

Differences in [^{99m}Tc]TRODAT-1 SPECT binding to dopamine transporters in patients with multiple system atrophy and Parkinson's disease

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Abstract. *Purpose:* Multiple system atrophy (MSA), a disorder causing autonomic dysfunction, parkinsonism, and cerebellar dysfunction, is difficult to differentiate from other movement disorders, particularly early in the course of disease. This study evaluated whether [^{99m}Tc]TRODAT-1 binding to the dopamine transporter differentiates MSA from other movement disorders. *Methods:* Single-photon emission computed tomographic brain scans were acquired in 25 MSA patients, 48 age-matched controls, and 130 PD patients, 3 h after the injection of 740 MBq (20 mCi) of [^{99m}Tc]TRODAT-1. Regions of interest (ROIs) were placed manually on subregions of both basal ganglia and distribution volume ratios (DVRs) were calculated. Regional DVRs were compared between study groups in MSA patients. Student's *t* tests were used to compare MSA patients with other study groups. Spearman correlations were used to compare DVRs with NP measures. *Results:* Based upon various motor scores, MSA and PD patients had comparable motor impairment, and were significantly impaired compared with controls. Mean DVRs in the basal ganglia of MSA patients were significantly less than those of controls, but generally higher ($p < 0.05$) than in PD patients. In particular, the MSA patients had significantly increased DVRs in the posterior putamen (mean 0.49 ± 0.30) compared with PD patients (0.74 ± 0.25). *Conclusion:* Movement disorder patients could be differentiated from controls, but MSA and PD patients could not be easily differentiated from each other. As a group, MSA patients had significantly higher mean [^{99m}Tc]TRODAT-1 binding, particularly in the posterior putamen, compared with PD patients and significantly lower binding compared

with controls. This may reflect different pathophysiological processes of the two neurodegenerative diseases.

Keywords: Dopamine transporter – Parkinson's disease – Multiple system atrophy – Single-photon emission computed tomography

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Introduction

Multiple system atrophy (MSA) is a neurodegenerative disorder characterized by a combination of autonomic dysfunction, parkinsonism, cerebellar dysfunction, pyramidal dysfunction, and urinary dysfunction [1]. The typical age of onset of MSA is 52–56 years, and the mean survival is 9.3 years [2]. Clinically, MSA is characterized by autonomic dysfunction and/or urinary dysfunction which may be associated with parkinsonian symptoms in 80% of patients (MSA-P) or with cerebellar ataxia in 20% of patients (MSA-C). Since parkinsonism is a presenting feature or occurs at an early stage in the majority of MSA-P patients, it is often difficult to clinically differentiate MSA-P from Parkinson's disease [3].

Parkinson's disease (PD) (paralysis agitans) itself is a common neurodegenerative disorder [4, 5] that has a prevalence of 1–2 per 1,000 among the general population and of up to 2% among people aged over 65 years [6]. Its cardinal features include tremor, rigidity, bradykinesia, and postural instability, and disturbances of gait are also common [7]. The diagnosis of PD is currently based on clinical interpretation of signs and symptoms [4]. Two clinicopathological studies published in the early 1990s found that the accuracy of the clinical diagnosis of PD was approximately 75% at the last clinical visit prior to autopsy [8, 9]. The clinical diagnostic accu-

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racy of PD has now improved to approximately 90% with long-term follow-up and the application of strict diagnostic criteria [10, 11], but an accurate diagnosis remains difficult early in the course of the disease.

Therefore, it is important to identify diagnostic procedures that may help to differentiate between these movement disorders [12]. However, part of the reason for the difficulty in differentiating MSA and PD is that these disorders not only share symptom profiles but also produce dysfunction in similar brain regions. This prevents various brain imaging techniques from being able to adequately separate patients with these disorders. However, such imaging studies can still provide important information about the pathophysiology of MSA and PD.

Since the dopaminergic system is particularly affected in movement disorders such as MSA and PD, many radiopharmaceuticals have been used in brain imaging studies to evaluate presynaptic and postsynaptic dopaminergic receptors in these patients. Imaging studies of MSA and PD have included both single-photon emission computed tomography (SPECT) and positron emission tomography (PET) in order to help diagnose and follow up these patients. It has been suggested that presynaptic dopamine transporter receptor tracers might be particularly useful in the study of MSA and PD. PET studies using the presynaptic tracer [¹⁸F]fluorodopa have generally shown decreased uptake in the striatum in both MSA and PD patients. SPECT studies with ^{99m}Tc-labeled dopamine transporter ligands have also shown decreased uptake in the striatum in PD and MSA patients [13, 14]. [¹²³I]β-CIT has been used to study patients with PD and has shown similar findings, with significantly decreased uptake in the striatum [15, 16]. The question remaining is, How well can various imaging techniques help distinguish patients with PD from those with other parkinsonian syndromes?

The purpose of this study was to evaluate the use of [^{99m}Tc]TRODAT-1, a radiolabeled tropane that binds to dopamine transporters (DAT), in differentiating MSA patients from PD patients. [^{99m}Tc]TRODAT-1 has several characteristics that make it a useful imaging agent. [^{99m}Tc]TRODAT-1 selectively binds to DAT, allowing for effective and specific imaging of the dopaminergic system [17, 18]. In addition, [^{99m}Tc]TRODAT-1 may be more easily used in the clinical setting and is more readily available and less expensive than PET or ¹²³I-based tracers. An important drawback of [^{99m}Tc]TRODAT is the relatively lower specific binding compared with other tracers, like [¹²³I]β-CIT.

In this study, [^{99m}Tc]TRODAT-1 was used to image DAT in the analysis of striatonigral degeneration in 25 patients with MSA-P, 130 patients with PD, and 48 healthy controls. Data analysis tested the following hypotheses:

1. There are significant differences in [^{99m}Tc]TRODAT-1 binding between PD patients and MSA-P patients and how these groups compare with controls.
2. The pattern of [^{99m}Tc]TRODAT-1 binding will effectively differentiate individual MSA-P and PD patients on the basis of receiver operator curves.

Materials and methods

All procedures were approved by the Institutional Review Board and Radiation Safety Committee of the University of Pennsylvania and by the Food and Drug Administration.

PD and MSA patients

The sample comprised 25 MSA-P patients (17 male, 8 female; mean age ± SD 65.9±9.4 years; age range 46.4–80.2 years) and 130 PD patients (87 male, 43 female; mean age ± SD 63.4±10.4 years; age range 39.0–84.2 years). The mean duration of illness for MSA was 4.9±3.6 years and for PD, 6.4±5.4 years. The mean follow-up for final clinical diagnosis for MSA was 3.3±0.6 years and for PD, 3.5±0.7 years. In both MSA and PD patients the clinical diagnosis was made by experienced neurologists specializing in movement disorders. All patients had a Hoehn and Yahr stage of 2 or worse, with values that were generally comparable, although motor function tests (see below) were used to better assess the disease severity in patients. The MSA patients were diagnosed on the basis of the characteristic features of the disease, including a progressive disorder, the presence of parkinsonism, autonomic or urinary dysfunction, cerebellar dysfunction, or corticospinal tract dysfunction [1]. PD patients had to have a progressive disorder, with the presence of at least two of the three cardinal signs of PD (bradykinesia, rigidity, tremor), as well as the presence of two of the following: marked response to levodopa, asymmetry of signs, asymmetry at onset, absence of characteristics of alternative diagnoses, or absence of another etiology known to cause similar features [19].

The past medical histories of all subjects were not remarkable for a disease or event that could have affected brain structure (assessed by magnetic resonance imaging when necessary) or function. Patients were included in the study if the results of their medical history, physical examination, and laboratory studies were not indicative of an underlying disease that could have caused or maintained the movement disorder. Medications were allowed to be continued and most patients were scanned while “on” their medications since previous studies have shown no substantial interaction with dopaminergic medications and [^{99m}Tc]TRODAT-1 binding [20].

Healthy volunteers

The control sample contained 48 age-matched healthy volunteers (23 male, 25 female; mean age ± SD 61.8±11.0 years; age range 40.9–83.3 years). All healthy volunteers included in the study had no significant medical, neurological, or psychiatric diseases.

Neuropsychological examination

The neuropsychological tests administered in this study were compiled by the neuropsychology section of the University of Pennsylvania Mental Health Clinical Research Center and are intended to assess cognitive processes thought to be mediated by dopaminergic function. This battery of neuropsychological tests [21] in-

cludes assessments of motor function with the thumb finger sequential touch (TFST) [22], the finger oscillation test [23], and the Grooved Pegboard [24]. Neuropsychological testing was conducted following injection of the radiopharmaceutical and prior to SPECT imaging. For the purposes of this study, the motor function portion of this battery was used to establish similar disease severity between the MSA and PD groups.

SPECT imaging acquisition protocol

Individuals were placed at rest on the imaging table in the supine position. Vital signs and EKGs were monitored for 10 min prior to injection. An intravenous catheter was placed in an antecubital vein and capped with a well containing normal saline. Subjects were then injected with 740 MBq (20 mCi) of [^{99m}Tc]TRODAT-1. Post-injection vital signs and EKGs were recorded at 5-min intervals for another 10 min. Next, patients underwent 2 h of neuropsychological testing followed by a lunch break.

Patients were scanned 3–4 h following the administration of [^{99m}Tc]TRODAT-1. All images were acquired on a triple-headed gamma camera equipped with fan-beam collimators (Picker Prism 3000XP, Cleveland, OH), with characteristics that have been described previously [25]. The acquisition parameters included a continuous mode with 40 projection angles over a 120° arc to obtain data in a 128×128 matrix with a pixel width of 2.11 mm and a slice thickness of 3.56 mm.

Image processing

All images were processed and reconstructed using the same procedure. Transverse reconstruction backprojection was applied to the raw data. A Butterworth, low-pass filter was then applied with an order of 4 and a cutoff of 0.351 cm⁻¹. Photon attenuation correction was performed by Chang's first-order correction method using an attenuation coefficient of 0.11 cm⁻¹ [26].

Image analysis

The frames that were acquired from 3 h to 4 h after the injection of [^{99m}Tc]TRODAT-1 were summed and imported into an image analysis package called PETVIEW. Image analysis was performed blinded to the clinical diagnosis of each patient. A previously reported standardized template [27] containing six regions of interest (ROIs) was transposed manually onto subregions of the right and left basal ganglia (including the right and left caudate, right and left anterior putamen, and right and left posterior putamen). The ROIs, which are smaller than the areas they are designed to sample, were only placed on the three slices that contained the most intense activity in order to minimize effects of volume averaging in the axial direction. In this way, the ROIs represent a "punch biopsy" of the selected areas. Distribution volume ratios (DVRs) were calculated for these areas based upon a reference region consisting of the supratentorial structures above the basal ganglia and the following equation: (ROI–Reference Region)/Reference Region.

Statistical analysis

Statistical analysis began with unpaired Student's *t* tests in order to compare mean DVRs between patient groups and between pa-

tient groups and controls. Receiver operator curves were generated and logistic discriminant analysis was performed to determine the sensitivity and specificity of various uptake values for differentiating patients with movement disorders from each other and from controls. The statistical software was JMP version 5.1 (SAS Institute, Cary, NC).

Results

The MSA-P and PD patients both performed significantly worse on basic motor function than did age-matched controls (Table 1). There were no significant differences in disease status, disease duration, or severity of motor function between MSA-P and PD patients. Mean DVRs for each of the six subregions of the basal ganglia were calculated along with the standard deviations and are shown in Table 2, which also indicates statistically meaningful differences (*p*<0.05) with 95% confidence.

DVRs for all subregions of the basal ganglia in MSA-P patients were significantly less than those of controls (*p*<0.05). PD DVRs for all subregions were also significantly different from those of controls (*p*<0.05). Receiver operator curves generated for the values for each subregion demonstrated that patients could be differentiated from controls with the accuracy, sensitivity,

Table 1. Comparison of movement tests in MSA-P, PD, and control subjects. Subjects were tested on medications

	MSA-P	PD	Control
Right tap average	37±12*	35±9*	43±9
Left tap average	36±9	34±8*	39±9
Right peg time	153±92*	164±93*	89±30
Left peg time	152±69*	177±85*	107±74
Right TFST	5.8±1.5	6.0±1.6*	6.9±1.9
Left TFST	5.7±1.3	6.0±1.4*	6.9±2.2

*Significantly lower than controls (*p*<0.05)

There were no significant differences between MSA-P and PD patients.

Table 2. Mean DVRs (±1 SD) calculated for each of the six subregions of the basal ganglia, as well as the mean whole striatum

Region	Controls (<i>n</i> =48)	MSA-P (<i>n</i> =25)	PD (<i>n</i> =130)
Right caudate	1.46±0.28	1.20±0.50	1.04±0.33
Left caudate	1.46±0.26	1.11±0.35	1.02±0.34
Right anterior putamen	1.25±0.31	0.86±0.43*	0.62±0.32
Left anterior putamen	1.28±0.27	0.75±0.37	0.58±0.32
Right posterior putamen	0.74±0.29	0.51±0.34*	0.32±0.18
Left posterior putamen	0.74±0.22	0.47±0.27*	0.32±0.19

*MSA values that were significantly higher than PD patient values (*p*<0.05). Note that all values in the MSA-P and PD patient groups were significantly lower (*p*<0.05) than values in controls.

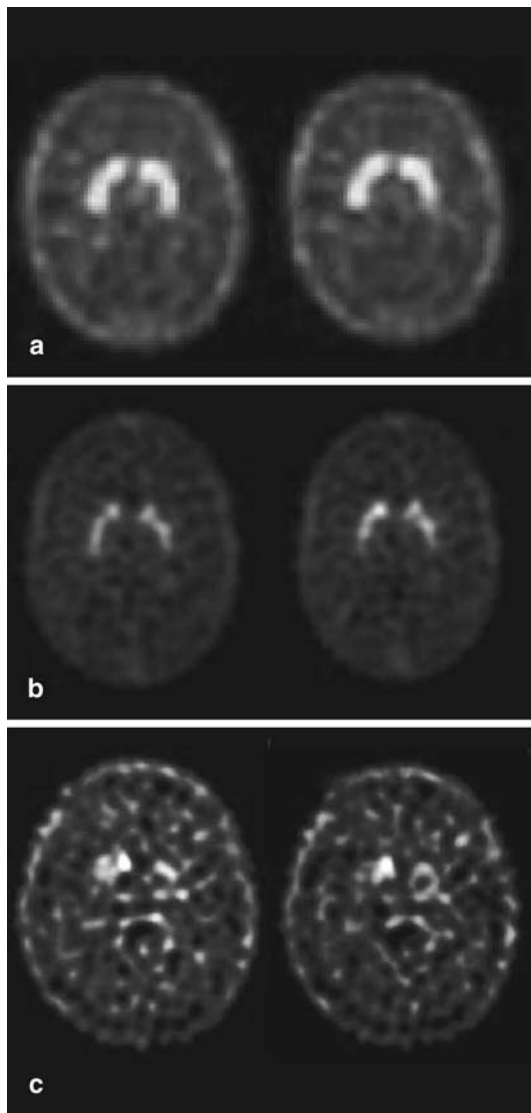


Fig. 1. TRODAT-1 Images of **a** healthy control subject, **b** MSA-P patient, and **c** PD patient

and specificity values shown in Table 3. The best results for distinguishing patients from controls for both PD and MSA were obtained for the posterior putamen (Fig. 1).

All mean values for striatal regions were higher in MSA-P patients than in PD patients. MSA-P and PD patient mean DVRs were significantly different in the right posterior putamen (0.51 ± 0.34 and 0.32 ± 0.18 , respectively, $p < 0.05$) and left posterior putamen (0.47 ± 0.27 and 0.32 ± 0.19 , respectively, $p < 0.05$). On the basis of receiver operator curves, MSA patients could not be adequately distinguished from PD patients.

It should be noted that, overall, the MSA patients had only a 21% decrease in the caudate compared with controls, and a 34% decrease in the anterior and posterior putamen compared with controls. PD patients had a comparable decrease in the caudate of 29% compared with controls, but values in the anterior and posterior

Table 3. Accuracy, sensitivity, and specificity for various striatal structures when all patients (including MSA and PD) were compared with controls. These results were derived from the receiver operator curves for each of the respective values

Structure	Accuracy (%)	Sensitivity (%)	Specificity (%)
Right caudate	64.5	89.6	56.8
Left caudate	74.4	83.3	71.6
Right anterior putamen	83.7	77.1	85.8
Left anterior putamen	81.3	81.3	81.3
Right posterior putamen	83.7	52.1	93.5
Left posterior putamen	85.2	81.3	86.5

putamen were approximately 51% lower than those in controls. The implication is that the putamen is affected to a much greater degree in PD patients than in MSA-P patients.

Discussion

Our results support hypothesis 1, that there are group differences in [^{99m}Tc]TRODAT-1 binding between PD patients and MSA patients. The specific subregions of the basal ganglia that showed significant differences in MSA-P patients compared with PD patients in this study were the right anterior putamen, the right posterior putamen, and the left posterior putamen ($p < 0.05$). In all of these regions, DVRs were higher in MSA-P patients than in PD patients. All subregions of the basal ganglia showed significantly lower DVRs in MSA-P patients than in healthy controls ($p < 0.05$). Thus, the basal ganglia DVRs in MSA-P patients were lower than those in healthy controls and higher than those in PD patients. Slight laterality of the findings in MSA patients did not correlate with any laterality of symptoms and may have been related to statistical artifact since MSA is generally a bilateral disease.

Other imaging studies of dopamine transporters in MSA patients have reported varying results: A study by Kim et al. using [^{123}I] β -CIT SPECT to assess dopamine transporters demonstrated that the posterior putamen is more involved than the caudate in MSA, which is consistent with our results [28]. Also, using [^{123}I] β -CIT SPECT, Berding et al. reported that basal ganglia uptake in MSA patients was similar to that in PD patients, although the differences between caudate and putamen were less marked [29]. On the other hand, in a study of [^{18}F]fluorodopa PET, Brooks et al. demonstrated that mean caudate uptake was significantly lower in MSA than in PD, although it was higher than in the putamen [30]. Using [^{18}F]fluorodopa PET, Antonini et al. showed that the putamen was more involved than the caudate in both MSA and PD [31]. A more recent study using [^{99m}Tc]TRODAT reported lower binding in the basal

ganglia in MSA patients than in controls, but did not report higher binding in the caudate in MSA patients compared with PD patients [14]. One of the primary reasons for this discrepancy is that in the aforementioned study, MSA patients had significantly worse disease, whereas in our sample the disease severity based upon neuropsychological testing was relatively comparable between the two patient groups.

Studies of other components of the dopaminergic system have also reported varying results. For example, [¹¹C]raclopride studies have shown decreased D₂ receptor binding in the striatum in MSA but not in PD patients [31–34]. A decrease in postsynaptic D₂ receptors in PD has also been observed with SPECT tracers such as [¹²³I]iodobenzamide [35]. A study comparing the SPECT tracers [¹²³I] β-CIT (to measure dopamine transporters) and [¹²³I]iodobenzofuran (to measure the D₂ receptors) reported a decrease in dopamine transporter binding in both MSA and PD, while the PD patients had increased D₂ binding and MSA patients had decreased D₂ binding [28]. However, future studies will need to be performed to fully evaluate the sensitivity and specificity of these tracers in the differentiation of MSA and PD.

Neuropathological changes in patients with MSA may include high density of glial cytoplasmic inclusions associated with degenerative changes in the putamen, caudate nucleus, globus pallidus, substantia nigra, locus coeruleus, inferior olives, pontine nuclei, cerebellar Purkinje cells, autonomic nuclei of the brainstem, and the intermediolateral cell columns and Onuf's nucleus in the spinal cord. However, neuropathological studies suggest that there may be more severe neuronal cell loss and gliosis in the putamen than in the caudate [36]. In agreement with neuropathological studies and other SPECT studies, imaging with [^{99m}Tc]TRODAT-1 demonstrates that DAT concentrations are higher in the caudate than in the putamen of MSA-P patients.

Inspection of mean DVRs for subregions of the basal ganglia in healthy controls indicates that dopamine transporter levels in the caudate are greater than those in the anterior putamen, which are greater than those in the posterior putamen. This pattern of decreasing dopamine transporter levels moving from anterior to posterior in basal ganglia is also seen among MSA-P patients and PD patients. Presynaptic dopamine transporters are located in axon terminals of dopaminergic neurons originating in relatively distant regions of the brain, primarily the substantia nigra. Transporter concentrations, as measured by [^{99m}Tc]TRODAT-1 SPECT, are thought to reflect primarily the vitality of these distant dopaminergic neurons, rather than that of the neurons they enervate in the basal ganglia. It follows that degeneration of dopaminergic neurons will cause a decrease in the dopamine transporter levels, and a thus a decrease in uptake of [^{99m}Tc]TRODAT-1 that is uniform between subregions of the basal ganglia. This pattern of roughly uniform decreases within the basal ganglia occurred in both MSA-P

and PD patients in this study. The specific subregion that deviated from this pattern was the posterior putamen in PD patients. This deviation may underlie the clinical differentiation between MSA-P and PD.

Given the significant difference between PD and MSA patients with regard to mean [^{99m}Tc]TRODAT-1 binding values in the striatum, these values were compared to determine how well such measures could actually distinguish these patient groups. The receiver operator curves comparing all patients (both MSA and PD) with controls showed strong areas under the curve, with the anterior and posterior putamen having the best ability in distinguishing the groups. The accuracy was approximately 85%, which is perhaps slightly lower than the 90% that has been reported for clinical diagnosis obtained after long-term follow-up. However, [^{99m}Tc]TRODAT-1 binding values may still have a benefit in the early workup of such patients, when the accuracy of clinical diagnosis is much lower, although this will have to be evaluated in future studies of patients with early and questionable clinical findings. The receiver operator curve analysis did not support hypothesis 2, that individual patients with PD or MSA-P could be adequately distinguished. This is most likely related to the substantial overlap of values between the patient groups, as has been reported by other research groups. In addition, the striatal regions such as the posterior putamen often have markedly decreased binding of [^{99m}Tc]TRODAT-1, which also results in greater variability of values and consequently limits the ability to differentiate patients with different movement disorders.

Conclusion

Differentiation between MSA-P and PD is a current challenge for clinicians, owing to the lack of diagnostic tests. As a group, MSA-P patients in this study had statistically higher [^{99m}Tc]TRODAT-1 binding in the striatum compared with PD patients, and both patient groups had significantly lower binding compared with controls. This may represent differences in the pathophysiology of these two disorders. However, the ability to differentiate individual patients with MSA and PD may require an integrated approach utilizing clinical and diagnostic information.

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