Relationship between striatal [^{123}I]β-CIT binding and four major clinical signs in Parkinson's disease

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We investigated the correlation between clinical severity and striatal [^{123}I]β-CIT binding in 12 patients with Parkinson's Disease (PD: 6 men and 6 women, age: 65 ± 7 years, Hoehn & Yahr stage: 1 to 3). The clinical severity of PD patients was measured with the Unified Parkinson's Disease Rating Scale (UPDRS) after withdrawal of antiparkinsonian medication at least 12 hours before assessment. [^{123}I]β-CIT binding in the caudate and putamen was measured at 3 hours [V''$_3$ (day 1)], and at 24 hours [V''$_3$ (day 2)] after tracer injection with small square ROIs. The specific striatal uptake index (day 2) was calculated with large square ROIs that encompassed the whole striatum. The best correlation ($r = -0.82$, $p < 0.0012$) was between putamenal V''$_3$ (day 2) and the motor UPDRS scores. When the motor UPDRS scores were divided into four subscales, bradykinesia was the only sign that correlated significantly with putamenal V''$_3$ (day 2) ($r = -0.81$, $p < 0.002$). [^{123}I]β-CIT SPECT is a useful marker of disease severity in PD with potential utility in the serial monitoring of disease progression.

Key words: Parkinson's disease, single photon emission computed tomography, β-CIT, dopamine, transporter

INTRODUCTION

PARKINSON'S DISEASE (PD) is a common movement disorder, and has four cardinal signs: tremor, rigidity, akinesia, and postural instability. Clinical scales are based on combinations of these major signs, and commonly used to quantify the severity of PD[1] but it is often difficult for advanced PD patients to withdraw from antiparkinsonian drugs for the evaluation of disease severity. Therefore, an objective measure of disease severity without the need to withdraw patients from medical treatment is needed to assess disease progression of PD for the evaluation of possible neuroprotective drugs.[2] The progression of motor signs and symptoms in PD is believed to arise from progressive loss of nigrostriatal dopaminergic neurons.

Positron emission tomography (PET) studies of [^{18}F]fluorodopa (FDOPA) uptake in the striatum have been the gold standard for functional evaluation of nigrostriatal dopaminergic neurons in PD.[3–7] Measurements deriving from FDOPA PET have been shown to have a direct linear relationship to the clinical severity of PD[3–5] and also to the nigral cell count.[6,7] There have been two attempts to measure disease progression of PD with FDOPA PET.[8,9]

The cocaine derivative [^{123}I]($1R$)-2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT) has recently been introduced to visualize striatal dopamine transporters *in vivo* in the human brain with single-photon emission tomography (SPECT).[10–12] The dopamine transporter is a protein located in the presynaptic membrane on the terminals of nigrostriatal dopaminergic neurons; it provides a marker of dopamine terminal innervation without the need to withdraw patients from antiparkinsonian medications such as L-dopa.[13] Prior SPECT imaging studies have shown that the reduction in striatal [^{123}I]β-CIT binding in PD patients is correlated with the disease severity.[14–18] In the present study, we compared three methods to measure striatal [^{123}I]β-CIT binding, and also investigated the correlation between four clinical major

signs of PD and striatal [^{123}I]β-CIT binding. This study was performed as a part of the initial trial of [^{123}I]β-CIT SPECT in Japan.

MATERIALS AND METHODS

Subjects

Twelve patients (age, 65 ± 7 years) with PD (Hoehn-Yahr stages 1–3) were enrolled in the study after obtaining informed consent (Table 1). Patients fulfilled the clinical criteria for the diagnosis of PD.[19] Magnetic resonance imaging of the brain was normal in all patients. All patients were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS)[1] by one of the investigators (H.S.) within a month of the SPECT study. All antiparkinsonian medications were withdrawn at least 12 hours before clinical assessment to produce a practically defined "off state."

Data acquisition and analysis

Patients were allowed to take their antiparkinsonian medication on the day of tracer administration. All patients received supersaturated potassium iodide solution (800 mg orally) prior to tracer injection. SPECT-studies were performed with a triple-head rotating scintillation camera (Picker Prism 3000 Odyssey) equipped with low-energy, ultrahigh resolution collimators, and the spatial resolution was 7 mm full width at half maximum in all three axes. The patient was laid in the supine position to obtain images. [^{123}I]β-CIT [Daiichi Radioisotope Co., Tokyo, 185 (n = 5) or 275 (n = 7) MBq] was injected as a single bolus in each patient. SPECT scans were performed for 24 minutes starting at 3 hours (day 1), and 24 hours (day 2) after tracer injection. Images were acquired with the energy window set at 159 ± 24 keV, and reconstructed with a ramp filter. The high frequency waves were cut off by the Butterworth filter (cutoff = 0.75 cycle/sec, power

factor = 8 for day 1 scan, and cutoff = 1.35 cycle/cm, power factor = 8 for day 2 scan), and attenuation correction was performed by Chang zero-order correction based on an ellipse fit to brain with a linear attenuation factor (μ = 0.08 /cm). 5-mm thick cross-sectional images oriented parallel to the cantho-meatal plane were displayed in 128 × 128 matrices (pixel size = 2 mm/pixel).

The ratio specific to non-displaceable uptake in the striatum, also designated striatal V''_3 (unit-less), is proportional to the density of the transporter (Bmax) within the region of interest (ROI), if one assumes that striatal [^{123}I]β-CIT uptake does not change during imaging.[11] To calculate striatal V''_3, two contiguous transaxial slices (10 mm thickness) representing the most intense striatal uptake were summed. Then three contiguous square ROIs (10 mm × 10 mm) were placed for the caudate, anterior putamen and posterior putamen on both hemispheres, and one large square ROI was placed in the occipital area. Putamenal [^{123}I]β-CIT uptake was calculated as the average of [^{123}I]β-CIT uptake in the anterior and posterior putamens on both hemispheres. Data were expressed as counts per minute per pixel (cpm/pixel) for each brain region. Assuming that occipital uptake is equal to the non-displaceable uptake in the striatum, striatal V''_3 for both day 1 scan and day 2 scan was calculated with the following equations.[11]

Striatal V''_3 = [Striatal uptake (cpm/pixel) − occipital uptake (cpm/pixel)]/occipital uptake (cpm/pixel)

Another method was used to calculate a specific striatal uptake index (SSUI) that represents specific [^{123}I]β-CIT binding in the whole striatum. To calculate SSUI, ten contiguous transaxial slices (50 mm thickness) covering the whole striatum were summed. One large square ROI encompassing the whole striatum was placed on both hemispheres, and one large square ROI was placed in the occipital area. SSUI (day 2) was calculated as described

Table 1 Patient demographics

Patient	Age/Sex (yr)	Dominant side	Duration of illness (yr)	Hoehn & Yahr stage	Total UPDRS scores	Motor UPDRS scores	Treatment
1	68/F	Left	0.5	1	7	4	T 6 mg
2	67/M	Right	3	1	12	9	Nil
3	45/F	Left	5	1	24	16	D 300 mg, P 750 μg
4	64/F	Right	4	1	44	19	D 400 mg, P 750 μg
5	62/F	Left	4	2	24	17	D 200 mg, T 6 mg
6	66/F	Right	6	2	26	19	D 300 mg, T 2 mg
7	72/M	Right	2	2	43	28	D 200 mg, T 4 mg
8	65/M	Right	4	2	44	34	D 400 mg
9	66/F	Right	6	2	44	23	D 300 mg, B 5 mg, T 6 mg
10	77/M	Symmetric	4	3	34	25	D 400 mg
11	64/M	Left	3	3	46	32	D 300 mg, T 4 mg
12	64/M	Left	3	3	51	37	D 500 mg, T 6 mg

UPDRS: Unified Parkinson's Disease Rating Scale, Motor scores: motor scores of the UPDRS, D: L-dopa/DCI, T: Trihexyphenidyl, P: pergolide, B: bromocriptine
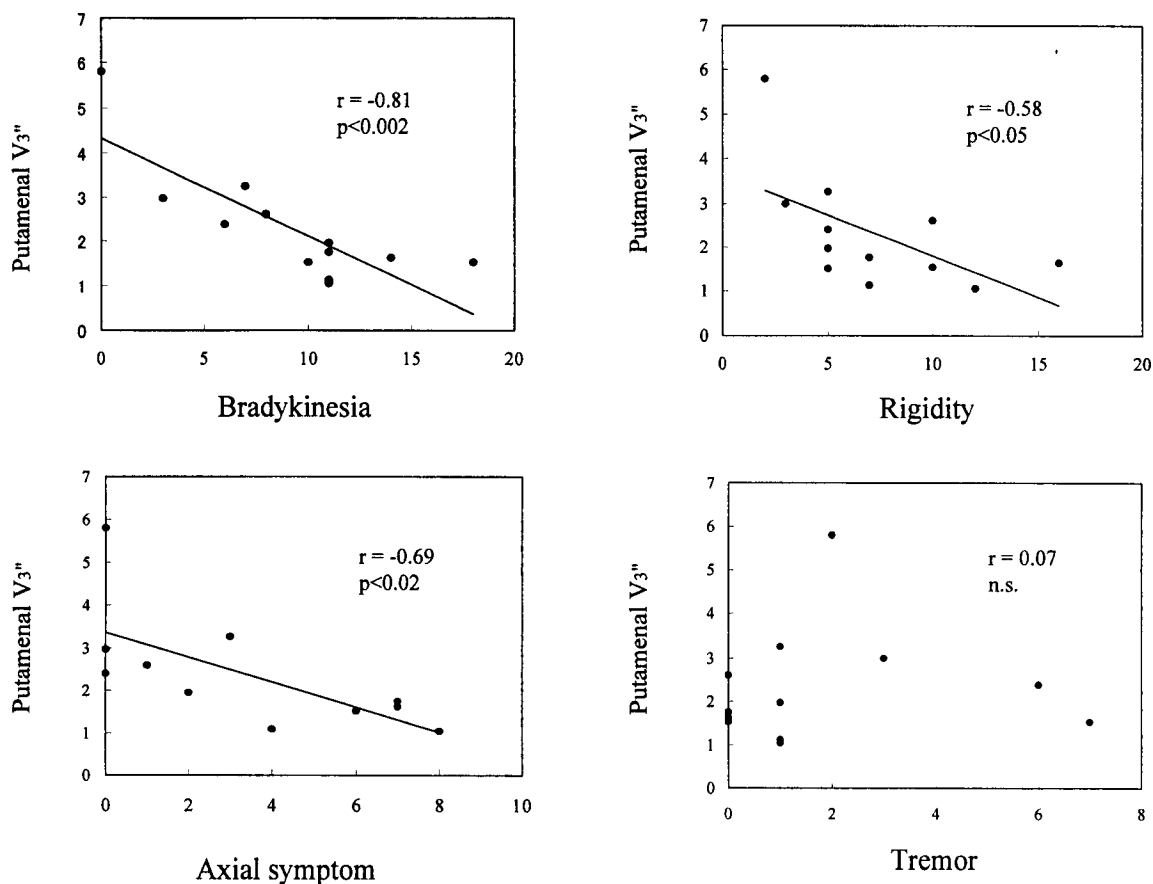
Fig. 1 Correlation between the four subscales of the UPDRS (bradykinesia, rigidity, tremor, and axial symptoms) and the putamenal V''_3 (unitless). For the UPDRS score, a higher score indicates greater disability.

below.

Specific striatal uptake (cpm) = Total striatal uptake (cpm) − [occipital uptake (cpm/pixel) × striatal ROI area (pixel)]

Then,

SSUI (ml) = [specific striatal uptake (cpm)/occipital uptake (cpm/pixel)] × pixel volume (ml/pixel)

Statistical analysis

We performed separate regression analyses for the motor UPDRS scores (UPDRS items 19–31)[1] on the results of SPECT outcome measures [$V''3$ (day 1, day 2), and SSUI]. We selected the method of [^{123}I]β-CIT SPECT analysis that correlated best with the motor UPDRS scores to analyze further the correlation between clinical symptoms and SPECT results. To compare the degree of correlation of the major signs of PD with $V''3$, four subscales were extracted from the motor UPDRS scores: (1) bradykinesia score: facial expression, speech, the six repetitive movements of the limbs, and generalized bradykinesia; (2) rigidity score: rigidity of the four limbs and the neck; (3) tremor score: tremor in the four limbs

and head; (4) axial score: posture, postural stability, standing up from a sitting position, and gait. Then a stepwise multiple regression of putamenal $V''3$ on the subscales for bradykinesia, rigidity, tremor and axial symptoms was carried out. The reported results do not include corrections for multiple comparisons, but a conservative multiple comparison adjustment would require a significance level of $p < 0.005$.

RESULTS

Putamenal $V''3$ (day 2) correlated best with the UPDRS scores in PD patients ($r = -0.82$, $p < 0.002$) and was selected as the SPECT reference for the rest of the study. Caudate $V''3$ (day 2) correlated less with motor UPDRS scores than putamenal $V''3$ (day 2) ($r = -0.76$, $p < 0.005$). SSUI correlated even less with clinical severity ratings than caudate and putamenal $V''3$ (day 2) ($r = -0.68$, $p < 0.016$). There was no significant correlation between caudate ($r = -0.37$, n.s.) and putamenal $V''3$ (day 1) ($r = -0.49$, n.s.) and clinical severity.

Among the four major clinical signs of PD, the bradykinesia score had the highest correlation ($r = -0.81$, $p <$

0.002) with putamenal V''_3 (day 2) (Fig. 1). The correlations between putamenal V''_3 (day 2), the axial score (r = -0.69, p < 0.02), and the rigidity score (r = -0.58, p < 0.05) were insignificant. The tremor score showed no correlation with putamenal V''_3 (day 2). After stepwise multiple regression, the bradykinesia score was the only subscale that contributed significantly to the overall correlation with putamenal V''_3 (day 2) (r = -0.81).

DISCUSSION

[^{123}I]β-CIT is a ligand with high affinity for dopamine and serotonin uptake sites, and [^{123}I]β-CIT binding is virtually exclusive to dopamine transporters in the striatum.[11] In the present study, [^{123}I]β-CIT SPECT was used to examine dopamine transporter density in the striatum as a measure of the integrity of nigrostriatal dopaminergic neurons in PD. We found a prominent reduction in striatal [^{123}I]β-CIT binding as clinical severity advanced in our patients.

We calculated V''_3 (day 1) in addition to V''_3 (day 2) as a measure of striatal [^{123}I]β-CIT binding. If V''_3 (day 1) is a useful measure to assess the disease severity of PD, it would not be necessary for patients to come for the day 2 scan, but we did not find any significant correlation between V''_3 (day 1) and the UPDRS scores in PD patients. Equilibrium of striatal [^{123}I]β-CIT binding is assumed for the calculation of V''_3, but it has been shown that striatal [^{123}I]β-CIT binding reaches a plateau around 20 hours after injection.[11] Therefore, the calculation of V''_3 (day 1) may not be adequate as an index of dopamine transporter binding. We also calculated SSUI (day 2) as an index of dopamine transporter binding in the whole striatum, but we found less correlation between SSUI and clinical severity rating in PD patients than with putamenal V''_3 (day 2). The present results suggest that putamenal V''_3 (day 2) is the best measure of disease severity in PD, in keeping with the predominant motor function of the putamen and the concentration of the pathology in this region. The present results also indicate that SSUI may be less accurate than striatal V''_3 (day 2). Since SSUI is calculated by using large ROIs that encompass the whole striatum, SSUI may be more susceptible to effects of errors derived from estimates of the non-displaceable uptake in the striatum by using the occipital uptake. The occipital uptake may not be exactly equal to the non-displaceable uptake in the striatum not only biologically but also technically, since the errors in scatter and attenuation correction of gamma lines in the striatum and occipital areas may be different.

We found by stepwise multiple regression that the bradykinesia score was the only sign that correlated significantly with putamenal V''_3 among the four major clinical signs of PD. Previous SPECT studies with [^{123}I]β-CIT have also shown good correlation with clinical parameters in PD.[14-18] Seibyl et al.[14] investigated the

correlation between UPDRS scores, bradykinesia, tremor and striatal V''_3 in 28 patients with PD. They found a good correlation between the bradykinesia score and striatal V''_3, but no significant correlation between the tremor score and striatal V''_3. In their study, however, they did not investigate the correlation between striatal V''_3 and rigidity or axial scores. Brücke et al.[15,16] investigated the correlation between subscales of the UPDRS and striatal V''_3 in 113 patients with PD. They found the best correlation between striatal V''_3 and axial scores, followed by rigidity and bradykinesia scores. They did not find any correlation between striatal V''_3 and tremor scores. In their study, however, the clinical severity ratings were performed in PD patients on antiparkisonian medication[16] so that their clinical severity ratings might not truly reflect disease severity in their patients. Rinne et al.[17] investigated the correlation between the Hoehn-Yahr stage and the putamen/cerebellum ratio of [^{123}I]β-CIT binding at 7 hours postinjection, but they did not measure the clinical severity of PD patients with UPDRS. Kim et al.[18] studied 46 patients with PD, and found a significant correlation between striatal V''_3 and the motor disability of the PD patients, assessed by the Hoehn-Yahr stage and the UPDRS scores, but they did not investigate the correlation between striatal V''_3 and subscales of the UPDRS scores.

Several FDOPA PET studies have shown a good correlation between clinical severity ratings and FDOPA uptake in PD.[3-5] Vingerhoets et al.[5] investigated which clinical sign among four major signs best reflects the nigrostriatal lesion in 35 PD patients by FDOPA PET. All antiparkinsonian medications were withdrawn at least 12 hours before assessment to produce an "off state" as in our study. They found that bradykinesia scores correlated best with FDOPA uptake, followed by axial and rigidity scores. The tremor score did not correlate significantly with striatal FDOPA uptake. The present results are in good agreement with their results. The four major parkinsonian signs differ pathophysiologically.[20] Among the four major clinical signs, bradykinesia may be the most directly related to the dopaminergic deficiency in the nigrostriatal system.

FDOPA PET and [^{123}I]β-CIT SPECT measure different functions of the nerve terminals of the nigrostriatal dopaminergic neurons. Striatal FDOPA uptake represents L-aromatic amino acid decarboxylase activity (LAAAD) to produce dopamine and [^{18}F]fluorodopamine, and the vesicular storage capacity to store them.[6,7] LAAAD activity in the remaining nigrostriatal dopaminergic neurons may be increased in PD,[21] whereas dopamine transporter in the nigrostriatal dopaminergic neurons may be decreased in PD. Nevertheless, the present results suggest that striatal [^{123}I]β-CIT SPECT is as good as a measure of clinical severity as FDOPA PET.

Although a significant age-dependent decline in striatal [^{123}I]β-CIT binding has been reported (5 to 8% of the mean ratio per decade),[14,22] age-correction was not per-

formed in this study. But all the PD patients except one were in the seventh and eighth decades in this study, and it has been reported that the age-dependent decline in striatal [^{123}I]β-CIT binding is smaller in PD patients than in healthy subjects.[23] In our study, the patients stopped medication before the clinical assessment but did not discontinue medication before the SPECT scans according to the protocol of the trial of the [^{123}I]β-CIT, since typical clinical doses of L-dopa/carbidopa do not induce significant occupancy of the [^{123}I]β-CIT binding sites.[13]

In summary, [^{123}I]β-CIT SPECT is a useful marker of disease severity in PD with potential utility in the serial monitoring of disease progression. This technique may also be useful for the preclinical diagnosis of PD, selection of antiparkinsonian drugs, optimization of the drug dosage schedule, and prediction of the prognosis of PD.

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