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Comparable investigation in dopamine transporters with ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT in Parkinson's disease patients

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Abstract Dopamine transporter (DAT) mediates the regulation of dopaminergic function. Two agents of TRODAT-1 and FP-CIT were observed in evaluating DAT change of Parkinson's disease (PD). The relationship between them was also evaluated. The results suggested that ^{99m}Tc-TRODAT-1 SPECT and ^{131}I-FP-CIT SPECT may serve as sensitive and objective *in vivo* markers to reflect the severity of PD. The ^{99m}Tc-TRODAT-1 image is more accurate and clearer compared with ^{131}I-FP-CIT.

Key words ^{99m}Tc-TRODAT-1 SPECT, ^{131}I-FP-CIT SPECT, Parkinson's disease

CLC numbers R445, R445.6

1 Introduction

^{99m}Tc-TRODAT-1([2-[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]oct-2-yl]methyl](2-mercaptoethyl) amino] ethyl] amino] ethanethiolato (3-) -*N2*, *N2'*,*S2*,*S2*']oxo-[1*R*-(*exo-exo*)]) is a radiolabeled tropane that binds Dopamine transporter (DAT) [1,2]. It has been widely used as an effective probe for investigating the dopaminergic system in Parkinson's disease (PD) patients.

The ^{123}I-labeled DAT ligand N-ω-fluoropropyl-2-β-carbomethoxy-3-β- (4-iodophenyl) nortropane (^{123}I-FP-CIT) is increasingly used in diagnosing patients with Parkinsonian syndrome in developed countries. For accurate diagnostic decision-making, a comparison of ^{99m}Tc- TRODAT-1 and ^{123}I-FP-CIT SPECT is advisable. Nevertheless, there is no ^{123}I available in China. We conducted this study as a trial with ^{131}I-FP-CIT SPECT, which may provide some information for future investigations with ^{123}I-FP-CIT SPECT. To the authors' knowledge, cross study with ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT has not been reported up to now.

2 Patients, materials and methods

2.1 Patients

Thirty-one patients with various severities of PD were prospectively studied with both ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT. The PD patients were diagnosed by the Department of Neurology of Huashan Hospital according to generally accepted criteria [3]. They received neurological examinations by two experienced neurologists. A clinical diagnosis of idiopathic PD required display of at least two of the following symptoms: resting tremor, akinesia, and rigidity, with a favorable response to L-dopa therapy. The patients, 21 men and 10 women, aged 39~73 (mean:51.7±7.3) and had a PD history of 1~15 years. Assessed by the Hoehn and Yahr Scale (HYS) and the motor examination of the Unified PD Rating Scale (UPDRS), their UPDRS ranged form 6 to 17, and

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HYS ranged from stage 1 to stage 4. Among them, 11 were HYS 1-1.5 (8 men and 3 women, aged 39–73 with mean age at 56.5±8.8), 10 were HYS 2 (7 men and 3 women, aged 51–69 with mean age at 58.0±5.9), and 10 were HYS 4 (6 men and 4 women, aged 42-65 with mean age at 56.8±7.5). Each patient underwent ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT within a month. All subjects gave their informed consent for participation in the study, which was approved by the institution research boards. Six age-matched healthy volunteers (4 men and 2 women, aged 46~60 with mean age at 52.50±4.72) served as controls. Their brain CT and MRI were normal.

2.2 Radiopharmaceuticals

^{99m}Tc-TRODAT-1 was prepared from a freeze-dried kit (provided by Institute of Wuxi National Atomic Energy Research) by adding 1,110 MBq (30mCi) of freshly eluted ^{99m}Tc- pertechnetate to 0.5 mL of saline preparation [1], and was autoclaved for 30 min to complete the labeling. The ^{99m}Tc-TRODAT-1 was obtained in a neutral solution (pH 7.0~7.5), and its radiochemical purity was more than 90% in 6 hours after labeling, as determined by high-performance liquid chromatography. ^{131}I-FP-CIT was prepared as previously described [4].

2.3 Imaging and data analysis

2.3.1 ^{99m}Tc-TRODAT-1 SPECT

The patients were asked to lie supine, and the position of their head was fixed with a holder. The data acquisition commenced 2.5~3.5h after injection of 1,110 MBq of ^{99m}Tc-TRODAT-1, using a dual-head camera (Siemens e.cam Variable Angle) equipped with fanbeam collimators. The data were acquired in a 128×128 matrix with a 1.4 zoom, obtaining multiple views over 360° (180° for each detector) in 30s of acquisition time per projection at an angular step of 6°.

2.3.2 ^{131}I-FP-CIT SPECT

^{131}I-FP-CIT SPECT imaging was implemented 5 to 7 days after the ^{99m}Tc-TRODAT-1 SPECT. Before the ^{131}I-FP-CIT SPECT acquisition, all subjects were required to orally take compound iodine solution for three days (1mL, tid). During the ^{131}I-FP-CIT SPECT imaging, all patients were kept in almost the same condition as that during the ^{99m}Tc-TRODAT-1 SPECT imaging. Data were acquired at 3~4h after injection of 111MBq of ^{131}I-FP-CIT, using the same SPECT with medium energy collimators. The time after tracer injection for SPECT imaging was selected based on previous reports demonstrating that the time window between 3 and 6 hours allows stable measurement of specific-to-nondisplaceable ratio of ^{123}I-FP-CIT [5]. The data were collected at 40 k counts per slice with the same matrix, zooming and rotating in the same way as in ^{99m}Tc-TRODAT-1 SPECT imaging. The duration was about 30 min.

2.3.3 Image reconstruction and ROI technique

Images were reconstructed using a Butterworth filter (cut-off, 0.5 cycles/pixel; order, 10) and corrected for attenuation using Chang's algorithm. The SPECT images were analyzed along the level of the canthomeatal line. Regions of interest (ROI) were marked for the striatum of each hemisphere, on images showing the highest basal ganglia activity. The occipital cortices (OC) were also drawn on the same images and served as background areas. Specific uptake ratios (SUR) in the striatum were calculated by dividing the mean counts per pixel in the whole striatum region by the mean counts per pixel in the background, i.e. striatum (ST)/ OC.

Contralateral striatum is opposite to the limbs with clinical symptoms or the first limbs suffered from clinical symptoms, and ipsilateral striatum is the same side striatum of those limbs.

2.4 Statistical analysis

The relationship between SUR in contralateral striatum and disease severity (UPDRS) was tested by Spearman rank correlation and the relationship between the SUR of ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT. Two-tailed tests were used in comparison analysis. All *P* values were two-sided and set at a significance of 0.05.

3 Results

Uptake of ^{131}I-FP-CIT and ^{99m}Tc-TRODAT-1 decreased bilaterally in the PD patients and was more profound with HYS (Table 1). Table 2 showed a significant difference in specific uptake of ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT between contrala-

teral striatum and ipsilateral striatum among HYS groups, except ^{99m}Tc-TRODAT-1 SPECT of the HYS4 group. In the HYS groups, the striatal SUR of ^{131}I-FP-CIT was higher than that of ^{99m}Tc-TRODAT-1.

Table 1 Specific uptake ratios of striatum of PD patients in different HYS and UPDRS scales

Patient No	Sex	Age	Symptom side	History of PD/a	HYS	UPDRSII	^{99m}Tc-TRODAT-1		^{131}I-FP-CIT	
							R	L	R	L
1	M	73	L	2	1	9	1.24	1.39	1.36	1.34
2	M	56	R	7	2	10	1.17	1.12	1.4	1.4
3	F	50	L	2	1	11	1.22	1.16	1.3	1.37
4	F	58	L	5	2	10	1.48	1.54	1.74	1.91
5	F	56	R	1	1	9	1.27	1.3	1.33	1.2
6	M	54	R	3	1.5	8	1.43	1.29	2.39	2.16
7	M	55	L	2	1	9	1.12	1.12	1.86	2.21
8	M	62	R	2	2	8	1.68	1.45	1.26	1.24
9	M	52	L	2	2	6	1.13	1.26	1.78	1.87
10	M	62	L	5	2	13	1.04	1.13	1.08	1.16
11	F	60	L	3	2	17	0.88	0.92	1.34	1.37
12	M	63	R	4	4	12	1.56	1.61	1.55	1.56
13	F	50	R	5	2	10	1.38	1.35	1.37	1.36
14	F	55	L	7	4	9	1.23	1.25	1.28	1.32
15	M	55	R	3	1.5	15	1.58	1.59	1.36	1.27
16	F	39	L	1	1	9	1.43	1.64	1.62	1.57
17	M	69	L	3	2	12	1.16	1.23	1.21	1.21
18	M	60	R	5	1	12	1.93	1.86	1.28	1.24
19	M	60	L	4	4	10	1.37	1.27	1.31	1.39
20	F	56	L	3	4	12	1.07	1.14	1.39	1.5
21	M	65	L	5	4	12	1.09	1	1.28	1.17
22	M	55	L	1	1	6	1.19	1.28	1.55	1.71
23	F	42	R	10	4	13	1.21	1.14	1.58	1.34
24	M	56	R	9	1.5	15	1.2	1.13	1.48	1.3
25	M	68	R	5	1	12	1.26	1.15	1.16	1.49
26	F	65	R	8	4	10	1.23	1.15	1.78	1.61
27	M	60	R	10	2	12	1.28	1.15	1.47	1.22
28	M	59	B	8	4	12	1.35	1.14	1.56	1.69
29	M	56	B	6	4	12	1.21	1.19	1.45	1.57
30	M	47	B	15	4	11	1.3	1.16	1.51	1.55
31	M	51	R	2	2	7	1.56	1.53	1.95	1.81

Table 2 SUR of contralateral striatum (CL ST) and ipsilateral striatum (IL ST) in two imaging modality

HYS	^{99m}Tc-TRODAT-1			^{131}I-FP-CIT		
	CL ST	IL ST	*P*	CL ST	IL ST	*P*
1~1.5(*n*=11)	1.32±0.23	1.38±0.24	0.024**	1.49±0.30	1.60±0.37	0.006*
2 (*n*=10)	1.23±0.21	1.32±0.23	0.002*	1.42±0.26	1.50±0.30	0.016**
4 (*n*=10)	1.25±0.16	1.22±0.14	0.27	1.43±0.13	1.51±0.18	0.028**

* $P<0.01$ ** $P<0.05$

In addition, greater loss of uptake in ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT was found in the striatum, as interpreted by quantitative analysis (Fig.1) and directly visual images (Fig.2).

PD patients' UPDRS had a significant negative correlation with SUR of the contralateral striatum in both ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT (Fig.3), but there was no correlation between UPDRS and SUR in ipsilateral striatum.

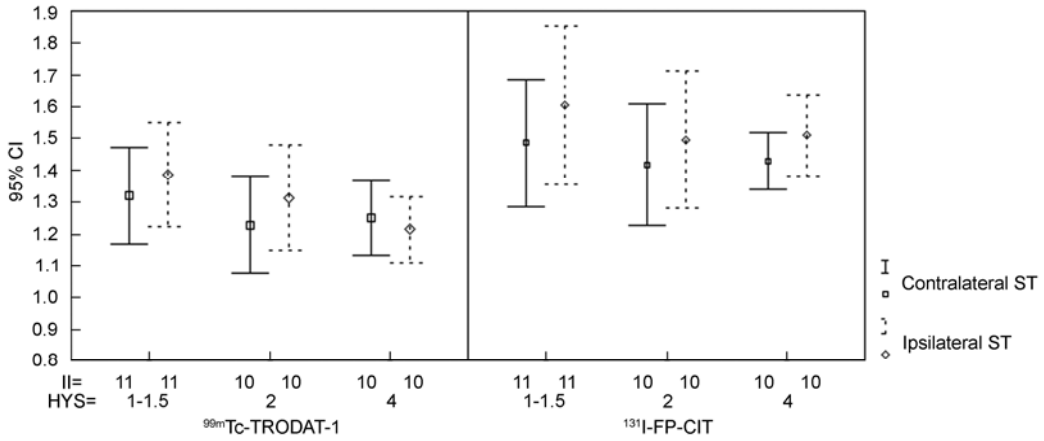

Fig.1 The means of striatal SUR of HYS 1-1.5, 2 and 4 PD groups in ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT.

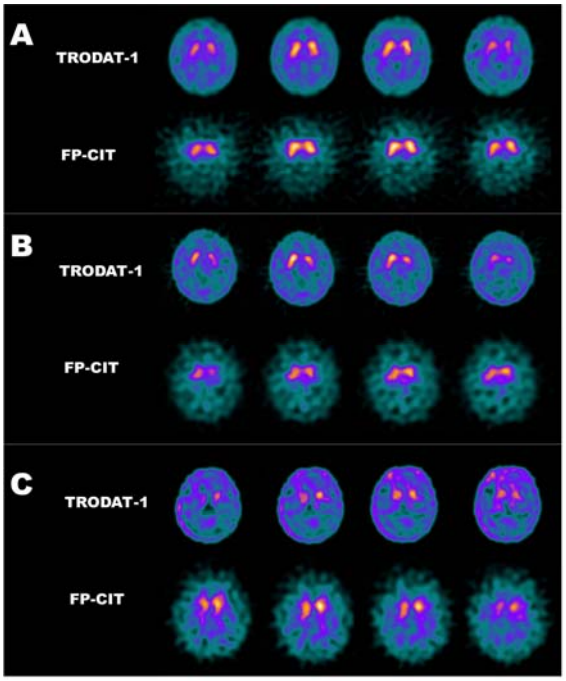

Fig.2 Representative transverse ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT images of healthy volunteer (A), patient with HYS II PD (B) and patient with HYS IV PD (C).

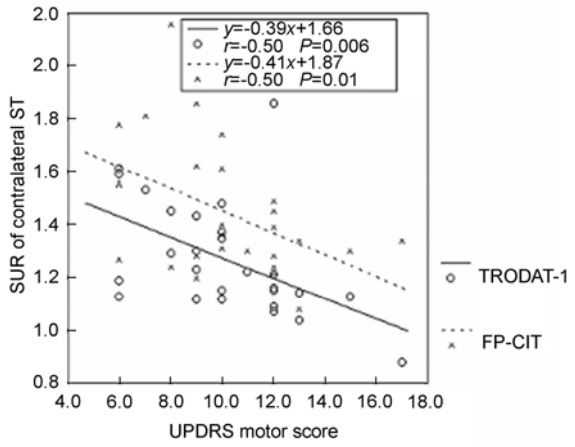

Fig.3 Correlation between UPDRS and the SUR of contralateral striatum in ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT: r=-0.50, -0.50; P=0.006, 0.01.

4 Discussion

The results showed that both ^{99m}Tc-TRODAT-1 and ^{131}I-FP-CIT SPECT imaging could provide dopamine transporters (DAT) evidence in PD patients interpreted by visual inspection and specific uptake value, suggesting that both imaging may serve as a sensitive and objective *in vivo* marker to reflect the onset and severity of PD.

The picture of ^{99m}Tc-TRODAT-1 SPECT [1] is clearer than that of ^{131}I-FP-CIT SPECT. We did some studies [6~10] with ^{125}I labeling beta-CIT, in a hope to do ^{123}I SPECT imaging some day. It is true that ^{131}I-FP-CIT SPECT imaging is not as clear as ^{123}I SPECT imaging, but still, it can indicate the contralateral striatum to the more affected limbs and disease severity (HYS) of PD by the average SUR of ^{131}I-FP-CIT SPECT (Table 2).

Implication of ^{99m}Tc-TRODAT-1 SPECT for monitoring central dopamine-related disorders has recently been intensively investigated. There was no report about investigation with both ^{99m}Tc-TRODAT-1SPECT and ^{131}I-FP-CIT SPECT. This study can be a preparation trial for ^{123}I-FP-CIT SPECT in China in the future.

Owing to limited resolution of a dual-head SPECT camera, the SUR of caudate and putamen nuclei did not allow separate measurements. However, the SPECT imaging still allow discernable detection of putamen nuclei which were impaired worse than caudate nuclei in PD patients.

5 Conclusion

Our results suggested that ^{99m}Tc-TRODAT-1 SPECT and ^{131}I-FP-CIT SPECT may serve as a sensitive and objective *in vivo* marker to reflect the severity of PD and the former is more accurate and more clear than the latter.

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