

Limited role of I-123 IPT brain
SPECT in differentiating essential
tremor from early stage of
Parkinson's disease

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SPECT in differentiating essential
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Abstract

Limited role of I-123 IPT SPECT in differentiating essential tremor from early stage of Parkinson' s disease

The study was to assess clinically applicable cut-off value in differential diagnosis among early stage of Parkinson' s disease(PD) and essential tremor(ET) and normal control(NL) groups on I-123-N-(3-iodopropen-2-yl)-2[beta]-carbomethoxy-3[beta]-(4-cholorophenyl) tropane (IPT) SPECT using dual head gamma camera both quantitatively and qualitatively.

50 NL (mean age 27.9), 20 early PD (mean age 58.2), 30 advanced PD (mean age 63.1) and 20 ET (mean age 39.9) were included and performed brain SPECT, 2 hours after administration of I-123 IPT

using dual head gamma camera. Reconstructed SPECT data were assessed for specific/nonspecific binding ratio of striatum using right and left basal ganglia-occipital cortex/ occipital cortex (RBG-OCC/OCC, LBG-OCC/OCC) uptake ratio.

RBG-OCC/OCC and LBG-OCC/OCC ratio were decreased with increasing grade of Hoehn & Yahr (H-Y) stage in PD. Mean value of specific/nonspecific binding ratio was significantly different between advanced PD group and NL group. However, significant overlap of striatal specific/nonspecific binding ratio were observed between PD group and ET group. Suggested cut-off value of striatal binding ratio which can diagnose PD would be 2.1.

In conclusion, although I-123 IPT SPECT may be a useful method for the diagnosis of advanced PD and objective evaluation of progress of clinical stages, care should be made in the differential diagnosis of subclinical and early stage of PD and other motor disturbances mimicking PD such as ET in view of significant overlap in striatal I-123 specific/nonspecific binding ratio.

Key Words : Dopamine transporter, I-123 IPT SPECT, Essential tremor, Parkinson' disease

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I. Introduction

Imaging the presynaptic dopamine transporter with cocaine analogues and single-photon emission tomography (SPECT) has proven to

be a potential diagnostic tool for classifying the extent and degree of dopaminergic nerve cell loss. Iodine-123-N-(3-iodopropene-2-yl)-2- β -carbomethoxy-3 β -(4-chlorophenyl) tropane (^{123}I -IPT) is a dopamine transporter ligand that selectively binds the dopamine reuptake sites. Single-photon emission tomography with cocaine analogues such as [^{123}I] -CIT or [^{123}I]IPT is an accepted method for assessing the dopamine transporter function.

The motor symptoms of patients with Parkinson's disease (PD) are mostly attributed to a striatal dopaminergic deficit secondary to the degeneration of dopaminergic neurons in the substantia nigra. Reuptake of dopamine via the dopamine transporter terminates dopaminergic neurotransmission. Since the dopamine transporter is located on dopaminergic neurons only, its density is considered to closely reflect the integrity of presynaptic dopaminergic neurons in the striatum. The disease develops insidiously, with a prolonged presymptomatic phase during which a loss of dopaminergic neurons occurs.^{1,2} Patients with PD present first with unilateral symptoms that gradually progress to involve both sides. In recent decades advances in nuclear medicine have made possible the imaging of presynaptic mesencephalic dopaminergic neuron pathology in vivo.

Currently interest is particularly focused on dopamine transporter imaging, an alternative approach to evaluate striatal dopaminergic nerve terminals. The dopamine transporter is a macromolecular structure embedded in the axonal membrane.³ The transporter regulates the concentration of free dopamine within the synaptic cleft by facilitating its reuptake into the presynaptic button. Since the dopamine transporter is only located on dopaminergic nerve terminals, it is considered to closely reflect the integrity of presynaptic dopaminergic neurons in the striatum.⁴ Recently various cocaine analogues have been introduced to assess dopamine transporter availability with positron emission tomography (PET) and SPECT. Whereas PET is not readily available for routine use, SPECT can be applied in the evaluation of a large number of patients with manifest PD or those at risk for it. Therefore, dopamine transporter imaging with SPECT may have an impact on the detection of preclinical PD, the monitoring of progression of disease, and the assessment of the efficacy of putative neuroprotective drugs. In patients with unilateral disease (Hoehn and Yahr stage I), degeneration of dopaminergic neurons innervating the ipsilateral striatum compared with the affected side of the body has not yet resulted in

parkinsonian signs. Thus, a loss of dopaminergic innervation in this part of the brain might be considered preclinical.

Essential tremor (ET) is the most common movement disorder, characterized by a 4- to 12-Hz postural tremor affecting the distal part of upper limbs. By definition, patients with ET should not have other neurologic deficits, including parkinsonism. However, the elderly patient with ET may also have rest tremor and mild parkinsonian features, including stooped posture, expressionless face, reduced arm swing, and mild rigidity. Neuronal lesions underlying rest tremor seen in patients with ET are unknown. Pharmacologic and electrophysiologic studies also have failed to differentiate the tremor of such patients from that of benign tremulous PD.

Using a ligand selective for striatal dopamine transporter, ^{123}I -IPT, we performed SPECT on patients with essential tremor. The results were compared with those of control subjects and the patients with early PD. This study was to assess clinically applicable cut-off value in differential diagnosis among early stage of Parkinson's disease and essential tremor and normal control groups on ^{123}I -IPT SPECT using dual head gamma camera both quantitatively and qualitatively.

II. Materials and Methods

We studied 20 patients with essential tremor (12 with postural tremor only and 8 with postural tremor and resting tremor) and 20 patients with early Parkinson's disease and 30 patients with advanced Parkinson's disease. We also included 50 normal, control subjects. At the time of brain SPECT study, all patients had never been treated for the tremor or Parkinson's disease. The means of the ages of the control subjects are 34 ± 16 years and the patients with essential tremor are 39 ± 9 years. The means of the ages of early PD and advanced PD are 58 ± 12 years and 62 ± 11 years. The mean (\pm SD) duration of isolated postural tremor was 16.2 ± 7.1 years. In the patients with postural and rest tremor, the mean (\pm SD) duration of postural tremor was 18.8 ± 8.1 years. They manifested rest tremor 4 to 18 years after the onset of postural tremor. Videotapes of the patients with isolated postural tremor and those with postural and rest tremor were analyzed by two neurologists (M.S.Lee & U.Lee). In all patients with postural and rest tremor, postural tremor predominated over rest tremor. Many of them had mild parkinsonian

features, but they were considered normal for their ages, and none had definite parkinsonism. The mean (\pm SD) duration of PD was 3.55 (\pm 1.81) years. The mean of their Hoehn and Yahr scores was 1.73 (SD = 0.47).

Each group was treated with 150mg of potassium iodide contained in Lugol solution 24 hrs before the study. The subject was laid in supine position and the head was securely positioned in the head holder. Brain SPECT scans were started at 20 minutes and 2 hours after intravenous bolus injection of 6.23 ± 1.37 mCi of ^{123}I labeled with IPT. Data were acquired with a triple-headed gamma camera equipped with medium-energy, ultra-high-resolution and parallel-hole collimators. The data acquisition parameters included a 13.5-cm rotational radius, 20% energy window at 159 keV, 120 projection angles over 360 degrees, and a continuous mode for the Triad 88 SPECT (Trionix, Twinsburg, OH). The matrix size for the Triad 88 was 128×128 (pixel width = 3.2 mm; slice thickness = 3.2 mm). The projection images were reconstructed using a Hamming filter with a cutoff frequency of 0.75 cycles/cm. We used Chang's first-order correction method with an effective attenuation coefficient equal to 0.10 cm^{-1} to compensate for ^{123}I photon attenuation in the human brain. The

reconstructed IPT images were rotated in three orthogonal directions and then sliced in planes parallel to the one containing the anterior and the posterior commissure lines. Regions of interest in the basal ganglia and occipital cortex were drawn on the selected basal ganglia slice at the later time point. The mean counts/voxel/mCi/minute in these regions was measured by dividing the mean counts by the number of voxels in regions of interest, the absolute injection dose, and the duration of the scan. The ratios of basal ganglia-occipital cortex/occipital cortex ($[BG-OCC]/OCC$) uptake were calculated. We calculated the means of the left and the right (BG-OCC)/OCC ratios in the control subjects and the patients with essential tremor and PD. In the patients with PD, we also calculated the (BG-OCC)/OCC ratios of the sides ipsilateral and the contralateral to side with the more severely affected limbs separately. Using analysis of variance (ANOVA), the means of the (BG-OCC)/OCC ratios of the patients with ET and early and advanced stage of PD (means of sides contralateral and ipsilateral to the severely affected limbs) were compared with those of the normal, age-matched control subjects.

III. Result

RBG-OCC/OCC and LBG-OCC/OCC ratio were decreased with increasing grade of Hoehn & Yahr (H-Y) stage in PD (Figure 1 and Figure 2). The mean value of specific/nonspecific binding ratio was significantly different between advanced PD group and NL group (Figure 3). I-123IPT SPECT images also showed decreased uptakes of both basal ganglia in both early and advanced PD (Figure 5 and Figure 6), but there were no significant different in bilateral basal ganglia uptakes between normal control group and essential tremor patient after injection of I-123IPT (Figure 7 and Figure 8). In the patients with PD, the means of the (BG-OCC)/OCC ratios of the sides ipsilateral (2.32 ± 0.32) and contralateral (1.815 ± 0.44) to the more severely affected limbs were significantly lower than in the control subjects. (Table 1) However, significant overlap of striatal specific/nonspecific binding ratio were observed between PD group and ET group (Figure 4). The mean of the (BG-OCC)/OCC ratios of postural and resting tremor patients in ET group was 2.745. The lower 95% of CI was 2.137. Consequently, suggested cut-off value of striatal

binding ratio which can diagnose PD would be 2.1.

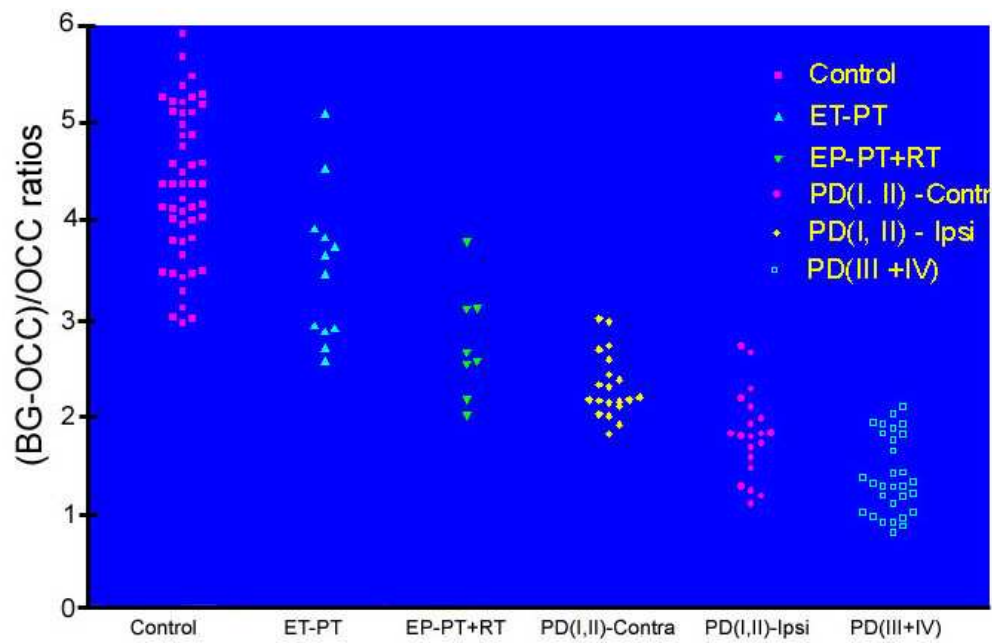


Figure 1. Scatterplot showing (BG-OCC)/OCC ratios of Each Group

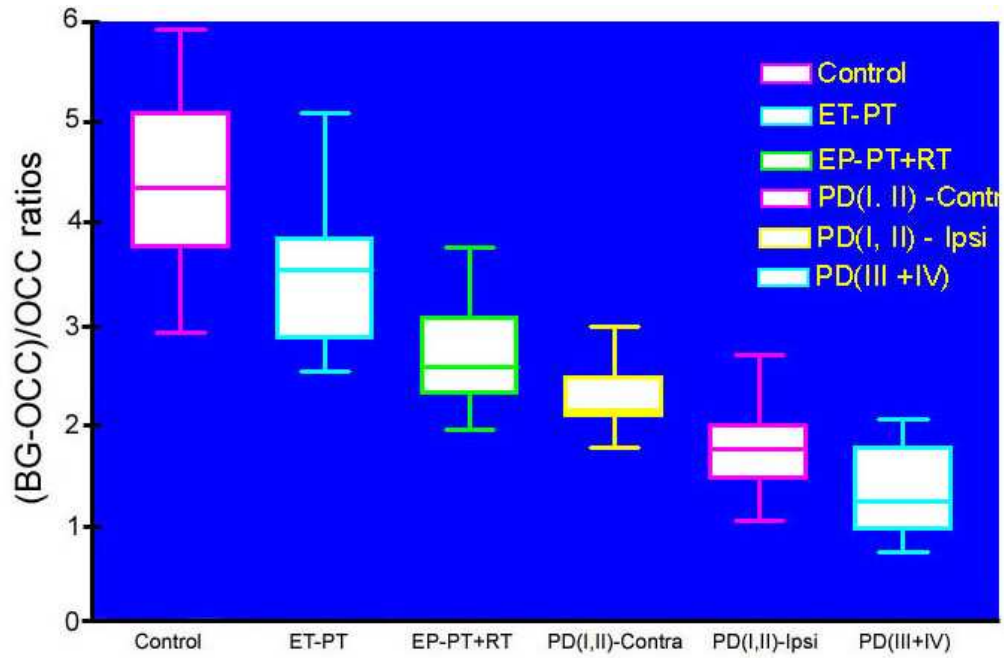


Figure 2. (BG-OCC)/OCC ratios (Mean \pm 2SD) of Each Group

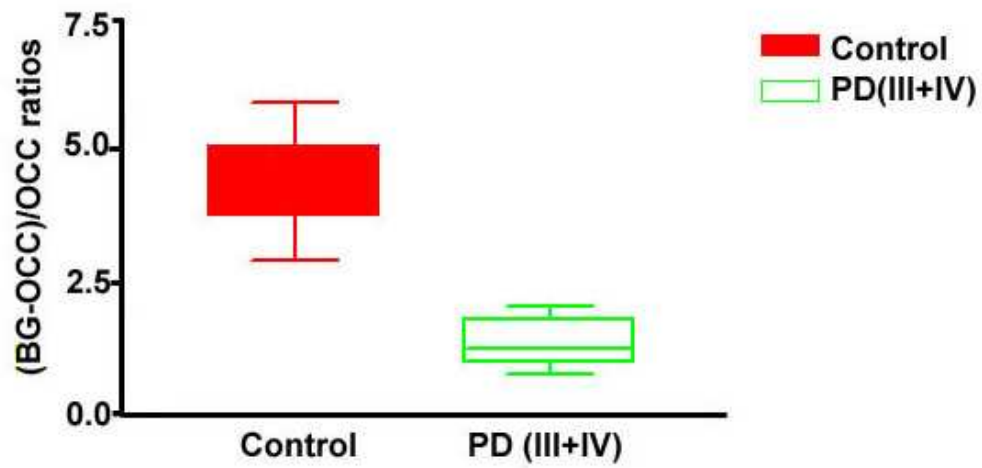


Figure 3. Comparison of (BG-OCC)/OCC ratios between Control Group and Advanced Parkinsonism

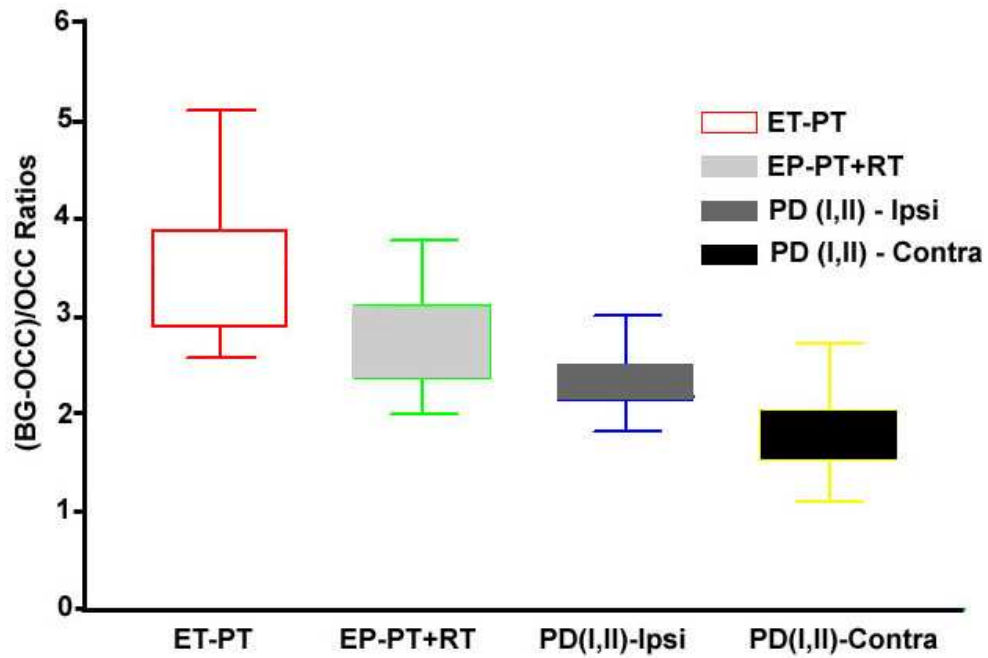


Figure 4. Comparison of (BG-OCC)/OCC ratios between Essential tremor group and Early Parkinsonism

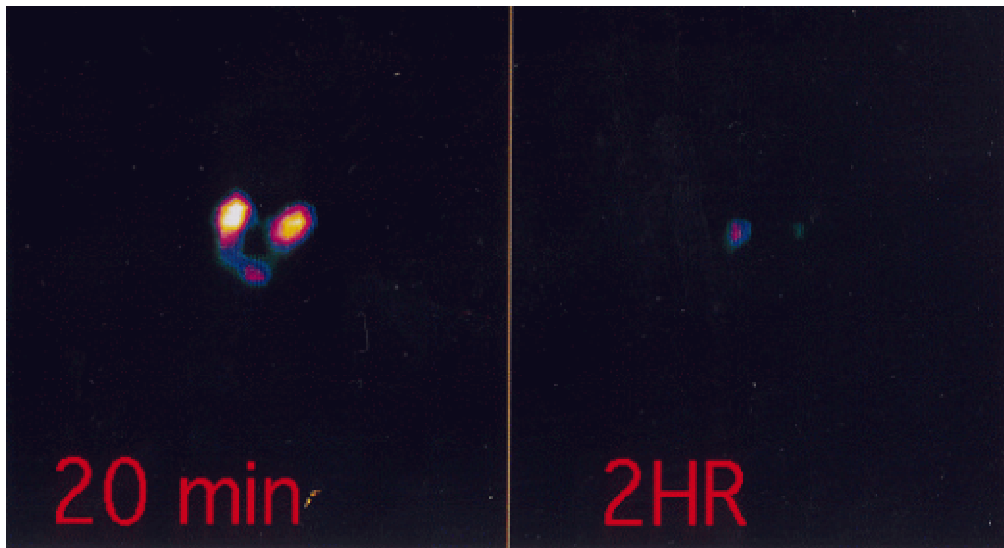


Figure 5. I-123 IPT SPECT of the patient with early parkinsonism
20 minutes image showed non-specific bindings were noted in both basal ganglia and subthalamic nucleus, hence 2 hour image showed uptakes of left basal ganglia were decreased comparing to the right side.

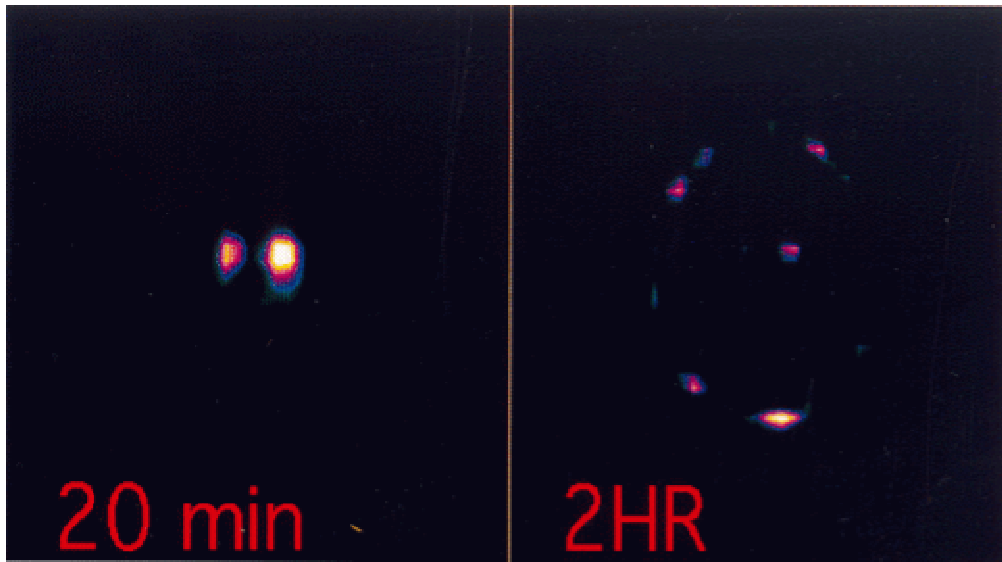


Figure 6. I-123 IPT SPECT images of the patient with advanced parkinsonism

20 minutes image shows non-specific uptakes are noted in both basal ganglia, but severely decreased uptakes are seen in both basal ganglia in 2 hour image.

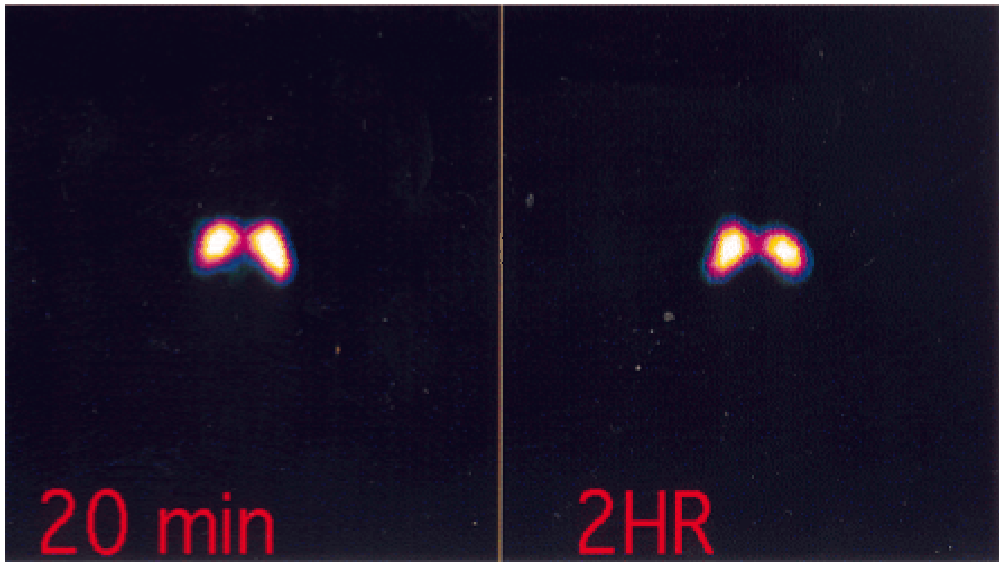


Figure 7. I-123 IPT SPECT images of normal control group
After injection of I-123IPT, 20 minutes and 2 hour images show symmetric uptake of both basal ganglia.

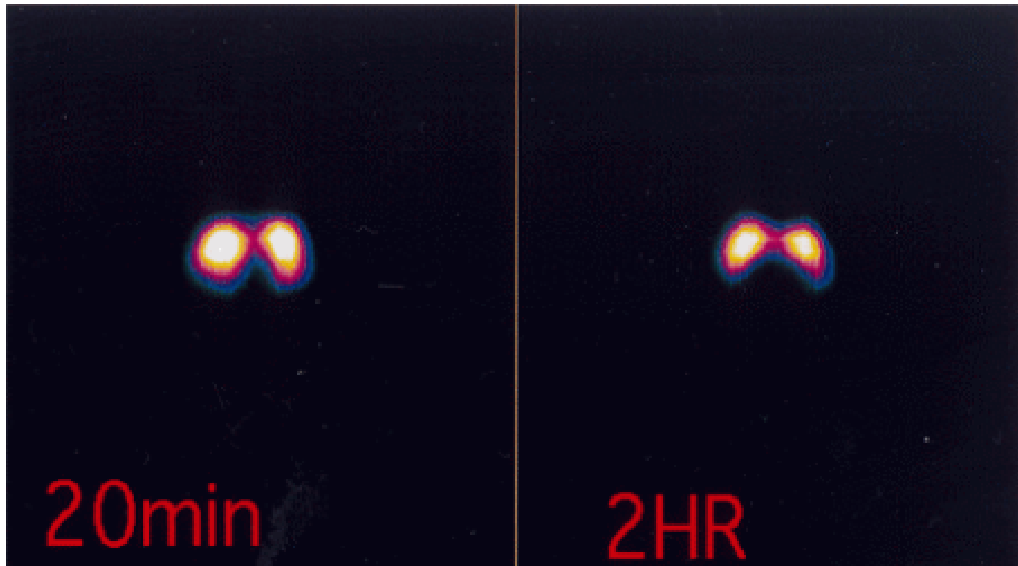


Figure 8. I-123 IPT SPECT image of the essential tremor patient
20 minute image shows symmetric uptakes in both basal ganglia. 2 hour
image also shows bilateral symmetric uptakes in both basal ganglia.

	Control	PT	PT+RT	EP-Ipsi	EP-Contra AP	
No of Pts	50	12	8	20	20	30
Minimum	2.960	2.580	2.010	1.830	1.110	0.8100
Median	4.380	3.565	2.615	2.190	1.820	1.305
Maximum	5.930	5.110	3.790	3.010	2.730	2.100
Mean	4.358	3.528	2.745	2.320	1.815	1.393
Std. Deviation	0.7662	0.7741	0.5720	0.3293	0.4435	0.3946
Lower 95% CI	4.140	3.036	2.137	2.165	1.607	1.246
Upper 95% CI	4.576	4.019	3.223	2.474	2.023	1.541

Table 1. Clinical characteristics of control group and patients with essential tremor and Parkinson' disease

IV. Discussion

Elderly patients with ET have larger-amplitude and lower-frequency postural tremor than younger patients.¹⁰ They may also have rest tremor and other mild parkinsonian features not sufficient to make a diagnosis of PD. The Consensus Statement of the Movement Disorder Society on tremor classified such patients as a subgroup of ET (indeterminate tremor syndrome).⁴

There is a group of patients who present with rest tremor as an initial manifestation and then remain stable for many years, with development of minimal or no other parkinsonian deficits.^{5,6,11,12} Such patients have been described as having monosymptomatic rest tremor,³ symptomatic ET,¹³ variant form of ET,^{6,11} atypical tremor,⁷ forme fruste of PD, benign tremulous PD,⁵ or PD.¹²

There is a subgroup of patients with PD, however, whose onset is preceded by postural hand tremor for more than 5 years. They are classified arbitrarily as having parkinsonian tremor syndrome (type

II),⁴ or ET-PD.^{14,15,16} They constitute 3% to 24% of the patients diagnosed as having PD.^{4,14,15,16}

However, there are no objective scales for deciding acceptable amounts of extrapyramidal features in making the diagnosis of ET. A survey showed that approximately half of 98 movement disorder specialists considered the presence of parkinsonism as an exclusion criterion for the diagnosis of ET, but the remaining half did not.¹⁵ Because of such uncertainties, many contradictory results of clinical and epidemiologic studies of the association between ET and PD have been reported.^{14,16,17}

In monkey studies, isolated damage confined to the substantia nigra rarely causes typical parkinsonian rest tremor, and combined lesions interrupting the rubro-tegmentospinal or rubro-olivocerebellar neuronal pathway are needed to produce rest tremor.²³ However, in humans with focal brain lesions, damage to the dentatorubrothalamic pathway may cause postural or kinetic tremor, and interruption of the nigrostriatal pathway may cause rest tremor.²⁴ Characteristic parkinsonian tremor was observed in four of seven patients with

parkinsonism induced by 1-methy-4-phenyl-1,2,3,6-tetrahydropyridine, which causes selective neuronal damage in the substantia nigra.²⁵

In two neuropathologic studies of six patients with postural and rest tremor, neither Lewy body nor neuronal loss was observed in the substantia nigra. The authors concluded that rest tremor observed in the patients with ET was due to an age-related natural evolution. However, they did not count the number of nigral neurons, and the normal elderly rarely have rest tremor.^{26,27} In an ¹⁸F-dopa brain PET study of 20 patients with postural tremor, 13 of the 20 patients also had rest tremor and 6 of the 13 had additional mild extrapyramidal features, but the mean putamen ¹⁸F-dopa uptake of the 20 patients was comparable with that of normal control subjects. Again, these findings suggest that rest tremor seen in the patient with ET is not caused by nigral neuronal loss.⁵

Although ¹⁸F-dopa brain PET study is an established method for detecting subclinical damage to nigrostriatal neurons,²⁸ putamen ¹⁸F-dopa uptake can be influenced by aromatic amino acid decarboxylase hyperactivity compensating for nigral neuronal loss.²⁹ ¹²³I-IPT brain SPECT study is a sensitive modality that can demonstrate small nigral

neuronal losses associated with age. In normal people, it shows a linear decrease in striatal IPT uptake up to the age of 60 years, but no further decrease after that age. Also, its results correlate well with the severity of PD.^{30,31}

In the current study, RBG-OCC/OCC and LBG-OCC/OCC ratio were decreased with increasing grade of Hoehn & Yahr (H-Y) stage in PD. The mean value of specific/nonspecific binding ratio was significantly different between advanced PD group and NL group. In the patients with PD, the means of the (BG-OCC)/OCC ratios of the sides ipsilateral and contralateral to the more severely affected limbs were significantly lower than in the control subjects. However, significant overlap of striatal specific/nonspecific binding ratio were observed between PD group and ET group.

We suspect that some of the patients with a long history of postural tremor may acquire rest tremor in association with mild nigral neuronal loss. Follow-up neurologic examinations and brain SPECT studies seem to be helpful for clarifying the association between ET and PD. Neuropathologic studies counting nigral neurons

are needed to confirm the mild nigral damage in patients with postural and rest tremor.

V. Conclusion

In conclusion, although I-123 IPT SPECT may be a useful method for the diagnosis of advanced PD and objective evaluation of progress of clinical stages, care should be made in the differential diagnosis of subclinical and early stage of PD and other motor disturbances mimicking PD such as ET in view of significant overlap in striatal I-123 specific/nonspecific binding ratio.

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국문요약

초록 (Abstract)

파킨슨병은 비교적 흔한 운동장애질환으로 흑질(substantia nigra)의 도파민성 신경세포와 해당되는 기저핵의 도파민 함유 신경말단의 퇴행성 변화에 의하여 발병된다. 이러한 신경말단의 퇴행성 변화로 인하여 파킨슨병 환자에 있어 선조체에서의 도파민 운반체 농도도 감소하는 것으로 알려져 있다. 최근에는 PET 와 SPECT 를 이용하여 파킨슨병 환자의 도파민 신경말단의 분포를 나타내는 추적지표로서 도파민 운반체를 영상화할 수 있는 I-123 IPT 를 이용한 도파민 운반체 영상이 국내에서도 시행되고 있다. 본 연구의 목적은 이중헤드 감마카메라를 이용하여 I-123 IPT SPECT 에서 선조체의 도파민 특이결합과 후두엽 뇌피질간의 비특이결합 비율을 이용하여 파킨슨병 환자군과 본태성 진전 등의 다른 운동장애 질환군, 정상 대조군과의 감별을 위한 cut-off value 를 정량적, 정성적으로 분석하여 보고자 하였다.

정상 대조군 50 명(평균 나이 27.9)과 초기 파킨슨병 환자군 20 명(평균 나이 58.2), 진행된 파킨슨병 환자군 30 명(평균 나이 63.1), 본태성 진전 환자군 20 명(평균 나이 39.9)을 대상으로 I-123 IPT 를 정맥 주사후 20 분과 2 시간 후에 이중 헤드 감마카메라를 이용하여 SPECT

영상을 획득하고 재구성하였다. 모든 환자군에서 선조체의 I-123 IPT 의 특이 결합/ 비특이 결합 비율 (RBG-OCC/OCC, LBG-OCC/OCC)을 구하여서 각 군간의 차이를 정량적 및 정성적으로 비교하여 보았다.

I-123 IPT 투여 후 20 분 및 2 시간의 (RBG-OCC/OCC, LBG-OCC/OCC)/mCi 의 비율은 Hoehn-Yahr stage 가 높아짐에 따라 점차 감소하는 경향을 보였다. 정상 대조군과 본태성 진전 환자군에서는 2 시간 영상이 20 분 영상에 비하여 섭취율도 높게 나타났고 표준 편차도 적었다. Hoehn-Yahr stage 가 높은 환자에서는 20 분 영상과 2 시간 영상에서 섭취율과 표준 편차의 차이가 없었다. 선조체의 I-123 IPT 의 특이 결합/ 비특이 결합 비율은 진행된 파킨슨병 환자군과 정상 대조군에서는 평균값의 차이가 유의하였다. 하지만 상당한 I-123 IPT 의 특이 결합/ 비특이 결합 비율이 초기 파킨슨병 환자군과 본태성 진전 환자군 사이에 관찰되었다. 편측 파킨슨병 환자에서 I-123 IPT 의 특이 결합/ 비특이 결합 비율은 증상이 나타난 반대측 선조체에서 뿐만 아니라 같은쪽 선조체에서도 정상 대조군이나 본태성 진전군에 비하여 유의하게 감소되어 있었다. 대상 초기 파킨슨 환자 20 명중 편측 증상을 보인 7 명의 환자에서 I-123 IPT SPECT 상의 좌우측 선조체간의 특이 결합/ 비특이 결합 비율 간의 차이를 이용한 편측화 결과는 임상 증상의 편측화와 일치하였다.

결론적으로 I-123 IPT SPECT 는 진행된 파킨슨병의 진단과 치료에 따른 임상경과 진행의 객관적인 지표로서의 역할을 할 수 있을 것으로

생각되며 특히 결합/ 비특이 결합 비율 (RBG-OCC/OCC, LBG-OCC/OCC)의 cut-off value 로서는 2.1 을 사용할 수 있겠지만 임상 증상이 발현되기 전단계의 조기 파킨슨병의 진단이나 파킨슨병과 유사한 운동증상을 보일 수 있는 다른 운동질환군과의 감별진단에 있어서는 각 군간의 중첩되는 비율이 있음에 적용에 신중을 기해야 함을 알 수 있었다.

핵심되는 말 : 도파민 수용기, I-123IPT SPECT, 본태성 진전, 파킨슨병