Preliminary clinical application of dopamine transporter imaging with technetium-99m TRODAT-1 and SPECT on the early and differential diagnosis of Parkinson's Disease

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Abstract The aim of the study was to demonstrate the degeneration of the dopaminergic nigrostriatal pathway in Parkinson's disease(PD) and Essential Tremor (ET) by using the cocaine derivative ^{99m}Tc-TRODAT-1 SPECT and correlate the findings to the clinical severities (Hoehn and Yahr scale, H/Y). 28 patients with idiopathic Parkinson's disease, 10 patients with Essential Tremor and 19 healthy volunteers were investigated. The acquisition were performed 3 h postinjection of ^{99m}Tc-TRODAT-1. ROIs were drawn over the images of striatum and cerebellum, and ratios of striatum to cerebellar(ST/CB) were calculated. Ratios differed significantly between PD and controls, but ratios didn't show significant difference between ET patients and controls. A significant correlation didn't exist between ratios and clinical severities. Hemiparkinson's patients revealed significantly diminished ^{99m}Tc-TRODAT-1 binding not only clinically affected but unaffected side. Our findings indicated that ^{99m}Tc-TRODAT-1 SPECT is not only a reliable method to discriminate between PD and controls but also a useful tool for differential diagnosis in clinically unclear cases such as ET resembling PD.

Keywords Parkinson's disease, SPECT, Dopamine transporter, ^{99m}Tc

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1 INTRODUCTION

Pankinsonism is a feature of a number of subcortical degenerations, including Pakinson's disease (PD), multiple system atrophy, progressive subcortical gliosis, essential

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tremors. These various parkinsonian syndromes may be difficult to be precisely diagnosed with clinical criteria alone. This is especially the case in their early stages when distinguishing clinical features are absent, only 70%–80% PD patients can be diagnosed correctly.[1]

PD is characterized pathologically by degeneration of pigmented and other brainstem nuclei, particularly the substantia nigra compacta, in association with the formation of neuronal eosinophilic Lewy's inclusion bodies. Clinical symptoms usually appear when there is a 50% loss of pigmented cells in nigra compacta and a 80% loss of dopamine in putamen.[2]

In recent years, dopaminergic neurotransmitter and receptor imagings are highly active area of investigation. It has been discovered that dopamine transporter which serves to remove dopamine from the synaptic cleft is located in the presynapse of dopaminergic neurons. The change of dopamine transporter is more sensitive and direct than dopamine receptor in PD patients. The experiments demonstrated that ^{99m}Tc-TRODAT-1 is a radiolabelled tropane that binds dopamine transporters.[3]

The aim of the present study is to investigate patients with Parkinson's disease of different severity to evaluate alterations of dopamine (DA) transporters in the striatum in comparison with healthy volunteers and patients with Essential tremor and to correlate these results with clinical data.

2 MATERIALS AND METHODS

2.1 Patients

The sample included 28 patients with clinically diagnosed Parkinson's disease (14 women and 14 men, age range 24-77 year with median of 59 year), and 10 patients with Essential tremor (4 females and 6 males, age range 28–83 year). The interval between symptom onset and participation in this study ranged from 4 months to 6y (mean 2.43±2.40 year) for PD patients, and from 1–20 year for ET patients, (mean 8.6±9.5 year). Patients were examined neurologically by three experienced physicians. The severity of disease was classified according to Hoehn and Yahr (H/Y), 13 patients in stage I, 5 in stage II, 8 in stage III and 2 in stage IV, each patients suffered from at least 2 of the four cardinal feature of Pakinson's disease. The exclusion criteria were designed to prevent patients with a history of any other neuropsychiatric disease, patients with only 1 of the 4 cardinal features of the disease and patients didn't have a favorable response to dopamine replacement therapy during their illness were excluded. ET patients were diagnosed mainly by continuous postural tremor primarily in dual hands for more than 3

years without significant bradykinesia, rigidity or other neurological disorders. 19 healthy volunteers (5 females and 14 males, age range 37–84, year mean 58 year) were also included in this study. The study was approved by the local ethics committee and informed consent was obtained from each subject. Therapy with l-(-)-deprenyl was stopped at least 18 h before ^{99m}Tc-TRODAT-1 application.

2.2 Radiopharmaceuticals preparation

The TRODAT-1 was manufactured by State Key Laboratory of Nuclear Medicine, Wuxi, Jiangsu, CHINA. High performance liquid chromatography (HPLC) and thin layer chromatography (TLC) were used to evaluate the radiochemical purity of ^{99m}Tc-TRODAT-1. Radiochemical purity was greater than 94% and the specific activity was >18.5 TBq/mmol.

2.3 SPECT procedure

600 mg sodium perchlorate were administered before tracer injection. Each subject received a mean dose of 66.6×10^7 Bq (55.5×10^7–74×10^7Bq) of ^{99m}Tc-TRODAT-1 intravenously. SPECT image acquisition was performed at 3 h afterinjection. Slices were acquired 100 s/frame. All scans were obtained with a dual head SPECT; PICKER, AXIS equipped with high resolution collimator. The acquisition parameters included a continuous mode with 30 projection angles over a 180° arc to obtain data in a 64×64 matrix with pixel width of 4.24 mm.

2.4 Image processing

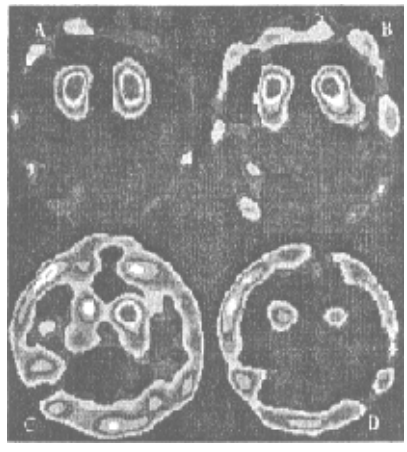
All images were reconstructed with iterative correction. WEINER filter (order of 0.50) was applied, and Chang's first order correction method was used to compensate for photon attenution. For analysis of striatal ^{99m}Tc-TRODAT-1 binding, the ratio of specific to non specific binding was calculated by summing up two transversal slice representing the most intense striatal binding. Analysis were performed blind to the clinical data. ROIs were drawn manually on two slice-views by one investigator over the right and left striatum, respectively, including cerebellum (size: 50–55pixels each) using a brain atlas for help. Right and left striatal values were calculated separately, and cerebellar ROIs were obtained on the slice of best visualization, usually the 10 th slice below the striatum. Cerebellum were taken as reference. In that case, we calculate the ratio of striatum to cerebellum (ST/CB) for semiquantitation.

2.5 Statistics

The calculated specific binding as well as binding ratios were compared among controls and PD and ET groups using Student t-test. In patients of different H/Y stages, ratios of ipsi and contralateral to clinical symptoms of the H/Y-1 stage were also compared using Student's t-test for paired data. Correlations between striatal ratios and H/Y stages were evaluated with one way ANOVA and regression analysis. $p < 0.05$ was regarded as significant. Values are group means ±SD.

3 RESULTS

Visual analysis of the ^{99m}Tc-TRODAT-1 images demonstrated marked reduction in the striatal uptake in PD patient, compared with the healthy control subjects, but doesn't show pronounced difference between ET and volunteers, as shown in Fig.1. Visual evaluation also demonstrated that there was relatively greater loss in the posterior striatum. ^{99m}Tc-TRODAT-1 also show significant left/right asymmetry of striatal uptake relative to the controls. It didn't reveal marked difference between ET and controls groups.



A: Healthy controls B: Essential tremors
C:PD(H/Y=I) D:PD(H/Y=IV)

Fig.1 ^{99m}Tc-TRODAT-1 uptake

The ratios of specific to non specific striatal ^{99m}Tc-TRODAT-1 binding in PD patients are shown in Table 1, that of ET patients and controls are shown in Table 2. All ratios in patients with Parkinson's disease were significantly lower than controls and ET patients, no marked differences were revealed between ET groups and healthy controls ($p > 0.05$).

Comparing the data of whole striatum in patients with unilateral Parkinson's disease (H/Y=1, n=13) with the healthy controls, striatal-cerebellar binding ratios were bilaterally significantly reduced (ipsilateral: $p < 0.01$, $t > 2.89$; contralateral $p < 0.001$, $t < 4.62$), but the ratios of contralateral to clinical symptoms was reduced more than ipsilateral (t=2.16, $p < 0.05$). Correlation was not found between clinical severity of PD according to H/Y (r=0.115, $p > 0.05$).

Table 1 The ratio of ST/CB and clinical severity in PD patients

Region	PD							
	H/Y-1 (n=13)		H/Y-2 (n=5)		H/Y-3 (n=8)		H/Y-4 (n=2)	
	Ipsi	Contra	Left	Right	Left	Right	Left	Right
Whole striatum	1.38±0.30	1.31±0.18	1.36±0.13	1.24±0.21	1.29±0.16	1.30±0.17	1.29±0.13	1.33±0.21
Caudate	1.45±0.32	1.40±0.27	1.41±0.13	1.34±0.26	1.38±0.18	1.49±0.24	1.30±0.11	1.49±0.37
Putamen	1.38±0.11	1.30±0.09	1.38±0.15	1.20±0.19	1.29±0.18	1.24±0.14	1.31±0.15	1.29±0.14

Notes: Where values are group means ±SD, PD= Parkinson's disease. H/Y=Hoehn and Yahr Staging scale

Table 2 The ratio of ST/CB in ET patients and controls

Region	ET (n =10)		Controls (n=19)	
	Left	Right	Left	Right
Whole striatum	1.76±0.15	1.78±0.17	1.82±0.13	1.80±0.17
Caudate	1.79±0.17	1.86±0.26	1.83±0.14	1.88±0.23
Putamen	1.84±0.17	1.83±0.16	1.90±0.16	1.86±0.23

Notes: Where values are group means ±SD, ET=essential tremor

4 DISCUSSION

Parkinson's disease is a progressive neurodegenerative disease characterized by an insidious onset. The ability of routine lives and working were severely injured. Early diagnosis of PD seemed to be more critical, especially if neuroprotective pharmacological interventions are being considered. Moreover, there is increasing evidence that nigrostriatal dopamine dysfunction can develop many years in a subclinical form in genetically predisposed individuals.[4]

PET and SPECT allow examination of the presynaptic nigrostriatal dopaminergic system in the human brain *in vivo*. Various ligands for imaging DA transporter have been introduced successfully.[5,6] Using ^{11}C-nomifensine and PET, it has been shown that patients with Parkinson's disease can be distinguished from controls. Frost *et al*[7] and Rinne *et al*[8] showed a clear loss of DA transporters in PD by means of ^{11}C-win 35, 428 and PET. ^{123}I-β-CIT also showed a severe loss of striatal dopamine transporter in PD, more pronounced in the putamen than the caudate neucleus. However, slow

kinetics of ^{123}I-β-CIT is a serious drawback, because an adequate image acquisition should be performed about 24 h after injection which is highly inconvenient for outpatient evaluations.

We found significantly lower striatal binding ratios in PD compared to controls. In the PD groups, a preferential loss of DA transporter binding was found in the putamen, which is probably due to the more extensive degeneration of subpopulations of DA neurons. Interestingly, the striatal binding of patients with unilateral Parkinson's disease (H/Y=1) were significantly reduced bilaterally, indicating that ^{99m}Tc-TRODAT-1 SPECT constitutes a tool for identifying patients in the preclinical phase of the disease, who might benefit from therapy with these agents and monitor their disease progression.

Unexpectedly, in the Parkinson's disease group, regression analysis revealed that the clinical severity of disease (H/Y stage) didn't correlate with ^{99m}Tc-TRODAT-1 striatal ratios, as shown in another study,[9] possibly due to the relatively small group of patients. However, methodological differences regarding the SPECT camera and procedure, especially heterogeneous group of PD patients may also underlie the discrepancy between our findings and those reported by Ishikawa *et al.*[10] More patients need to be examined to seek more accurately the correlation between disease severity and ^{99m}Tc-TRODAT-1 SPECT measures.

In ET patients, the ^{99m}Tc-TRODAT-1 image and binding ratios of only one patient was similar to PD patients, but the others showed significant difference, indicating that ^{99m}Tc-TRODAT-1 SPECT might be a useful tool for differentiating PD patients from the essential tremor resembling PD and other Parkinsonism.

It follows from all these observations that ^{99m}Tc-TRODAT-1 SPECT is a reliable method to discriminate between Parkinson's disease patients and healthy controls but also a useful tools for differential diagnosis in clinically unclear cases such as essential tremor resembling PD. Unilateral Parkinson's disease showed a bilateral loss of striatal TRODAT-1 binding. This finding indicates that ^{99m}Tc-TRODAT-1 SPECT can identify the subclinical patients with Parkinson's disease. Moreover, due to the rapid kinetics of ^{99m}Tc-TRODAT-1 compared to ^{123}I-β-CIT, the former radioligand has the practical advantage of detecting the presynaptic dopaminergic dificit as early as 2–3 h after injection, which may be more convenient for outpatients. In addition, ^{99m}Tc is more easily available than ^{123}I.

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