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Preoperative Regional Cerebral Blood Flow and Postoperative Clinical Improvement in Patients With Parkinson's Disease Undergoing Subthalamic Nucleus Deep Brain Stimulation

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Abstract

Preoperative regional cerebral blood flow (rCBF) was measured in 92 patients with Parkinson's disease (PD) by iodine-123 N-isopropyl-p-iodoamphetamine single-photon emission computed tomography. Quantitative mapping of rCBF was performed using the stereotactic extraction estimation method. The clinical features of the patients were assessed according to the Unified Parkinson Disease Rating Scale (UPDRS). The correlation between rCBF and improvement in the UPDRS score following surgery was examined. rCBF in the fusiform gyrus, superior and inferior parietal gyri, middle occipital gyrus, superior frontal gyrus, and middle temporal gyrus of the Talairach Daemon Level 3 was significantly correlated with UPDRS part II (off stage) and III (on stage) scores ($p < 0.05$). rCBF in the middle temporal gyrus ($p = 0.00147$), medial frontal gyrus ($p = 0.00713$), and cerebellum ($p = 0.048$) of the Talairach Daemon Level 3 was significantly greater in 47 patients with $>60\%$ improvement of UPDRS part III (off stage) score than in 37 patients with 40–60% improvement. The cutoff value of rCBF, which indicated that $>40\%$ improvement in the surgical outcome could be expected, was 38.8 ± 6.2 ml/100 g/min in the frontal lobe. This study indicated that rCBF in patients with PD might be related to their clinical features, suggesting that quantitative mapping of rCBF may be useful for predicting surgical outcome.

Key words: Parkinson's disease, deep brain stimulation, cerebral blood flow study

Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) is a well-established technique for treating the motor symptoms of patients with Parkinson's disease (PD). STN DBS is reversible and so can be adjusted as the medical condition changes, and is also superior to the best medical therapy for the manage-

ment of motor symptoms in PD. Patients who received DBS gained a mean of 4.6 hrs/day of on time without troubling dyskinesia compared with 0 hr/day for patients who received the best medication.^{8,31} The quality of life was assessed in 156 patients with PD using the Parkinson's Disease Questionnaire (PDQ-39), and found that DBS had greater effects on quality of life than only medica-

tion.⁷⁾ Moreover, patients undergoing STN stimulation required lower doses of dopaminergic agents than patients undergoing pallidal stimulation.⁷⁾

PD patients with medication-refractory on-off fluctuation and dyskinesia may be the best candidates for STN-DBS.^{6,27)} The beneficial effect of DBS surgery may persist in some patients, so preoperative selection of patients likely to benefit from DBS surgery is important. Single-photon emission computed tomography (SPECT) and tracer ethylcysteinate dimer were used to measure regional cerebral blood flow (rCBF) before and 6 months after DBS of the STN in 20 patients with advanced PD, and found significant increases of rCBF in the anterior cingulate gyrus/supplementary motor cortex in the 12 good responders to DBS.³⁾ Conversely, patients with poor responses exhibited significant worsening of cortical hypoperfusion, particularly in the prefrontal areas. Therefore, preoperative assessment of rCBF might be useful for selecting good candidates for DBS surgery.³⁾

The present study estimated preoperative rCBF using iodine-123 N-isopropyl-p-iodoamphetamine (¹²³I-IMP) SPECT and autoradiography. Three-dimensional surface projection (3D-SSP) findings were used to estimate the correlation between improvements of motor function and rCBF.

Materials and Methods

I. Patients

This study was approved by our institutional review board. All patients provided written informed consent. A total of 92 patients with PD, 42 men and 50 women with a mean age of 63.5 ± 7.8 years, un-

derwent bilateral STN-DBS at Nagoya University Hospital. The mean illness duration was 11.5 ± 9.1 years. The Unified Parkinson Disease Rating Scale (UPDRS) was utilized preoperatively and postoperatively to evaluate motor symptoms and activities of daily living. The preoperative mean scores of UPDRS parts II (on stage), II (off stage), III (on stage), and III (off stage) were 11.3, 28.0, 25.1, and 51.3, respectively. The 92 patients were divided into 3 groups based on the rate of improvement of UPDRS part III (off stage) score following DBS: Group A patients had >60% improvement of the score, Group B patients had 40–60% improvement, and Group C patients had <40% improvement. Patient characteristics are shown in Table 1. We calculated that a 100-mg daily dose of standard levodopa was equivalent to the following doses of other medications: 75 mg of levodopa plus entacapone; 1 mg of pergolide, pramipexole, or cabergoline; 5 mg of ropinirole; or 10 mg of bromocriptine. Patient age and postoperative levodopa doses were significantly different between Groups A and B ($p < 0.05$).

II. rCBF study

Preoperative ¹²³I-IMP autoradiography data acquisition was obtained following levodopa medication (on stage). SPECT data acquisition was performed using a 3-detector type gamma camera (GCA9300A/UI; Toshiba Medical Systems Corp., Otawara, Tochigi) equipped with a low-energy high-resolution fan beam collimator. ¹²³I-IMP (167 MBq; Nihon Medi-Physics Co., Ltd., Tokyo) was infused into the antecubital vein at a constant rate for 1 minute. Arterial blood sampling was performed 10 minutes after the injection of ¹²³I-IMP. Data acquisition for

Table 1 Patient characteristics

	Group A (n = 47)	Group B (n = 37)	Group C (n = 8)
Age (yrs)	60.9	65.7	63.9
Duration of disease (yrs)	15.8	17.6	16.4
Levodopa dose (mg/day) before surgery	534.6	613.1	428.1
Levodopa dose (mg/day) after surgery	379.8	484.1	359.4
UPDRS part II (off stage) score before surgery	24.4	28.6	28
UPDRS part II (on stage) score before surgery	9.3	12.8	11.3
UPDRS part III (off stage) score before surgery	49.1	56.3	54.4
UPDRS part III (on stage) score before surgery	18.1	23	35.5
UPDRS part II (off stage) score after surgery	9.3	14.5	18.4
UPDRS part II (on stage) score after surgery	7.1	11	10.9
UPDRS part III (off stage) score after surgery	15.7	26.8	36.4
UPDRS part III (on stage) score after surgery	13.8	19.1	33.1

Values are means. Group A: patients with rate of improvement of Unified Parkinson Disease Rating Scale (UPDRS) part III (off stage) score of >60%, Group B: patients with improvement of 40–60%, Group C: patients with improvement of <40%.

Table 2 Correlations of regional cerebral blood flow and Unified Parkinson Disease Rating Scale (UPDRS) score for Talairach Daemon Level 2

UPDRS		Frontal lobe		Parietal lobe		Temporal lobe		Occipital lobe	
Part	Stage	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
I		-0.19088	-0.21569	-0.13481	-0.14242	-0.23157	-0.23396	-0.13316	-0.1382
II	on	-0.15619	-0.16786	-0.15748	-0.12309	-0.20978	-0.20662	-0.16149	-0.14548
II	off	-0.14273	-0.16638	-0.3024	-0.28541	-0.35302	-0.35234	-0.3186	-0.30828
III	on	-0.39597	-0.38982	-0.25779	-0.24664	-0.24625	-0.24158	-0.22805	-0.23084
III	off	-0.03364	-0.04314	-0.14602	-0.13085	-0.18627	-0.1855	-0.161	-0.13855

UPDRS		Limbic lobe		Midbrain		Pons		Anterior lobe		Posterior lobe	
Part	Stage	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
I		-0.16217	-0.18963	-0.20492	-0.22327	-0.17208	-0.17074	-0.18259	-0.21602	-0.2508	-0.18059
II	on	-0.14711	-0.13217	-0.21624	-0.20926	-0.19042	-0.19467	-0.1387	-0.14797	-0.20062	-0.16434
II	off	-0.34282	-0.35075	-0.27325	-0.28173	-0.16871	-0.16128	-0.13701	-0.16767	-0.22923	-0.20581
III	on	-0.16556	-0.15038	-0.37103	-0.36039	-0.42306	-0.42329	-0.38395	-0.3773	-0.35575	-0.34987
III	off	-0.16885	-0.20693	-0.14242	-0.15016	-0.04818	-0.0396	-0.03632	-0.04874	-0.08437	-0.05848

brain scanning was performed 10–40 minutes after ^{123}I -IMP injection. SPECT data acquisition was performed for 360° with a matrix size of 128×128 at 4 sampling angles every 2 minutes, and was performed 15 times. The obtained projection data were corrected for scattered photons, and the images were reconstructed by filtered back-projection with a Butterworth filter (cutoff frequency 0.65 cycles/cm). Attenuation corrections were performed using the Chang method with the outline extracted from the head surface by the threshold on the sonogram of the projection data. To determine the concentration of radioactivity in the arterial blood at 10 minutes after ^{123}I -IMP injection (Ca10), the arterial blood samples were measured as 0.5-ml triplicate aliquots into tubes. After subtracting the background count, the tubes were measured for 3 minutes using an Auto-Well Gamma System ARC-370 (Aloka Co., Ltd., Mitaka, Tokyo). The rCBF value was calculated using Ca10 and ^{123}I -IMP SPECT according to the method described previously^{15–17)} (^{123}I -IMP autoradiography method).

3D-SSP is an image analysis method used to statistically compare the brain data of PD patients to those of normal subjects in the database, which includes data extracted from the brain surface, thus allowing assessment of the effects of brain atrophy and partial volume. Stereotactic extraction estimation analysis divides the image into regions to estimate the severity and extent of rCBF, and to characterize statistical values in the region of interest.^{20,21,24–26,29)}

The Talairach Daemon database was used to divide the brain into 5 hierarchical regions based on volume occupancy. Talairach Daemon Levels 1, 2, 3,

4, and 5 classify the brain into the cerebrum and cerebellum, lobes, lobules, tissue types, and Brodmann areas, respectively^{21,29)} (Fig. 1). Analysis of different Talairach Daemon Levels might be useful for investigating the various features of PD.

III. Surgical and perioperative procedures

The patient was placed in a sitting position, and a stereotactic headframe (Leksell Model G; Elekta Instrument AB, Stockholm, Sweden) was affixed to the head. The patient underwent magnetic resonance (MR) imaging prior to the first procedure and prior to the second procedure. MR images were transferred to the workstation computer in the operating room in a digital imaging and communications in medicine format and imported into the computer software (Brainlab AG, Feldkirchen, Germany). The anterior commissure (AC) and posterior commissure (PC) were identified. Then, an initial target 3.5–4 mm below and 12–13 mm lateral from the AC-PC level, and 2–2.5 mm posterior to the midpoint of the AC-PC line was selected. The STN was confirmed by microelectrode recordings. After implantation of the stimulating electrode (Model 3387 or 3389; Medtronic, Inc., Minneapolis, Minnesota, USA), macrostimulation was initiated, and the patient was examined for symptom relief and side effects during stimulation at supra-therapeutic voltages. An implantable pulse generator (Model 7426; Medtronic, Inc.) was placed in the subcutaneous region. Stimulation parameters were then modified to achieve reduction by half of the preoperative dopaminergic medication dose to achieve optimal control of motor symptoms. Monopolar stimulation was applied independently at each of the 4 contacts. Stimulation

Fig. 1 Scheme showing T_1 -weighted surface images (MRI), and the Talairach Daemon Levels 1, 2, 3, and 5. Right lateral, left lateral, superior, inferior, anterior, posterior, right medial, and left medial slices are shown (from left to right).

Fig. 2 Scheme showing the correlation of regional cerebral blood flow with Unified Parkinson Disease Rating Scale part I, II (on and off stage), and III (on and off stage) scores at Talairach Daemon Level 2 ($n = 92$, Z score < -2.07). Right lateral, left lateral, superior, inferior, anterior, posterior, right medial, and left medial slices are shown (from left to right).

Table 3 Correlation of regional cerebral blood flow and Unified Parkinson Disease Rating Scale (UPDRS) score for Talairach Daemon Level 3

UPDRS Part	Stage	Superior frontal gyrus		Middle frontal gyrus		Inferior frontal gyrus		Medial frontal gyrus		Orbital gyrus		Rectal gyrys	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
I		-0.182591	-0.216022	-0.250802	-0.18059	-0.270109	-0.236404	-0.111688	-0.123232	-0.106987	-0.116914	-0.089703	-0.144837
II	on	-0.138701	-0.147972	-0.200619	-0.16434	-0.173804	-0.168414	-0.146355	-0.094499	-0.148788	-0.14803	-0.14659	-0.133864
II	off	-0.137014	-0.16767	-0.229232	-0.205811	-0.266512	-0.239072	-0.322656	-0.300221	-0.31675	-0.323221	-0.244413	-0.269487
III	on	-0.333955	-0.377299	-0.355751	-0.349868	-0.330686	-0.32897	-0.20304	-0.177291	-0.22176	-0.223162	-0.285504	-0.294552
III	off	-0.036321	-0.04874	-0.084368	-0.058478	-0.088503	-0.055403	-0.153805	-0.130552	-0.152979	-0.150881	-0.0914	-0.108262

UPDRS Part	Stage	Paracentral lobule		Precentral gyrus		Subcallosal gyrus		Superior parietal lobule		Inferior parietal lobule		Angular gyrus	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
I		-0.182591	-0.216022	-0.250802	-0.18059	-0.270109	-0.236404	-0.111688	-0.123232	-0.106987	-0.116914	-0.089703	-0.144837
II	on	-0.138701	-0.147972	-0.200619	-0.16434	-0.173804	-0.168414	-0.146355	-0.094499	-0.148788	-0.14803	-0.14659	-0.133864
II	off	-0.137014	-0.16767	-0.229232	-0.205811	-0.266512	-0.239072	-0.322656	-0.300221	-0.31675	-0.323221	-0.244413	-0.269487
III	on	-0.333955	-0.377299	-0.355751	-0.349868	-0.330686	-0.32897	-0.20304	-0.177291	-0.22176	-0.223162	-0.285504	-0.294552
III	off	-0.036321	-0.04874	-0.084368	-0.058478	-0.088503	-0.055403	-0.153805	-0.130552	-0.152979	-0.150881	-0.0914	-0.108262

UPDRS Part	Stage	Postcentral lobule		Precuneus		Supramarginal gyrus		Superior temporal gyrus		Middle temporal gyrus		Inferior temporal gyrus	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
I		-0.182591	-0.216022	-0.250802	-0.18059	-0.270109	-0.236404	-0.111688	-0.123232	-0.106987	-0.116914	-0.089703	-0.144837
II	on	-0.138701	-0.147972	-0.200619	-0.16434	-0.173804	-0.168414	-0.146355	-0.094499	-0.148788	-0.14803	-0.14659	-0.133864
II	off	-0.137014	-0.16767	-0.229232	-0.205811	-0.266512	-0.239072	-0.322656	-0.300221	-0.31675	-0.323221	-0.244413	-0.269487
III	on	-0.333955	-0.377299	-0.355751	-0.349868	-0.330686	-0.32897	-0.20304	-0.177291	-0.22176	-0.223162	-0.285504	-0.294552
III	off	-0.036321	-0.04874	-0.084368	-0.058478	-0.088503	-0.055403	-0.153805	-0.130552	-0.152979	-0.150881	-0.0914	-0.108262

UPDRS Part	Stage	Transverse temporal gyrus		Superior occipital gyrus		Middle occipital gyrus		Inferior occipital gyrus		Cuneus		Fusiform gyrus	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
I		-0.182591	-0.216022	-0.250802	-0.18059	-0.270109	-0.236404	-0.111688	-0.123232	-0.106987	-0.116914	-0.089703	-0.144837
II	on	-0.138701	-0.147972	-0.200619	-0.16434	-0.173804	-0.168414	-0.146355	-0.094499	-0.148788	-0.14803	-0.14659	-0.133864
II	off	-0.137014	-0.16767	-0.229232	-0.205811	-0.266512	-0.239072	-0.322656	-0.300221	-0.31675	-0.323221	-0.244413	-0.269487
III	on	-0.333955	-0.377299	-0.355751	-0.349868	-0.330686	-0.32897	-0.20304	-0.177291	-0.22176	-0.223162	-0.285504	-0.294552
III	off	-0.036321	-0.04874	-0.084368	-0.058478	-0.088503	-0.055403	-0.153805	-0.130552	-0.152979	-0.150881	-0.0914	-0.108262

UPDRS Part	Stage	Lingual gyrus		Thalamus		Cingulate gyrus		Parahippocampal gyrus		Anterior cingulate		Posterior cingulate		Uncus	
		Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt	Rt
I		-0.182591	-0.216022	-0.250802	-0.18059	-0.270109	-0.236404	-0.111688	-0.123232	-0.106987	-0.116914	-0.089703	-0.144837	-0.140808	-0.145032
II	on	-0.138701	-0.147972	-0.200619	-0.16434	-0.173804	-0.168414	-0.146355	-0.094499	-0.148788	-0.14803	-0.14659	-0.133864	-0.155414	-0.110604
II	off	-0.137014	-0.16767	-0.229232	-0.205811	-0.266512	-0.239072	-0.322656	-0.300221	-0.31675	-0.323221	-0.244413	-0.269487	-0.29158	-0.263029
III	on	-0.333955	-0.377299	-0.355751	-0.349868	-0.330686	-0.32897	-0.20304	-0.177291	-0.22176	-0.223162	-0.285504	-0.294552	-0.28433	-0.269184
III	off	-0.036321	-0.04874	-0.084368	-0.058478	-0.088503	-0.055403	-0.153805	-0.130552	-0.152979	-0.150881	-0.0914	-0.108262	-0.14773	-0.136294

was performed at 130 Hz with 60 μ s pulses. In most cases, the amplitude was increased slowly from 1.0 V to a maximum of 2.5 V using the contact on the dorsal part of the STN until optimal motor control was achieved.

IV. Statistical analysis

Differences between the 2 groups were compared using two sample *t*-tests. Pearson's correlation coefficient was calculated to determine the relationships of the parameters. A *p*-value of less than 0.05 was considered significant. Preoperative UPDRS score and postoperative improvement in UPDRS score were compared with rCBF on each Talairach Daemon Level. Probability values of less than 0.207 were considered significant.

Results

I. Correlation between preoperative UPDRS score and rCBF

Significant correlation between the preoperative UPDRS score and rCBF on the Talairach Daemon

Fig. 3 Graphs showing the improvement of Unified Parkinson Disease Rating Scale part III (off stage) score and regional cerebral blood flow (rCBF) in the temporal (upper left), limbic (upper right), and occipital lobes (lower left), and superior temporal gyrus (lower right). Group A: 47 patients with >60% improvement, Group B: 37 patients with 40–60% improvement, Group C: 8 patients with <40% improvement.

Level 2 was indicated by a threshold value coefficient ≤ -2.07 (Fig. 2, Table 2). UPDRS part II (off stage) and III (on stage) scores had stronger negative correlation than UPDRS part II (on stage) and III (off stage) scores with the rCBF on Level 2. UPDRS part II (off stage) score was significantly correlated to the rib in the parietal lobe, temporal lobe, occipital lobe, limbic lobe, and midbrain ($p < 0.05$). UPDRS part III (on stage) score was correlated with the frontal lobe, midbrain, pons, and cerebellum.

UPDRS part II (off stage) and III (on stage) scores were negatively correlated with rCBF in the fusiform gyrus, superior and inferior parietal gyri, middle occipital gyrus, superior frontal gyrus, and middle temporal gyrus of Talairach Daemon Level 3 (Table 3). In particular, rCBF in the middle frontal gyrus and medial frontal gyrus showed significant negative correlations with the UPDRS part II (off stage) and III (on stage) scores ($p < 0.05$), whereas rCBF in the cerebellum had significant positive correlations with UPDRS part II (off stage) and III (on stage) scores ($p < 0.05$).

Similarly, rCBF had significant negative correlations in Brodmann areas 6, 7, 8, 31, 39, 45, and 46 of the Talairach Daemon Level 5 ($p < 0.05$), with the highest coefficient in area 8. The limbic lobe, and the bilateral temporal lobes, parietal lobes, and occipital lobes formed a specific domain.

II. Postoperative improvement of motor function and rCBF

rCBF was significantly greater in Group A than in Group B in the frontal lobe, parietal lobe, temporal lobe, and occipital lobe of the Talairach Daemon Level 2 ($p < 0.05$) (Fig. 3). rCBF was significantly greater in Group A than in Group B in the middle temporal gyrus ($p = 0.00147$), medial frontal gyrus ($p = 0.00713$), and cerebellum ($p = 0.048$) of the Talairach Daemon Level 3. The rCBF values in Group C patients were measured to assess the cutoff value at which postoperative improvement of >40% could be expected. rCBF values in the frontal lobe, parietal lobe, temporal lobe, occipital lobe, and limbic lobe of Group C were 38.8 ± 6.2 , 39.5 ± 6.7 , 36.0 ± 5.8 , 36.6 ± 6.6 , and 35.2 ± 6.6 ml/min/100 g, respectively (Fig. 3).

Discussion

Various studies have reported changes in rCBF in patients with PD, but the findings were inconsistent. In most of these studies, the reduction in rCBF might have been related to cognitive function. In the present study, patients with PD conformed to the inclusion criteria of DBS, so patients with severe

dementia were excluded. Other studies have focused on the relationship between motor function and rCBF.²⁴⁾ Comparison of cerebral blood flow data for patients with PD to those of healthy controls by measuring rCBF using technetium-99m ethyl cysteinate dimer SPECT and statistical parametric mapping (SPM) analysis found that rCBF was significantly decreased in the middle frontal gyrus, right thalamus, left superior lobe, precuneus, right inferior parietal lobe, and right middle and inferior temporal lobes, and significantly increased in the vermis and right upper cerebellar hemisphere of patients with PD compared to healthy controls.^{4,10,15,16,18,19,24,27)} A cerebral blood flow study using technetium-99m hexamethylpropyleneamine oxime SPECT and SPM analysis^{5,9,22,23)} showed that cerebral blood flow was negatively correlated with the UPDRS part III scores in the parahippocampal gyrus, inferior parietal lobule, anterior cingulate gyrus, postcentral gyrus, and insular area.^{1,2,12-14)} These observations were consistent with our findings.

Few studies have examined rCBF in patients with PD undergoing STN DBS. Study of changes in rCBF following STN DBS in 20 patients with PD using SPECT and tracer ethylcysteinate dimer revealed significant increases in rCBF in the anterior cingulate gyrus/supplementary motor cortex in the 12 good responders to DBS.³⁾ Positron emission tomography with 18-fluorodeoxyglucose in patients with advanced PD before and after DBS showed that STN DBS suppressed cerebellar hypermetabolism and partly restored physiologic glucose consumption in the limbic and associative projection territories of the basal ganglia.¹¹⁾ These studies suggest that STN-DBS has variable effects on rCBF.

Careful patient selection is important for obtaining consistent DBS outcome. The criteria for the optimal outcome are advanced PD with optimal age, disease duration, and no or very mild cognitive and psychiatric impairment.^{28,30)} In our study, patients in Group A were significantly younger than those in Group B. Accurate assessment of these components or determination of the cutoff values remain difficult. This study found that rCBF of the middle temporal gyrus, medial frontal gyrus, and cerebellum was significantly correlated with the rate of improvement of UPDRS part III (off stage) score, and the cutoff value was >40% improvement after DBS. These findings suggest that preoperative measurement of rCBF may be useful for clarifying the surgical indications for DBS in PD patients.

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