Use of ^{99m}Tc-Trodat-1 SPECT to evaluate the efficacy of deep brain stimulation in Parkinson's disease

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Abstract

Objective: This study aimed to explore the availability of striatal dopamine transporter (DAT) after deep brain stimulation (DBS) by single photon emission computed tomography (SPECT) using technetium-99m-labeled tropane derivative (^{99m}Tc-Trodat-1). **Subjects and Methods:** In this cohort, 28 patients with PD were enrolled (including 18 males and 10 females). Among these patients, the age range was 55-75 years. All patients referred for optimized DBS programming were recruited for ^{99m}Tc-Trodat-1 imaging and symptom assessment. Dopamine transporter SPECT was performed under medication-off state before DBS and at the 6th month after DBS, respectively. The clinical scales including Unified Parkinson Disease Rating Scale (UPDRS), Modified Hoehn & Yahr Scale (MHYS) and Ability of Daily Life Scale (ADLS) were carried out before DBS and at 6 months after DBS under medication-on and medication-off, respectively. Dopamine transporter availability was assessed based on DAT SPECT. In addition, the correlation between DAT availability and clinical scales was investigated. The data were analyzed using SPSS 23.0. **Results:** The mean UPDRS total, MHYS and ADLS scores were 62.36, 2.23 and 42.07 under medication-on, respectively. The medication improvement rate of UPDRS total, MHYS and ADLS scores were 27.55%, 21.88% and 54.19%, respectively. Interestingly, we found PD patients with MHYS grade I usually presented unilateral symptoms, but DAT imaging showed that DAT uptake of the bilateral striatum was lower than that of the normal and the S-value of the contralateral side was significantly lower than that of the ipsilateral side. Furthermore, we found that DBS can improve the laterality of symptoms. The DBS improvement rate of UPDRS total scores, ADLS scores and DAT S-value were 37.65%, 72.51% and 18.21%, respectively. The symptom laterality was significantly correlated with the DAT S-value at baseline and at 6 months after DBS (r=0.63, 0.69 and 0.66, 0.75). The dosage of levodopa was 696.43±146.52 and was 455.36±107.44 before DBS surgery and at DBS-on, respectively. **Conclusion:** Deep brain stimulation can significantly improve the symptom of PD. Dopamine transporter S-value was well correlated with the change of symptoms laterality. Therefore, DAT imaging can be used to diagnose PD in the early stage and to evaluate the curative effect of DBS. However, the validation of this result requires further study.

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Introduction

Parkinson's disease (PD) is a chronic progressive disease that affects predominately dopaminergic neurons in substantia nigra, mostly seen in middle-aged and older adults. Approximately one percent of older adults over the age of 55 suffer from the disease. In general, the typical feature of PD is that the onset is insidious and gradually aggravated, and the most obvious tremor is at rest state. The stiffness of the limbs causes reduced movement and gradually loses normal work and living ability. Other changes include facial expression changes, mask-like face, slow speech, low pitch, monotonous tone, salivation, body in a bowed posture, and the oil overflows the skin [1-3].

Deep brain stimulation (DBS) has been used for PD for more than two decades and has shown efficacy in alleviating symptoms in advanced PD. Deep brain stimulation is considered to be the best treatment for PD, and is more and more accepted. Deep brain electrical stimulation is a stereotaxic neurosurgical procedure of implanting electrodes in deep brain nuclei and generating pulses through stimulation generators to chronically stimulate the nuclei. At present, the subthalamic nucleus (STN) is considered to be the best target for DBS [4].

Some studies have shown that greater benefit at ≥130Hz frequencies, while inert at lower frequencies (<50Hz) in rodent PD models [5, 6]. Many studies also have found the optimal frequency range of STN DBS is 90-220Hz to improve motor symptoms for PD in humans. However, some studies have reported that low frequency (<60Hz) is more conducive to improve gait/posture instability symptoms [7-10]. In the present study we use dopamine transporter (DAT) imaging to evaluate the impact of DBS in STN, and we use the unified Parkinson disease rating scale (UPDRS), modified Hoehn & Yahr scale (MHYS)

and ability of daily life scale (ADLS) to estimate clinical symptoms. The aim of this study is to investigate the impact on clinical symptoms after DBS.

Subjects and Methods

Data acquisitions

In this cohort, 28 patients with PD (according to the diagnostic criteria of primary PD in China) were enrolled continuously (including 18 males and 10 females), who underwent DBS at our institution between October 2014 and April 2019. The clinical information of this cohort is summarized in Table 1. Clinical symptoms were evaluated using UPDRS, MHYS and ADLS before DBS and then 6 months after DBS, under medication-on and medication-off, respectively. The mean age was 65.11±5.60 years (range from 55 to 75 years). The age diagnosed PD was 57.32±4.82 years. The mean UPDRS total scores, MHYS grade and ADLS scores were 86.07, 2.86 and 27.29 at medication-off, respectively. However, the average UPDRS total, MHYS and ADLS scores were 62.36, 2.23 and 42.07 at medication-on, respectively. Furthermore, at baseline, the correlation between MHYS grade and UPDRS-III was significant (r:0.91, P<0.001). The dosage of levodopa was 696.43±146.52, 455.36±107.44 before DBS surgery and at DBS-on, respectively. The mean clinical frequency was 143.32±8.47Hz. Dopamine transporter imaging was performed before DBS and then 6 months after DBS under medication-off, respectively. Patients demonstrating mild cognitive impairment or dementia or previous psychotic episodes were excluded.

Table 1. *Demographic and clinical features of the DBS patients.*

Baseline clinical data	Value (Mean±SD)
Age (years)	65.11±5.60
Sex	
Male	18
Female	10
Age at PD onset(years)	57.32±4.82
Age at STN-DBS(years)	61.21±5.05
UPDRS total medication-on score	62.36±16.38
MHYS medication-on score	2.23±0.86
ADLS medication-on score	42.07±8.05
Dosage of levodopa(mg)	696.43±146.52
Stimulation settings	
Amplitude (V)	2.94±0.11
Pulse width (μsec)	65.54±3.69
Frequency (Hz)	143.32±8.47

STN-DBS surgery

Withdrawal of all medications for PD 24 hours before operation. First, the head frame was installed under local anesthesia. Then, under computed tomography (CT)/magnetic resonance imaging (MRI) guiding, the stereotactic head frame mark and anatomical target location were confirmed, and quadripolar leads were precisely localized in STN. The micro-electrode recording system and test stimulation were used for the corresponding electrophysiological tests during the operation. Finally, the pulse generator was implanted in subclavicular area and connected to the subcutaneous electrode under general anesthesia. One month after DBS surgery, the stimulator was turned on and adjusted by the program-controlled doctor to the optimal parameters of brain pacemaker control. Some patients were treated with levodopa to achieve the best symptom control.

Assessment of symptom

Clinical symptoms were evaluated according to the protocol of our brain science center. Clinical scales were performed in 3 days before DBS surgery under medication-on and medication-off state using UPDRS, MHYS and ADLS, respectively. Clinical symptoms also were assessed at 6 months after DBS surgery under medication-on and medication-off state, with DBS-on and DBS-off, respectively. Deep brain stimulation-off values were recorded at least 30 minutes after DBS shutdown. Deep brain stimulation parameters and dosage of levodopa were adjusted based on the clinical symptom. The dosage of levodopa was recorded at each time point. Medication improvement rate (%)=(medication-on score - medication-off score)/medication-on score×100%.

^{99m}Tc-Trodat-1 imaging

Dopamine transporter imaging was performed using a dual-head single-photon emission computed tomography (SPECT) with Fan-Beam collimator at clinically optimized setting. The first DAT imaging was conducted in one week before the DBS surgery in medication-off state. The follow-up DAT imaging was conducted under medication-off and DBS-on at the 6th month, in two weeks after clinical assessment. Dopamine transporter SPECT was carried out at three hours after intravenous injection of 740MBq technetium-99m-labeled tropane derivative (^{99m}Tc-Trodat-1). Dopamine transporter images were acquired and reconstructed using a OSEM algorithm. Mean uptakes of both striatum and occipital cortex were obtained using region of interest (ROI). Then, uptake value of striatum (S-value) was calculated: (mean counts of the striatum ROI)/(mean counts of the occipital cortex ROI)]. Deep brain stimulation improve-ment rate (%)=(S_{post}-value - S_{pre}-value)/S_{pre}-value×100%.

Statistical analysis

SPSS 23 was used for statistical analysis. The continuous data of normal distribution were presented as mean±standard deviation or percentages, and paired t test was used for comparison. In this study, the correlation was analyzed using Pearson analysis and Spearman rank analysis for normal distribution data and for non-normal distribution data, respectively. There was significant difference if P<0.05.

Results

Improvement of clinical scales score under medication-on and DAT S-value under DBS-on

Compared with medication-off, the UPDRS score, MHYS grade and ADLS score at medication-on state were improved, and the difference was statistically significant (P<0.001). The improvement rate of UPDRS score, MHYS grade and ADLS score were 27.55%, 21.88% and 54.19% after medication-on, respectively (Table 2). In addition, compared to the baseline, the UPDRS score, ADLS score and DAT S-value were obviously improved after DBS-on (P<0.001). The improvement rates of UPDRS score, ADLS score and DAT S-value were 37.65%, 72.51% and 18.21 at DBS-on, respectively (Table 3, Figure 1). Furthermore, the improvement rate of UPDRS total scores at DBS-on was better than that of medication-on, and the improvement was statistically significant (P<0.001).

Table 2. *Comparison of various scales in medication-off and medication-on state before DBS (Mean±SD).*

Status	UPDRS-I	UPDRS-II	UPDRS-III	UPDRS-IV	HMYS	ADLS
Medication-off	6.54±1.64	20.14±4.69	53.79±11.94	5.61±1.59	2.86±1.07	26.46±6.36
Medication-on	4.71±1.51	15.07±4.35	36.86±10.60	5.7±1.44	2.20±0.93	42.07±8.05
Improvement rate （%）	27.87	25.18	31.47	-1.91	27.55	21.88
T value	4.13	3.44	6.67	-0.26	4.13	3.67
P value	0.00	0.00	0.00	0.48	0.00	0.00

Table 3. *Comparison of UPDRS, ADLS and DAT in DBS-off and DBS-on state (Mean±SD).*

Status (Med-off)	UPDRS total	ADLS	S-value
DBS-off	86.07±18.35	26.4±6.36	1.40±0.22
DBS-on	53.57±11.79	46.07±8.49	1.66±0.22
Improvement rate （%）	37.65	72.51	18.21
T	21.56	3.44	25.54
P	0.00	0.00	0.00

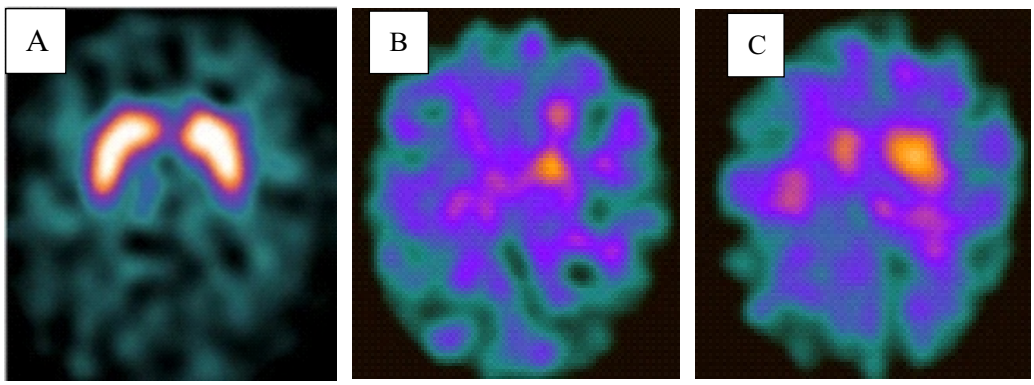

Figure 1. Picture A is a normal DAT SPECT. Picture B and C belong to a representative case. UPDRS total scores, MHYS grade and ADLS of the patient at baseline were 102, 4 and 20, respectively. And the DAT S-value was 1.11 of right side and 1.34 of left side at baseline [B], respectively. DAT SPECT also showed higher uptake in both striatum after DBS[C], which was a correct reflection of the changed symptom laterality. UPDRS total scores and ADLS of the patient were 64 and 38 at DBS-on, respectively.

Relativity between Symptom scores and DAT imaging

At medication-off state, there was a significant correlation between clinical scales scores and DAT S-value (Table 4, Figure 2). The correlation at baseline state between DAT S-value and UPDRS total score was significant (r:-0.63, P<0.001). The positive correlation at baseline state between DAT S-value and ADLS score was significant (r:0.69, P<0.001). Interestingly, the DAT S-value was also well correlated with the clinical scales scores even 6 months after DBS. The correlation at DBS-on/medication-off state between DAT S-value and UPDRS total score was significant (r:-0.66, P<0.001). At DBS-on/medication-off state, the positive correlation between DAT S-value and ADLS score was significant (r:0.75, P<0.001). We further assessed the correlation between improvement rate of DAT S-value and clinical scales to be significant (P<0.001, 0.001, respectively) (Figure 3).

Table 4. *Correlation analysis of UPDRS, ADLS and DAT imaging.*

Status (med.-OFF)	UPDRS total score (DBS-off)	UPDRS total score (DBS-on)	ADLS score (DBS-off)	ADLS score (DBS-on)
DAT S-value (DBS-off)	r: -0.63	/	r:0.69	/
	P:0.00		P:0.00	/
DAT S-value (DBS-on)	/	r: -0.66	/	r: 0.75
	/	P:0.00	/	P:0.00

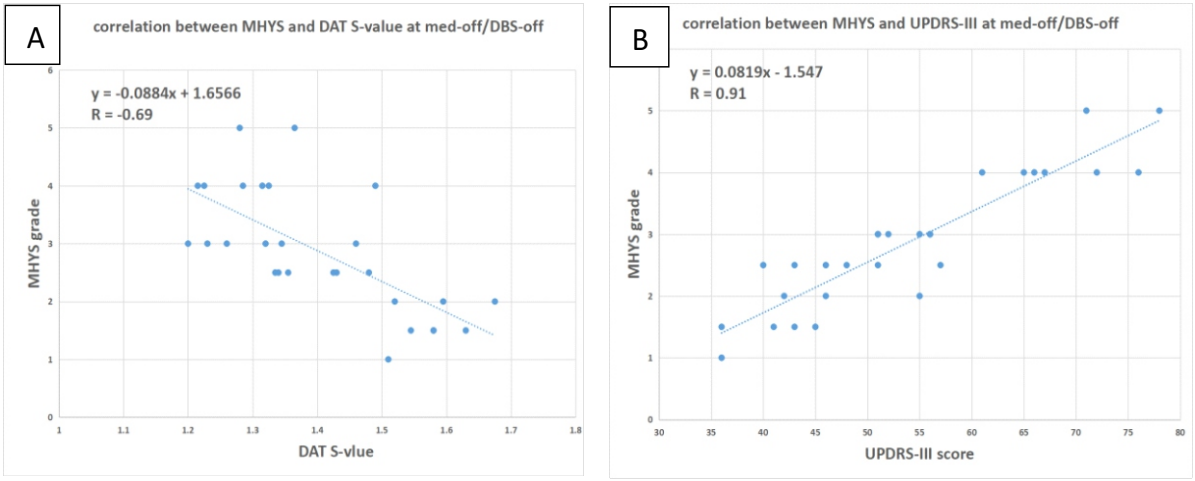

Figure 2. Correlation between MHYS grade and DAT imaging (A) and correlation between MHYS grade and UPDRS-III (B) at baseline.

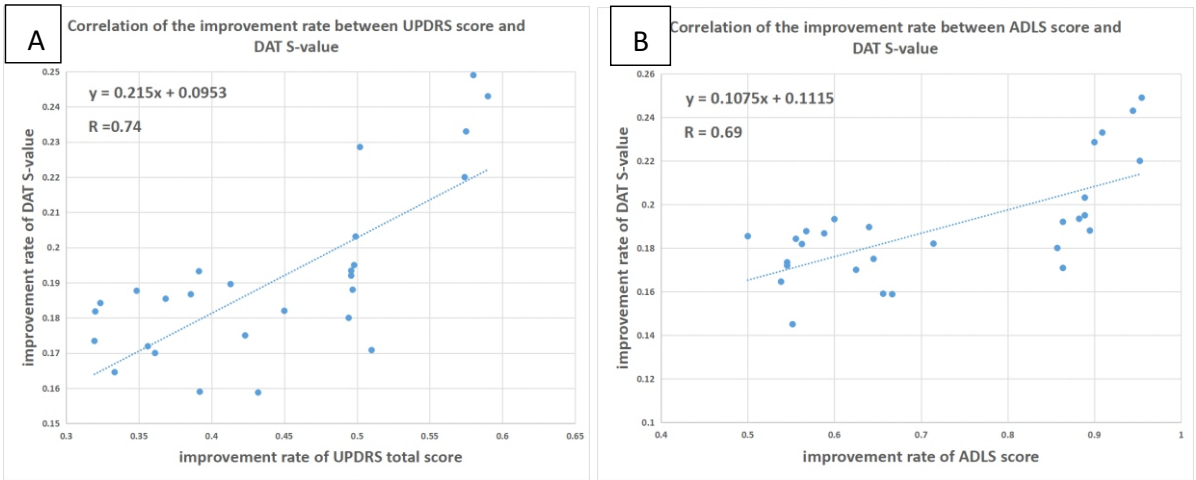

Figure 3. Correlation of improvement rate between UPDRS scores and DAT imaging (A) and correlation of improvement rate between ADLS scores and DAT imaging (B) after DBS.

Discussion

The study was designed as a single-center, self-control study before and after STN-DBS operation. In this study we first analyzed the correlation between UPDRS-III score, MHYS grade and DAT S-value under baseline state (medication-off before DBS), and we found that symptom laterality was very common at the early stage of PD patients and gradually involved bilateral with the progression of the disease. Our study also showed that the DAT S-value decreased with the progression of PD. Furthermore, we found that the DAT uptake decreased obviously in contralateral putamen at the early stage of PD patients. Thus, PD may be diagnosed accurately in the early stages by analyzing the DAT uptake of the contralateral striatum, especially of the putamen.

We also analyzed the correlation between UPDRS score, ADLS score and DAT S-value after DBS and found that DBS can improve the laterality of symptoms. The symptom laterality was significantly correlated with the DAT S-value not only in baseline state, but also at 6 months after DBS, indicating that DAT imaging can present the dynamic change of progress of PD.

For more than 20 years, DBS has been widely used to alleviate motor symptoms in PD patients. Despite such a long history, the mechanism of DBS on motor function is still unclear. However, it is well recognized that DBS can obviously improve motor function. In our study the DBS improvement rate of UPDRS-III was 31.45% at medication-off. Many studies reported that DBS was effective, safe, and durable in most PD [11-13]. A randomized trial with advanced PD showed that patients who received DBS had significantly improved the quality of life and UPDRS-III scores compared to medication only [11]. Some scholars also found that after DBS, the motor symptoms of early PD patients were alleviated, the quality of life was improved, and the motor complications induced by levodopa were reduced [12]. Another prospective study of early PD showed that DBS can slow down progress [14]. In this study, UPDRS-I, UPDRS-II scores were improved significantly after DBS ($P<0.001$), suggesting that in addition to motor symptoms, DBS also can improve the overall non-motor symptoms, such as anxiety and depression. The improvement rate of ADLS score was as high as 72.51%, indicating that the quality of life of PD patients was significantly improved after STN-DBS operation. Moreover, after DBS surgery, anti-PD medication was significantly reduced, and the levodopa reduction rate of mean dosage was 34.62%.

Interestingly, we found PD patients with MHYS grade I usually presented unilateral symptoms; however, DAT SPECT showed that not only the S-value of the contralateral side was significantly lower than that of the ipsilateral side, but the DAT uptake of the bilateral striatum was lower than that of the normal. These results indicated that there may be damage to the striatum before the onset of symptoms. In addition, many studies found that symptom asymmetry of PD is rooted in asymmetrical neuronal damage. Symptom asymmetry is a typical diagnostic point of PD, and it can exclude other types of neurodegenerative diseases, such as multisystem atrophy, supranuclear paralysis, and essential tremor [15-17].

Many studies reported that compared to patients with left-side-dominant symptom, their motor symptoms progressed rapidly, their muscle strength decreased obviously and they had more difficulties in attention and working memory, in PD patients with right-side-dominant. Moreover, patients with right-side-dominant symptom are more likely to suffer from psychosis. Interestingly, the PD patients with left-side-dominant symptom had a longer survival after diagnosis and delayed ambulatory inhibition than the patients with right-side–dominant symptom [18-21]. Therefore, it is very important for precise management of PD patients to accurately assess the laterality of symptoms. Unlike medications, DBS is advantageous in managing the symptom laterality owing to its asymmetrical stimulation to brain hemispheres. Of course, the success of DBS is closely related to the optimization of stimulation parameters, and the purpose of stimulation parameter optimization is to maximize the therapeutic effect and to minimize the adverse effect [22-24]. Therefore, we have made efforts to find an accurate of left-right balance. During 6 months after DBS, we continuously adjusted the maintenance dose and the DBS parameters until the patient was in a better state. However, we were unable to assess whether DBS could slow down the progression of PD because our study lacked a control group. We could observe the dynamic change of bilateral DAT S-value after DBS owing to the different beneficial effects from DBS. Therefore, the DAT imaging could provide more accurate laterality-balanced DBS parameters and could reduce the effort and time. We found that the optimized dose of levodopa was 455.36±107.44 and the appropriate stimulation frequency was 143.32±8.47Hz.

There were many neuroimaging tools to assess the laterality of symptom of PD, such as MRI and DAT imaging. Dopamine transporter SPECT was an important imaging examination to differentiate movement disorders whether induced by dopaminergic neuron degeneration. In this study we found DAT S-value was well correlated with disease duration and clinical scores in PD. The correlation between DAT imaging and MHYS grade was significant ($r=-0.69$, $P<0.001$) at baseline. The correlations between DAT imaging and UPDRS and ADLS scores were significant ($r=-0.63$, $P<0.001$ and $r=0.69$, $P<0.001$, respectively). The correlation of improvement rate between DAT S-value and UPDRS scores was significant after DBS ($r=0.74$, $P<0.001$). Interestingly, we also found that patients with a high DAT S-value at baseline usually experienced high improvement after DBS. These results clearly showed that we can monitor the dynamic change of the symptom laterality using DAT SPECT.

In our study, DAT SPECT was performed at medication-off state to reflect more realistic striatum function. We found that most of the patients experienced improvement after DBS. There have been preclinical studies that STN-DBS could enhance the survival of dopaminergic neurons in the rat model of PD [25-27]. However, there was a clinical study that DAT uptake of striatum was similarly decreased in the DBS group compared with the control group [28].

There were some limitations of this study. First, it was a single-center retrospective study, which might have result in

selection bias. Second, the number of patients of this cohort was relatively small. Third, the study lacked a proper control group. Last, the follow-up DAT SPECT was carried out only at DBS-on state, which may be affected by the stimulation of DBS. Therefore, further large-scale studies are required to assess the STN effects of DBS using DAT imaging with a proper control group.

In conclusion, the study showed the DAT S-value decreased with the progression of PD. We also found that the DAT uptake obviously decreased in contralateral putamen at the early stage of PD patients. Furthermore, our study showed that there was significant improvement of the symptom laterality after DBS, especially that of motor symptoms, which were evaluated by both clinical scales and DAT S-value. Furthermore, clinical scales and DAT S-value showed significant correlation at baseline and DBS-on. These results would be very important for precise management of the PD.

The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate

Institutional Review Board approval was obtained and all patients provided written informed consent. The experiment complies with the current laws of the country in which they were performed.

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