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Diagnostic accuracy of [^{99m}Tc]TRODAT-1 SPECT imaging in early Parkinson's disease

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Abstract

We evaluated the diagnostic accuracy of SPECT imaging using [^{99m}Tc]TRODAT-1 (TRODAT), a relatively inexpensive technetium-labeled dopamine transporter ligand, in distinguishing 29 patients with early PD from 38 healthy volunteers. Mean TRODAT uptake values were significantly decreased in the caudate ($p = 0.0097$) and anterior and posterior putamen ($p < 0.0001$) of PD patients compared to controls. Using the posterior putamen as the main region of interest resulted in the greatest accuracy (sensitivity 0.79, specificity 0.92). These findings show that TRODAT imaging can accurately differentiate early PD patients from controls and has the potential to improve the diagnosis of patients with early signs of PD.

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1. Introduction

The diagnosis of idiopathic Parkinson's disease (PD) is based on the interpretation of clinical signs and symptoms [1], and can be incorrect at the time of initial presentation when compared with neuropathological diagnosis at autopsy [2]. Although clinical accuracy can be improved to approximately 90% with the application of strict diagnostic criteria and long term follow-up [3,4], the diagnosis of PD remains difficult early in the course of the disease. This will be increasingly important as disease modifying strategies become available for PD. In vivo imaging of the dopaminergic system has the potential to improve the diagnosis of PD in its early stages.

The technetium-99m labeled tropane derivative, [^{99m}Tc]TRODAT-1 (TRODAT), is a radiopharmaceutical

which binds to the dopamine transporter and can be used to image the dopaminergic system. TRODAT has several logistical advantages over the most commonly used SPECT ligand, [^{123}I]β-CIT, including absence of thyroid uptake and faster pharmacokinetics, which allows image visualization within hours, rather than days, of tracer injection. Furthermore, ^{123}I is produced using a cyclotron, limiting its availability and making it relatively expensive. In contrast, TRODAT is easy to produce, and because ^{99m}Tc is widely available, TRODAT could be made in any nuclear medicine facility [5].

Previous studies have shown that TRODAT uptake is significantly reduced in the striatum of patients with PD and that TRODAT can accurately discriminate between patients with established PD and healthy volunteers [6,7]. The goal of this study was to determine the diagnostic accuracy of TRODAT imaging in distinguishing patients with early stage PD from normal individuals.

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2. Methods

2.1. Subjects

All patients were recruited from the Parkinson's Disease and Movement Disorders Center at Pennsylvania Hospital of the University of Pennsylvania Health System. Initial inclusion criteria for undergoing TRODAT imaging were (1) age > 35 years, (2) Hoehn and Yahr stage of 2 or less, and (3) duration of PD symptoms less than two years or UPDRS motor score off medications < 25. If patients were female, they had to be post-menopausal, surgically sterilized or have a negative urine pregnancy test at the time of the study. Patients were examined within three months of imaging with the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr Staging Scale (H&Y) while off medications for at least 12 h to assess the severity of illness. These patients were then followed for a mean of 2.1 years (range 1.4–3.1). During follow-up, the patients had to satisfy the UK Parkinson's Disease Society Brain Bank (UKPDSBB) Clinical Diagnostic Criteria for PD [8] in order to be included in the analysis. Thirty-four patients were imaged; 29 qualified for the study. Of the five patients excluded from analysis, two patients had multiple system atrophy (MSA), one patient had progressive supranuclear palsy (PSP), and two had psychogenic movement disorders. The 29 PD patients (20 men, 9 women; age range 39–75 years with a mean of 59.2 ± 11.8) were matched with 38 healthy volunteers (21 men, 17 women; age range 36–83 years with a mean of 60.8 ± 13.0). The volunteers had no history of neurologic or psychiatric disease, and were not taking medications other than oral contraceptives. Patients and volunteers gave written informed consent to the procedure, and the Institutional Review Board at the University of Pennsylvania approved all research protocols.

2.2. Image acquisition and processing

The TRODAT imaging protocol has been described in detail previously [6]. All individuals in the study were injected with a single bolus dose of 740 MBq (20 mCi) of [^{99m}Tc]TRODAT-1. Brain SPECT images were obtained from 3 to 4 h after injection at a framing rate of 5 min/scan, utilizing a triple-head camera equipped with fanbeam collimators (Picker 3000; Picker International, Cleveland, OH). All image data were acquired in a 128×128 matrix through 40 projection angles over a 120° arc with a pixel width of 2.11 mm and a slice thickness of 3.56 mm. Using a standard backprojection technique with a Butterworth low-pass filter, the images were reconstructed and reoriented according to the anterior–posterior commissural line. Attenuation correction was accomplished using Chang's first order correction method. A set of previously described standardized templates representing the basal ganglia and the whole brain was superimposed and fitted upon

the acquired images [9]. Each region of interest (ROI) on the template (e.g. caudate, anterior putamen, posterior putamen) was slightly smaller than the actual structure it represented, and conformed to the shape of the structure. The template was placed only on the two slices with the highest activity, in order to minimize problems with ill-defined edges and effects of volume averaging. The mean activity per pixel was first calculated for each ROI by adding up the total number of counts in each ROI and dividing by the total number of corresponding pixels. The mean specific uptake values (SUVs) for each region were then calculated by dividing the mean activity per pixel in a given ROI by the mean activity per pixel for the reference region using the equation: $(\text{mean activity ROI} - \text{mean activity reference}) / \text{mean activity reference}$. The reference region is a model for non-specific activity and in our analyses, the frontal and parietal supratentorial areas were used to model non-specific activity. The occipital cortex and cerebellum were not used to model non-specific activity since previous experience has demonstrated that these areas may have low counting rates which could destabilize kinetic analyses [6].

For our analyses, the side of the body that first developed motor symptoms was defined as ipsilateral. For those patients with symmetric presentations (3 of 29 patients) and for controls, the right side was defined as ipsilateral.

2.3. Statistical analysis

Descriptive statistics were calculated for demographic and baseline characteristics of patients and healthy volunteers. Where appropriate, patients and controls were compared using either chi-squared tests or *t*-tests.

Mean SUVs were calculated for ipsilateral, contralateral and mean caudate, anterior putamen and posterior putamen. Values for patients and controls were compared using unpaired *t*-tests. Analyses adjusting for sex and age showed no difference from unadjusted analyses and are not reported. Values are not corrected for multiple comparisons.

Sensitivity, specificity, and positive and negative likelihood ratios (LR) were calculated for each ROI using the standard formula for each ($\text{sensitivity} = \text{No. of true positives} / (\text{No. of true positives} + \text{No. of false negatives})$, $\text{specificity} = \text{No. of true negatives} / (\text{No. of true negatives} + \text{No. of false positives})$, $\text{positive LR} = \text{sensitivity} / (1 - \text{specificity})$, $\text{negative LR} = (1 - \text{sensitivity}) / \text{specificity}$). Receiver operating characteristic (ROC) curves were also calculated for each ROI. A ROC curve is a plot of the true positive rate of a test vs. the false-positive rate. An area under the ROC curve of 1.00 indicates a perfect diagnostic test. The greater the area under the ROC curve, the greater the diagnostic accuracy. The area under the ROC curve for various regions of interest was compared using a non-parametric approach [10]. For each ROI, the cut point identifying the greatest number of patients and controls correctly is reported. All statistical analysis was

carried out using STATA statistical software, version 7.0 (Stata Corp., College Station, TX, USA).

3. Results

Age and gender did not differ significantly between patients and controls. All patients had mild symptoms, with a mean UPDRS motor score off medication of 11.9 (range 3.5–23, SD \pm 5.5), and Hoehn and Yahr (H&Y) stage of 2 or less (mean 1.4, SD \pm 0.5). Only five patients were taking anti-parkinsonian medications at the time of the SPECT scan: one on carbidopa/levodopa only, two on dopamine agonists only, one on both carbidopa/levodopa and an agonist, and one on selegiline. The mean duration since symptom onset was 21.9 months (range 3–48, SD \pm 12.4).

Table 1 shows that the mean SUVs in PD patients were significantly lower than mean SUVs for controls. The difference was not as robust in the mean caudate values ($p = 0.0097$) as in the mean anterior or posterior putamen values ($p < 0.0001$). Overall activity was reduced by an average of approximately 42% in the posterior putamen, 31% in the anterior putamen, and 12% in the caudate. All brain regions of the patients had significantly decreased uptake, except for the ipsilateral caudate ($p = 0.11$). Among patients, the side contralateral to the more affected limb had a greater reduction in TRODAT binding when compared to the ipsilateral side in all regions (16 vs. 8%, in the caudate ($p = 0.04$); 38 vs. 26% in the anterior putamen ($p = 0.01$); and 44 vs. 40% in the posterior putamen ($p = 0.67$)). In comparison, the controls showed no significant asymmetry in uptake. Fig. 1 shows the TRODAT scans of a patient with early PD and a healthy control.

Table 2 shows the sensitivity, specificity, area under the ROC curve, and positive and negative likelihood ratios for the various striatal regions. Quantitative imaging analysis of TRODAT uptake using the mean value of the ipsilateral and contralateral posterior

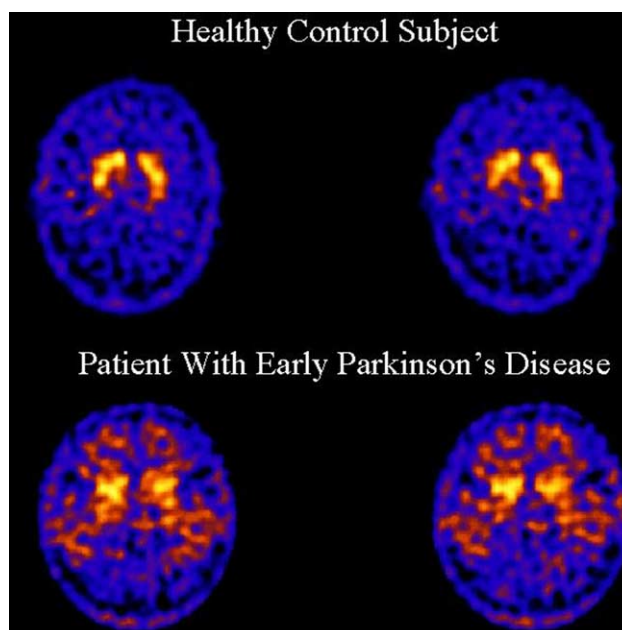


Fig. 1. TRODAT SPECT images of a healthy control (top) and a patient with early PD (bottom). The patient with early PD shows decreased TRODAT uptake in the striatum compared to the control, particularly in the posterior putamen.

putamen resulted in the greatest area under the ROC curve (0.92), and the greatest accuracy, with a sensitivity of 0.79 and a specificity of 0.92. Six of the 29 patients were classified as 'normal' because their TRODAT binding was above the cut-off that best differentiated patients from controls. There were no statistically significant differences between these six patients and the 22 whose TRODAT uptake fell below the cut-off point in terms of age, gender, UPDRS motor scores, UPDRS tremor subscores, or duration of disease.

Table 2
Diagnostic accuracy of quantitative [^{99m}Tc]TRODAT-1 imaging analysis

Region	Sensitivity	Specificity	Area under ROC curve	Likelihood ratio	
				Positive	Negative
<i>Caudate</i>					
Ipsilateral	0.31	0.84	0.61	1.94	0.82
Contralateral	0.55	0.82	0.70	3.06	0.55
Mean	0.48	0.84	0.68	3.00	0.62
<i>Anterior putamen</i>					
Ipsilateral	0.55	0.79	0.76	2.62	0.57
Contralateral	0.76	0.84	0.85	4.75	0.29
Mean	0.66	0.89	0.84	6.00	0.38
<i>Posterior putamen</i>					
Ipsilateral	0.72	0.76	0.82	3.00	0.37
Contralateral	0.83	0.87	0.86	6.38	0.20
Mean	0.79	0.92	0.92	9.88	0.23

ROC: receiver operating characteristic; positive likelihood ratio = sensitivity/(1 – specificity); negative likelihood ratio = (1 – sensitivity)/specificity.

Table 1

Mean specific uptake values (SUVs) in patients with early PD and age-matched volunteers

Region of interest	Patients ($n = 29$)	Volunteers ($n = 38$)	p Value
<i>Caudate</i>			
Ipsilateral	1.34 \pm 0.30	1.46 \pm 0.29	0.11
Contralateral	1.23 \pm 0.37	1.47 \pm 0.24	0.0028
Mean	1.29 \pm 0.31	1.46 \pm 0.23	0.0097
<i>Anterior putamen</i>			
Ipsilateral	0.92 \pm 0.35	1.24 \pm 0.25	<0.0001
Contralateral	0.75 \pm 0.33	1.20 \pm 0.25	<0.0001
Mean	0.84 \pm 0.29	1.22 \pm 0.22	<0.0001
<i>Posterior putamen</i>			
Ipsilateral	0.43 \pm 0.20	0.72 \pm 0.24	<0.0001
Contralateral	0.41 \pm 0.18	0.73 \pm 0.23	<0.0001
Mean	0.42 \pm 0.13	0.72 \pm 0.18	<0.0001

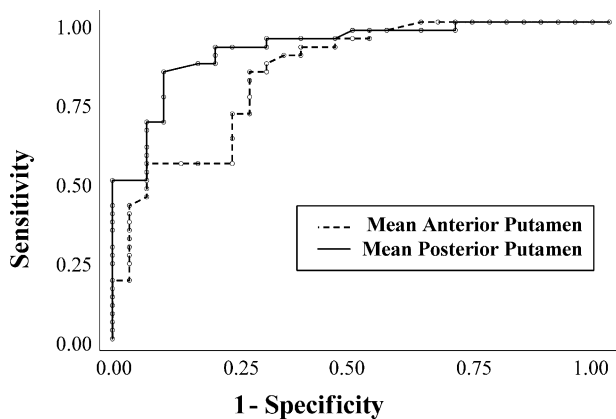


Fig. 2. Receiver operating characteristic (ROC) curves comparing diagnostic accuracy of TRODAT SPECT imaging using uptake values of the mean posterior putamen (area under the ROC curve 0.92) vs. the mean anterior putamen (area under the ROC curve 0.84).

The area under the ROC curve was smaller, and the diagnostic accuracy slightly lower, when using the anterior putamen or the caudate as the ROI. Fig. 2 compares the ROC curves between the mean posterior putamen and the mean anterior putamen. For each striatal region, the area under the ROC curve for the contralateral side was larger than the ipsilateral side, but similar to the area under the curve for the mean of both sides.

4. Discussion

Our results show that TRODAT SPECT imaging can accurately distinguish patients with early PD from neurologically normal individuals and suggest that TRODAT can be a useful test to improve the diagnosis of patients with early signs and symptoms of PD, a group in which clinical diagnosis is less reliable and supportive diagnostic testing is needed. This study extends the findings of previous research [6,7] by not only confirming differences in TRODAT uptake between early patients and controls, but also determining the sensitivity and specificity of TRODAT as a diagnostic test in this patient group. Our study also more closely approximates the setting in which a diagnostic test such as TRODAT would be utilized.

In our patients, we found an anterior-to-posterior gradient within the striatum for both degree of binding and diagnostic accuracy. The posterior putamen of our patients had the greatest decrease in specific binding, which resulted in the greatest ability to distinguish PD patients from controls, while the caudate had the smallest reduction in binding with the lowest capacity to differentiate between the two groups. The anterior putamen was intermediate between the caudate and posterior putamen. PET and SPECT studies using other ligands have also demonstrated a more pronounced abnormality in the posterior putamen of patients with idiopathic PD [6,7,11–16].

Results from previous SPECT studies using other tracers have suggested that the contralateral putamen is the region that most accurately discriminates between PD patients and healthy controls [14,16]. We found that analysis using the mean of the ipsilateral and contralateral posterior putamen resulted in the greatest accuracy. However, analysis using the contralateral posterior putamen was nearly as accurate (area under ROC curve = 0.92 vs. 0.87). Tissingh et al. [15] using [^{123}I] β -CIT, found that discriminant function analysis of both the ipsilateral and contralateral putamen classified 100% of their patients correctly, whereas analysis using only the contralateral putamen classified 92% of cases correctly. These results, along with ours, suggest that analysis using either the mean or contralateral putamen may accurately differentiate PD patients from healthy controls.

Our results show that TRODAT differentiates mild PD patients from normal individuals, but the accuracy of TRODAT in our study was somewhat lower than in the Parkinson Study Group's DOPASCAN study, which found that [^{123}I] β -CIT imaging was able to differentiate patients with PD from healthy controls with a sensitivity of 1.00 and a specificity of 0.95 [16]. There are several possible explanations for the difference in accuracy between the two studies. One is that our patients had milder disease (mean UPDRS 11.9 ± 5.5) than those in the DOPASCAN study (mean UPDRS 38 ± 17). A prior study examining TRODAT imaging in a group of PD patients similar to those in the DOPASCAN study showed that the accuracy of TRODAT was comparable to that of [^{123}I] β -CIT [6]. However, a direct comparison of the two agents in the same patients would be needed to quantify any differences between them. Another possibility is that the ratio of specific to background binding is lower for TRODAT than for DOPASCAN, which limits TRODAT's ability to detect mild changes in dopamine transporter density.

Although TRODAT may discriminate less accurately than other imaging modalities, it still yields diagnostic information that would be relevant to clinicians. For example, in a patient with equivocal signs of parkinsonism, where there is genuine uncertainty as to whether PD is present (pre-test probability of disease = 0.50), a positive TRODAT scan would result in a 91% post-test probability (positive predictive value) of having true disease. A negative test would reduce the post-test probability (negative predictive value) of having disease to 19%. Cutoff points could also be set higher or lower to improve the ability of TRODAT imaging to either rule-in or to rule-out disease.

Our study has several limitations. One is that the investigator analyzing the images was not blinded to whether the subjects were patients or controls. To minimize the impact of this problem, we focused on quantitative rather than visual analysis. Inadequate blinding may still affect quantitative analysis by causing subtle differences in the placement of regions of interest, but the amount of bias introduced is likely to be relatively small because the regions

of interest were placed on the slices with the most intense activity. A second limitation, common to studies evaluating diagnostic technology in PD, is the lack of a gold standard for diagnosis in living patients. Neuropathological examination at autopsy is currently the definitive diagnostic test, but following patients until death is impractical, and accuracy of clinical diagnosis of PD, when applying the UKPDSBB diagnostic criteria, is approximately 90% [3,4]. Thus, by including only patients with early, mild disease, and following them until they met UKPDSBB criteria for PD, we tried to approximate the clinical setting in which TRODAT imaging would be used, while at the same time, maintained a high probability that our patients had typical Lewy body PD.

Finally, our study only examined the ability of TRODAT to distinguish between patients with early PD and neurologically normal individuals. Patients with other parkinsonian syndromes, such as PSP, MSA, and corticobasal ganglionic degeneration (CBGD), were not included in our analysis. As previous PET and SPECT studies have shown decreased tracer uptake in patients with other parkinsonian syndromes [11,16,17], it is probable that TRODAT binding would also be affected in these patients. Future studies are needed to test the accuracy of SPECT imaging with TRODAT in cases of true diagnostic uncertainty. Nonetheless, TRODAT is a logistically favorable SPECT ligand, and our results suggest that it has the potential to improve the diagnosis of patients with early signs of PD.

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