, http://links.lww.com/CNM/A233).

Association of Symptom Laterality and DAT Laterality

At baseline, symptom laterality index and DAT laterality index showed significant correlation either on- or off-medication ($P = 0.015$, 0.017, respectively) (Fig. 1A, Table 2). Interestingly, the DAT laterality index was well correlated with the symptom laterality index even 6 and 12 months after DBS. Six months after DBS, the correlation was significant or trended toward significance regardless of stimulation or medication status ([r, P] = [0.682, 0.01] at on-medication on-stimulation, [0.565, 0.07] at on-medication off-stimulation, [0.496, 0.043] at off-medication on-stimulation, and [0.579, 0.01] at off-medication off-stimulation; Fig. 1B, Table 2). Also, the correlation was significant at 12 months after DBS (Fig. 1C, Table 2). Further analysis was done using off-medication score at baseline and off-medication/off-stimulation score at 6 and 12 months after DBS, assuming that off-medication/off-stimulation scores may be the most accurate surrogate of the disease status. Interestingly, the symptom laterality of the patients was altered in 10 among 19 patients during the 12-month period after DBS (Fig. 2, Table S2, Supplemental Digital Content 4, http://links.lww.com/CNM/A234). When the baseline characteristics of altered and unaltered patients were compared, there was no significant difference in onset duration, baseline UPDRS total, symptom laterality index (absolute value), H&Y, and LEDD. However, the DAT laterality index at baseline was higher in the unaltered patients ($P = 0.043$), indicating patients with more symmetric DAT uptake in both striatum are more prone to experience alteration of laterality after DBS. We assessed the agreements between DAT laterality and symptom laterality, which were found to be good to excellent at baseline and 6 and 12 months after DBS. The weighted κ values were 0.742, 0.736, and 0.813, respectively (Table 3). We further assessed the performance of DAT laterality index for determination of symptom laterality. The areas under the curve (AUCs) of DAT laterality index to determine symptom laterality (off-medication, off-stimulation) were 0.833 (confidence interval [CI], 0.577–0.966; $P = 0.046$), 0.982 (CI, 0.752–1.000; $P < 0.001$), and 1.000 (CI, 0.715–1.000; $P < 0.001$) at baseline and 6 and 12 months after DBS, respectively (Figs. 3A–C). Meanwhile, AUCs of DAT laterality index to determine symptom laterality (on-medication, on-stimulation) were 0.920 (CI, 0.663–0.997; $P < 0.001$), 0.933 (CI, 0.653–0.999; $P < 0.0001$), and 0.667 (0.334–0.908; $P = 0.438$) at baseline and 6 and 12 months after DBS, respectively (Figs. 3D–F). In addition, the optimized cutoffs for the best determination of symptom laterality were 0.91, 1.04, 1.03, 0.91, 0.85, and 0.88, respectively (Figs. 3A–F). Interestingly, DAT laterality index was more predictable for symptom laterality at off-medication and off-stimulation state than that at on-medication and on-stimulation state 12 months after DBS (AUC, 1.000 vs 0.667). Even though a patient experienced alteration of symptom laterality after DBS, DAT SPECT and DAT laterality index could reflect the alteration correctly (Fig. 4).

DISCUSSION

We found that the symptom laterality of PD can be changed after DBS. The symptom laterality was associated with the DAT laterality not only at baseline, but also at 6 and 12 months after DBS.

TABLE 2. Correlation Between Symptom Laterality Index and DAT Laterality Index

	Baseline			6 mo After DBS		12 mo After DBS	
	r	*P*		*r*	*P*	*r*	*P*
On-medication	0.549	0.015	On-stimulation	0.682	0.010	0.596	0.069
			Off-stimulation	0.565	0.070	0.635	0.036
Off-medication	0.542	0.017	On-stimulation	0.496	0.043	0.604	0.049
			Off-stimulation	0.579	0.012	0.689	0.019

DAT indicates dopamine transporter; *r*, correlation coefficient.

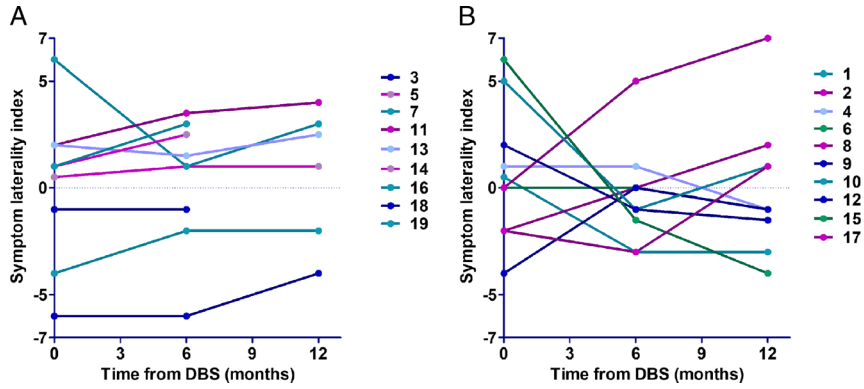

FIGURE 2. Symptom laterality index changes in patients with altered (**A**) and unaltered laterality (**B**) after DBS. Of note, symptom laterality index was calculated off-medication and off-stimulation.

These results indicate that DAT SPECT can reflect the dynamic change of PD laterality after DBS.

Deep brain stimulation was first applied to PD patients to alleviate motor symptoms in 1993, and DBS has been reported to be effective, safe, and durable in many studies including large-scale, randomized controlled clinical trials.[10,11,25] The first randomized trial was performed in 156 patients with advanced PD. The patients were randomly assigned to receive bilateral DBS of the STN or medication therapy. At 6 months, patients who received DBS had significantly better quality of life and motor scores compared with the ones who received medication only. The most beneficial effect of DBS was the improvement of motor function in the off state (when the effect of medication is the lowest).[10] More recently, a randomized trial in early PD patients also showed alleviated motor symptoms, better quality of life, and less levodopa-induced motor complications in the DBS group at 2-year follow-up.[11] Furthermore, it has been suggested that DBS could slow the progression. A prospective pilot clinical study randomized the 28 enrolled patients with early PD to receive DBS plus medication or medication only. At 6, 12, 18, and 24 months after the randomization, UPDRS-III was compared at the eighth day after 7 days of off-medication and off-stimulation. Interestingly, DBS plus medication group showed a lower rest tremor score change from baseline to 2 years and fewer new tremor symptoms compared with the medication-only group.[12] Because the patients were not randomized to have a control group in this study, the ability of DBS to slow the progression of neurodegeneration could not be evaluated. However, we were able to observe a significant level of alteration of DAT laterality index after DBS, which may be caused by different beneficial effects of DBS to both striatum.

Symptom asymmetry of PD is rooted from asymmetrical involvement of neuronal degeneration in the PD. In most cases of PD, symptoms begin on one side of the body and spread to the other side of the body.[26] The asymmetry is diagnostically important because it is a point of differential diagnosis from other types of neurodegenerative disorders such as multiple system atrophy, supranuclear palsy,[27] and essential tremor.[28] More recently, laterality has been found to be associated with prognosis of motor symptom, cognitive function, and nonmotor symptom such as psychosis.[29] Baumann et al[4] reported that PD patients with right-side–dominant symptom showed more rapid progression of the motor symptoms than the ones with left-side dominance. Frazzitta et al[30] reported patients with right-side–dominant symptom showed decreased muscle strength compared with patients with left-side–dominant symptom. Also, left-side–dominant symptom showed association with a longer survival after diagnosis and delayed ambulatory inhibition compared with right-side–dominant symptom.[31] The patients with right-side–dominant symptom experience more difficulties in attention and working memory.[32] Also, patients with extreme right-side–dominant symptom had more psychosis compared with the patients with left-dominant symptom.[29] Thus, accurate assessment of laterality is important for precise management of the patients with PD. Unlike other PD medications, DBS can stimulate brain hemispheres asymmetrically, which is advantageous in managing asymmetric appendicular symptom.[13] Also, the success of DBS partially depends on the optimization of stimulation parameters. Deep brain stimulation programming is an iterative process in the clinic to maximize the therapeutic effect while minimizing the adverse effect and to find the accurate left-right balance, which requires huge amount of time and efforts of both patients and clinicians.[33] Therefore, the information

TABLE 3. Agreement Between DAT Laterality and Symptom Laterality

A. Baseline				B. 6 mo After DBS				C. 12 mo After DBS			
DAT Laterality	Symptom Laterality		Sum	DAT Laterality	Symptom Laterality		Sum	DAT Laterality	Symptom Laterality		Sum
	LD	RD			LD	RD			LD	RD	
LD	10	1	11 (64.7%)	LD	7	2	9 (60.0%)	LD	6	1	7 (63.6%)
RD	1	5	6 (35.3%)	RD	0	6	6 (40.0%)	RD	0	4	4 (36.4%)
Sum	11 (64.70%)	6 (35.30%)	17*	Sum	7 (46.70%)	8 (53.30%)	15†	Sum	6 (54.50%)	5 (45.50%)	11‡

*Symmetric: 2 excluded.

†Symmetric: 3 excluded. No DAT SPECT: 1 excluded.

‡No DAT SPECT: 7 excluded. No DAT SPECT and UPDRS: 1 excluded.

LD indicates patients with left-dominant symptom; RD, patients with right-dominant symptom.

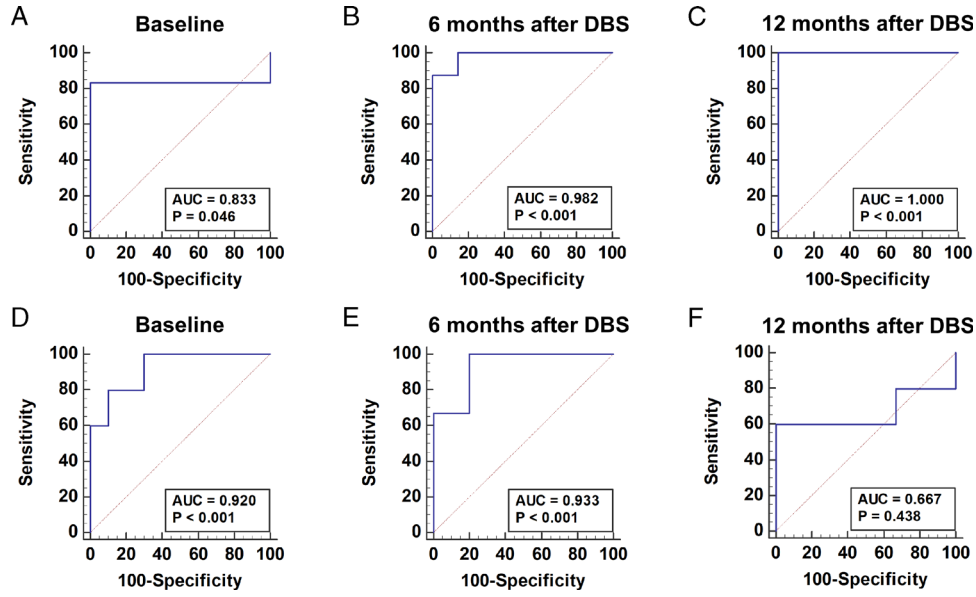

FIGURE 3. Receiver operating characteristic analysis of DAT laterality index for determination of symptom laterality before and after DBS. Determination of the symptom laterality (off-medication and off-stimulation) at baseline (**A**) and 6 months (**B**) and 12 months after DBS (**C**). Determination of the symptom laterality (on-medication and on-stimulation) at baseline (**D**) and 6 months (**E**) and 12 months after DBS (**F**).

of DAT laterality index may reduce the effort and time and potentially provide more accurate laterality-balanced DBS parameters. Specifically, DBS parameters are adjusted under consideration of the DBS electrode location and its association with clinical symptoms. In the clinic, it may be adjusted several times to find a maintenance dose in the short term after surgery. During 6 months after DBS, the patients should visit the hospital every month to adjust the DBS parameters. Even after the parameter was set, the parameters are adjusted at intervals of 6 to 12 months.[17–19] However, the availability of DAT SPECT will shorten the time frame and number of adjustments.

Laterality of PD can be assessed by neuroimaging tools including magnetoencephalography, MRI, and DAT SPECT. Magnetoencephalography revealed the asymmetry of beta activity during movement in patients with right- and left-dominant symptom.[8] Also, diffusion tensor imaging parameters were different significantly between both substantia nigra and putamen, and the diffusion tensor imaging results were well correlated with the symptom laterality.[7] Dopamine transporter–targeting PET and SPECT have been utilized to measure reduction of dopaminergic neuron.[34,35] Dopamine transporter imaging is useful for differentiating movement disorders between with and without dopaminergic neuron degeneration.[35] Dopamine transporter uptake in striatum has correlation with disease duration, clinical scores, and prognosis in PD.[36] Dopamine transporter SPECT was able to reflect the

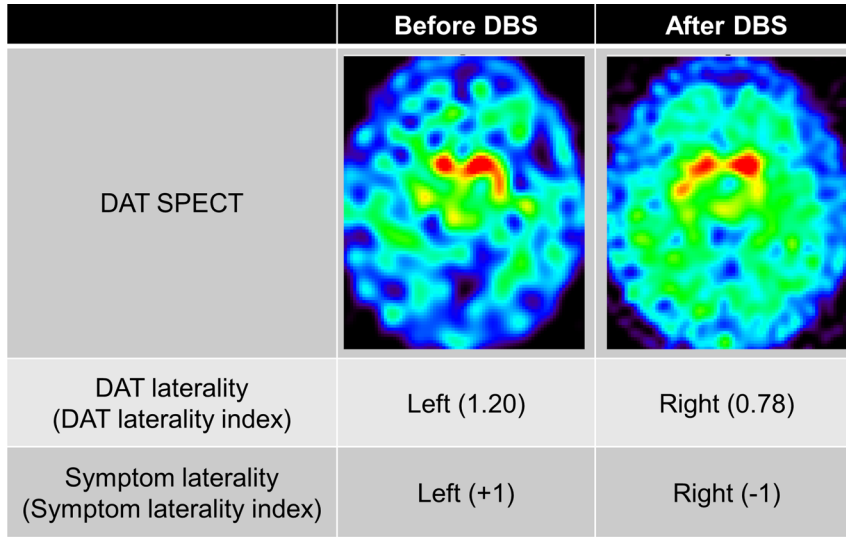

FIGURE 4. Representative case. One patient with left-side–dominant symptom at baseline showed right-side–dominant symptom after DBS. The symptom was tested at off-medication and off-stimulation state. The DAT SPECT showed higher uptake in the left CP at baseline, but the uptake was higher in the right CP after DBS, which was a correct reflection of the changed symptom laterality.

laterality, which has an association with symptom laterality.[6] However, there has not been a study to evaluate the alteration of laterality after DBS using a neuroimaging tool. This study clearly showed that we can monitor the laterality even after DBS using DAT SPECT. Also, we also found that patients with a low DAT laterality score at baseline are prone to experience alteration of the laterality after DBS. There were also patients with highly asymmetric symptom at baseline who experienced the changed laterality after DBS. Specifically, patient 15 was one of the most highly asymmetric to the left side with a symptom laterality index of 6 at baseline but changed to right-sided with symptom laterality index of −4 after DBS (Fig. 2B). We reviewed the electrode position using fusion image of postoperative CT (1 month after) and preoperative MRI and found the left electrode was off located from the target to the medial side (Fig. S3, Supplemental Digital Content 5, http://links.lww.com/CNM/A235). We assume that the misplacement of the electrode may have altered the patient's symptom laterality.

In our study, DAT SPECT was performed at on-medication and on-stimulation state to acquire the best image quality. The enrolled patients were not taking any medicine that potentially changes the DAT SPECT finding such as cocaine, amphetamine, ephedrine, modafinil, or adrenergic agonists.[37] The patients were under levodopa treatment that does not influence the finding of DAT SPECT.[38] However, it has not been investigated whether DBS stimulation can influence the DAT SPECT or not. In our study, we observed that DAT SPECT (performed on-medication and on-stimulation state) was more predictive of the symptom laterality at off-medication and off-stimulation state than that at on-medication and on-stimulation state, especially at 12 months after DBS (Figs. 3C, F). This result indicates that DAT SPECT may not be affected by DBS stimulation because DBS stimulation was applied asymmetrically to adjust the symptom asymmetry.

There has not been a study that assessed whether laterality is altered after bilateral DBS. A recent study showed alteration of laterality after unilateral DBS in patients with highly asymmetric symptom.[16] In our study, we found that more than half of the patients experienced altered laterality after DBS. The altered laterality on DAT SPECT could be caused by (1) asymmetric preservation of dopaminergic neurons by DBS, (2) asymmetric progression of dopaminergic neuron after DBS, and (3) direct effect of the stimulation. We assume it was not caused by the direct effect of the stimulation because DAT laterality index (obtained on-stimulation) showed correlation with not only on-stimulation symptom laterality index but also off-stimulation symptom laterality index. Currently, we are not sure if the altered laterality is caused by asymmetric neuroprotection or neurodegeneration because we do not have the matched control group. However, there have been preclinical studies that support the notion of the neuroprotective effects of DBS. In a study using an MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)–induced monkey model of PD, DBS reduced beta oscillation, which is related to the abnormally enhanced synchronized output.[39] Piallat et al[40] reported that subthalamic lesion provides neuroprotection in the rat model of PD. Temel et al[41] also reported that the silencing of the hyperactive STN by DBS could enhance the survival of dopaminergic neurons in the rat model of PD. However, in a clinical study using DAT SPECT, DAT binding in striatum was similarly decreased in the DBS group compared with the nonoperated group.[42] Thus, further large-scale study is warranted to evaluate the neuroprotective effects of DBS using DAT SPECT with proper control group.

The limitation of this study includes the small number of enrolled patients especially at 12 months after DBS. However, there has not been a study that evaluates the possibility of DAT SPECT for evaluation of the laterality at multiple time points after DBS. The wide range of disease duration of the enrolled patients could be one of the limitations for statistical analysis. However, we did not consider this as a confounder, because the assessed symptom laterality and DAT SPECT laterality were normalized variables in each patient (using values from the left and right sides). Also, DAT SPECT was performed only on-stimulation state to obtain better image quality. Thus, it is hard to exclude the effect of the stimulation in the DAT image. However, interestingly, DAT laterality index was well correlated to the symptom laterality index regardless of the states (on/off-medication, on/off-stimulation). Further studies are warranted to evaluate the clinical significance and utility of the laterality assessed by DAT SPECT after DBS.

CONCLUSIONS

We found that the laterality could be changed after DBS, which was assessed both by symptom laterality index and DAT laterality index. Furthermore, symptom laterality and DAT laterality showed significant association before and after DBS. This finding could be further utilized for fine tuning of the DBS programming for precise management of the PD lateralized symptoms before and after DBS.

REFERENCES

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet*. 2015;386:896–912.
2. Starkstein S, Leiguarda R, Gershanik O, et al. Neuropsychological disturbances in hemiparkinson's disease. *Neurology*. 1987;37:1762–1764.
3. Katzen HL, Levin BE, Weiner W. Side and type of motor symptom influence cognition in Parkinson's disease. *Mov Disord*. 2006;21:1947–1953.
4. Baumann CR, Held U, Valko PO, et al. Body side and predominant motor features at the onset of Parkinson's disease are linked to motor and nonmotor progression. *Mov Disord*. 2014;29:207–213.
5. Spicer KB, Roberts RJ, LeWitt PA. Neuropsychological performance in lateralized parkinsonism. *Arch Neurol*. 1988;45:429–432.
6. Scherfler C, Seppi K, Mair KJ, et al. Left hemispheric predominance of nigrostriatal dysfunction in Parkinson's disease. *Brain*. 2012;135:3348–3354.
7. Wang J, Yang QX, Sun X, et al. MRI evaluation of asymmetry of nigrostriatal damage in the early stage of early-onset Parkinson's disease. *Parkinsonism Relat Disord*. 2015;21:590–596.
8. Heinrichs-Graham E, Santamaria PM, Gendelman HE, et al. The cortical signature of symptom laterality in Parkinson's disease. *NeuroImage Clin*. 2017;14:433–440.
9. Spiegel EA, Wycis HT, Marks M, et al. Stereotaxic apparatus for operations on the human brain. *Science*. 1947;106:349–350.
10. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med*. 2006;355:896–908.
11. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med*. 2013;368:610–622.
12. Hacker ML, DeLong MR, Turchan M, et al. Effects of deep brain stimulation on rest tremor progression in early stage. *Parkinson Dis*. 2018;91:e463–e471.
13. Lizarraga KJ, Luca CC, De Salles A, et al. Asymmetric neuromodulation of motor circuits in Parkinson's disease: the role of subthalamic deep brain stimulation. *Surg Neurol Int*. 2017;8:261.
14. Duffus S, Chukwueke U, Strowd R, et al. Unilateral vs. bilateral subthalamic stimulation in Parkinson's disease. *Neurology*. 2015;84(14 Suppl):P1.168.
15. Taba HA, Wu SS, Foote KD, et al. A closer look at unilateral versus bilateral deep brain stimulation: results of the National Institutes of Health COMPARE cohort. *J Neurosurg*. 2010;113:1224–1229.
16. Ehm G, Kim HJ, Kim JY, et al. Effect of unilateral subthalamic deep brain stimulation in highly asymmetrical Parkinson's disease: 7-year follow-up. *J Neurosurg*. 2018;1–6.
17. Picillo M, Lozano AM, Kou N, et al. Programming deep brain stimulation for Parkinson's disease: the Toronto Western Hospital algorithms. *Brain Stimul*. 2016;9:425–437.
18. Volkmann J, Moro E, Pahwa R. Basic algorithms for the programming of deep brain stimulation in Parkinson's disease. *Mov Disord*. 2006;21(suppl 14): S284–S289.
19. Paek SH, Kim HJ, Yoon JY, et al. Fusion image-based programming after subthalamic nucleus deep brain stimulation. *World Neurosurg*. 2011; 75:517–524.

20. Kim H-J, Jeon BS, Paek SH, et al. Bilateral subthalamic deep brain stimulation in Parkinson disease patients with severe tremor. *Neurosurgery*. 2010; 67:626–632.
21. Lee JY, Han JH, Kim HJ, et al. STN DBS of advanced Parkinson's disease experienced in a specialized monitoring unit with a prospective protocol. *J Korean Neurosurg Soc*. 2008;44:26–35.
22. Lee JS, Lee DS, Kim YK. Quantification of brain images using Korean standard templates and structural and cytoarchitectonic probabilistic maps. *Korean J Nucl Med*. 2004;38:241–252.
23. Darcourt J, Booij J, Tatsch K, et al. EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2. *Eur J Nucl Med Mol Imaging*. 2010;37:443–450.
24. Joutsa J, Johansson J, Kaasinen V. Is occipital cortex a valid reference region in ^{123}I-FP-CIT SPECT imaging? *Clin Nucl Med*. 2015;40:615–616.
25. Moro E, Lozano AM, Pollak P, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. *Mov Disord*. 2010;25:578–586.
26. Djaldetti R, Ziv I, Melamed E. The mystery of motor asymmetry in Parkinson's disease. *Lancet Neurol*. 2006;5:796–802.
27. Suchowersky O, Reich S, Perlmutter J, et al. Practice parameter: diagnosis and prognosis of new onset Parkinson disease (an evidence-based review): report of the quality standards Subcommittee of the American Academy of neurology. *Neurology*. 2006;66:968–975.
28. Thenganatt MA, Louis ED. Distinguishing essential tremor from Parkinson's disease: bedside tests and laboratory evaluations. *Expert Rev Neurother*. 2012;12:687–696.
29. Cubo E, Martin PM, Martin-Gonzalez JA, et al. Motor laterality asymmetry and nonmotor symptoms in Parkinson's disease. *Mov Disord*. 2010;25:70–75.
30. Frazzitta G, Ferrazzoli D, Maestri R, et al. Differences in muscle strength in parkinsonian patients affected on the right and left side. *PLoS One*. 2015; 10:e0121251.
31. Munhoz RP, Espay AJ, Morgante F, et al. Long-duration Parkinson's disease: role of lateralization of motor features. *Parkinsonism Relat Disord*. 2013;19: 77–80.
32. Yoon JE, Kim JS, Seo JY, et al. The association between motor laterality and cognitive impairment in Parkinson's disease. *Dement Neurocogn Disord*. 2016;15:142–146.
33. Hickey P, Stacy M. Deep brain stimulation: a paradigm shifting approach to treat Parkinson's disease. *Front Neurosci*. 2016;10:173.
34. Sung C, Lee JH, Oh JS, et al. Longitudinal decline of striatal subregional [(18)F]FP-CIT uptake in Parkinson's disease. *Nucl Med Mol Imaging*. 2017;51:304–313.
35. Marshall V, Grosset D. Role of dopamine transporter imaging in routine clinical practice. *Mov Disord*. 2003;18:1415–1423.
36. Ravina B, Marek K, Eberly S, et al. Dopamine transporter imaging is associated with long-term outcomes in Parkinson's disease. *Mov Disord*. 2012;27: 1392–1397.
37. Booij J, Kemp P. Dopamine transporter imaging with [(123)I]FP-CIT SPECT: potential effects of drugs. *Eur J Nucl Med Mol Imaging*. 2008;35: 424–438.
38. Schillaci O, Pierantozzi M, Filippi L, et al. The effect of levodopa therapy on dopamine transporter SPECT imaging with (123)I-FP-CIT in patients with Parkinson's disease. *Eur J Nucl Med Mol Imaging*. 2005;32: 1452–1456.
39. Meissner W, Leblois A, Hansel D, et al. Subthalamic high frequency stimulation resets subthalamic firing and reduces abnormal oscillations. *Brain*. 2005;128:2372–2382.
40. Piallat B, Benazzouz A, Benabid AL. Subthalamic nucleus lesion in rats prevents dopaminergic nigral neuron degeneration after striatal 6-OHDA injection: behavioural and immunohistochemical studies. *Eur J Neurosci*. 1996;8: 1408–1414.
41. Temel Y, Visser-Vandewalle V, Kaplan S, et al. Protection of nigral cell death by bilateral subthalamic nucleus stimulation. *Brain Res*. 2006;1120: 100–105.
42. Lokkegaard A, Werdelin LM, Regeur L, et al. Dopamine transporter imaging and the effects of deep brain stimulation in patients with Parkinson's disease. *Eur J Nucl Med Mol Imaging*. 2007;34:508–516.