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Original Article

Diagnostic evaluation of ^{99m}Tc-TRODAT-1 SPECT in parkinsonism: Original Article

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Abstract

Introduction: Parkinsonism as a group of movement disorders, exhibits similar clinical presentation. Therefore, clinically differentiating these diseases is difficult. We investigated the diagnostic value of ^{99m}Tc-TRODAT-1 SPECT in this setting. Due to the fact that this modality has some limitations in imaging small organs like the subregions of basal ganglia, we also evaluated the use of anatomical magnetic resonance imaging (MRI) along with functional SPECT imaging in parkinsonism.

Methods: This follow-up diagnostic test evaluation study was performed with 40 patients with the clinical presentation of parkinsonism, and 10 healthy subjects as controls. After administration of the radiopharmaceutical, SPECT images were acquired, then co-registered on MRI. Uptake values were evaluated in basal ganglia semi-quantitatively.

Results: In this study, ^{99m}Tc-TRODAT-1 SPECT was able to differentiate essential tremor and healthy subjects from progressive supranuclear palsy (PSP) and Parkinson's disease (PD) with a sensitivity of 76.47% and specificity of 100% at a cut-off of 0.53; however, findings were not significant in differentiation of PD from PSP (P>0.05), and the results were similar in SPECT and co-registered MRI/SPECT images. In evaluation of the uptake pattern in basal ganglia, the lateralization of decreased uptake was only seen in PD; and in PSP, the dysfunction was bilateral in all patients.

Conclusion: ^{99m}Tc-TRODAT-1 SPECT is sensitive and specific in diagnosing basal ganglia dysfunction; however, ^{99m}Tc-TRODAT-1 SPECT alone or co-registration on MRI are not adequate in differentiation of the etiologies of basal ganglia dysfunction.

Introduction

In the early 19th century James Parkinson described a new disease in the form of "shaking palsy". It is now known as Parkinson's disease (PD). But today, parkinsonism as a clinical syndrome is known for three extrapyramidal signs: tremor, bradykinesia and rigidity[1]; and is referred to multiple diseases mimicking the PD clinically and has many etiologies including structural or a functional process. Autosomal dominant mutations in a gene for a-synuclein and toxins such as MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) are responsible for structural and functional processes, respectively.[2] The overall prevalence is considered to be 0.3% among general population and 1% in population over 60 years of age.[3] Nowadays PD is differentiated from other causes of parkinsonism mostly by clinical features and developed criteria such as the MDS-PD criteria (Movement Disorder Society clinical diagnostic criteria for Parkinson Disease).[4] Tremor alone is seen as a common neurological finding. This movement disorder could also be accompanied by other symptoms such as cognitive dysfunctions, anxiety, anosmia and fatigue; specially in the early stages. The pathophysiology responsible for the clinical signs such as tremor, is the selective and progressive loss of dopaminergic neurons in the substantia nigra.[1] Other than PD, members of this mysterious syndrome are multiple system atrophy (MSA), progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), vascular parkinsonism (VP) and drug induced parkinsonism (DIP). These are referred to as atypical parkinsonian syndrome (APS) in the literature. Other diseases such as essential tremor (ET) could also present with similar signs and symptoms; turning the diagnosis into a dilemma for clinicians specially when the tremor is the dominant symptom.[5,6]

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Formerly, the accuracy of clinical diagnosis of PD in the last visits to the neurology clinics prior to autopsy was reported to be 75%[7,8]; while today, with evaluation of response to therapy and follow-up visits, it has reached to 90%.[9,10] Another study have declared the sensitivity and specificity of clinical diagnosis for differentiating PD from ET to be 76% and 80% respectively.[11] The accurate diagnosis and differential of such diseases is crucial in choosing the appropriate treatment, and clinicians are eagerly searching for various non-clinical diagnostic modalities. In recent decades, the need of non-invasive diagnostic methods has led to the use of magnetic resonance imaging (MRI) and dopamine transporter of single-photon emission computed tomography (DAT-SPECT).[12-14] MRI is an appropriate modality to detect anatomic and structural abnormalities,[15] such as VP, but does not suggest any specific findings except in the late stages.[16,17] positron emission tomography (PET) scan and SPECT are helpful in assessing parkinsonism and detecting functional abnormalities.[18] The latest studies have also shown that the use of SPECT may provide a reliable alternative to PET in the evaluation of PD patients.[19] Radiopharmaceuticals, such as ^{123}IB-CIT (iodine-123-beta-carbomethoxy-3beta-(4-iodophenyltrop)) and ^{99m}Tc-TRODAT-1, are used in SPECT for the diagnosis of parkinsonism; but rapid pharmacokinetics of TRODAT, unlike ^{123}IB-CIT, allows for more accelerated imaging. Also, ^{123}I is prepared via cyclotron, but TRODAT is less expensive and easily labelled with ^{99m}Tc, which makes it cost effective.[20,21]

Previous studies with TRODAT-SPECT showed variable results in differentiation of parkinsonism.[22-26] We evaluated its diagnostic value in this setting, and because the spatial resolution of functional imaging modalities is very limited, MRI could be complementary to the functional studies such as SPECT.[27] Considering the main pathophysiology of parkinsonian syndromes involving the basal ganglia, we also evaluated the co-registered SPECT on MR imaging in basal ganglia dysfunction.

Materials and Methods

Study population

All procedures performed in this study were in accordance with the ethical standards of the responsible research committee of Tabriz University of Medical Sciences. To determine the sample size, all subjects that met the inclusion criteria (clinical presentation of parkinsonism and a brain MRI done for exclusion of structural disease), were enrolled by census after obtaining the informed consent. The patient group consisted of 40 patients with an initial complaint of tremor, who had been diagnosed within the last three years. Ten healthy subjects without any previous neurologic or psychiatric disease served as a control group. Pregnancy and the presence of pathological findings on MRI were among the exclusion criteria. Additional exclusion criteria were a history of repeated strokes and cerebellar signs. All patients had previous brain MRI done within the last month before referral to nuclear medicine clinics. Drugs were stopped for patients who received CNS stimulants and SSRIs for at least 4 weeks. However, under the supervision of the neurologist, dopaminergic drugs were continued if necessary but stopped for 24 hours before obtaining the images. During the 4-hour period after the radiopharmaceutical injection, subjects were examined at 30-minute intervals by the clinician for any complications and none were seen. Patients were followed for 6 to 24 months until definite clinical diagnosis was established.

Image acquisition

Radiopharmaceutical was prepared as reported by Pars Isotope Company, Iran; and was labelled with ^{99m}Tc pertechnetate in a one mL volume.[28] The mean radiochemical purity ± SD was 95.1% ± 2.9%. ^{99m}Tc (1.110 MBq [30 mCi]) was administered intravenously, and brain SPECT images were done 4-hours later using dual head E-Cam gamma camera; Siemens. SPECT data were acquired in a 128 × 128 matrix through 360-degree rotation with 64 projections. The acquisition time for each projection was 50 seconds. Transverse slices were reconstructed with an ordered-subset expectation maximization iterative algorithm and formatted as a 128 × 128 matrix. Chang's method was used for attenuation correction of image datasets and for better anatomic delineation of the SPECT images. All subjects were fixed in a position while their heads were secured with a holder.

Image analysis

Areas with proper radiotracer uptake in basal ganglia were considered as normal, and basal ganglia with reduced uptake compared with normal subjects were considered abnormal and consequently positive for parkinsonism (Figure 1).

Image processing was done on camera workstation (E. soft). For semi-quantitative assessment, images were evaluated with region of interest (ROI) above basal ganglia. Results were normalized by quantitative parameter of the same ROI count in ipsilateral occipital region and presented as basal ganglia uptake ratio (BGUR).

Target ROI Index = (Target ROI – Ipsilateral Occipital Cortex ROI) / Ipsilateral Occipital Cortex ROI

On second phase of quantification, after co-registration of previously obtained MR images on SPECT, same assessments were done for basal ganglia, putamen nucleus uptake (PUR) ratio and caudate nucleus uptake (CUR) ratio (Figure 2).

Images were interpreted by a nuclear medicine specialist who was unaware of the clinical diagnosis; as well, the neurologist was unaware of the results of the SPECT-images.

Statistical analysis

Data were analysed for normality with Kolmogorov-

Smirnov and Shapiro-Wilk test. We used Welch's ANOVA and Student's *t* test for normally distributed variables. Non-parametric Kruskal-Wallis and Mann-Whitney U test were performed if the variables were not normally distributed. For qualitative analysis, chi-square and Fisher's exact tests were used. All data were analysed by SPSS version 16. To estimate the accuracy of the quantitative data, we used receiving operating characteristics (ROC) analysis by MedCalc software. Significance level was defined as $P \leq 0.05$ for all analyses.

Results

Ultimately, 40 patients with the demographic characteristics shown in Table 1 were included in this study. Patients then fell into three sub-categories according to the clinical diagnosis based on the UK Brain Bank criteria.[8] After follow-up, 24 patients were diagnosed as PD, 10 as PSP and 6 as ET. The control group consisted of 10 healthy individuals. Age and gender were compared between all subjects and the tremor side was evaluated in symptomatic subjects. Gender and tremor side were not significant among subjects ($P = 0.499$ and $P = 0.913$, respectively), age was however significant between subjects ($P < 0.001$). Therefore, Games-Howell post hoc analysis was done. This significancy was confirmed between PSP and the control group ($P = 0.007$), the ET group ($P < 0.001$) and the PD group ($P = 0.004$); which showed significant higher range of age for the PSP group. No significant age difference was seen between other groups ($P = 0.251$ for PD vs control, $P = 0.204$ for PD vs ET, $P = 0.888$ for ET vs control).

BGUR indices of the 4-hour SPECT images are presented in Table 2. All parameters are significantly higher in the ET and the control group, compared to the PSP and the PD.

As shown in Figure 3 mean BGUR for the ET and the control group are higher than the PSP and PD and there is no overlapping of parameters between ET with PD or with PSP, but an overlap exists between the PD and the PSP group; likewise, between the ET and the control group. The significant differences between BGUR indices shown in Table 2 were confirmed by the pairwise comparison; there was no significant difference between the PD and the PSP group; however, significance was seen between PD and PSP with ET and the control group (Table 3).

In the next step, to better delineate the subregions of basal ganglia, co-registration of brain MRI on SPECT images were done in patients with pathology of basal ganglia; the subregional uptake ratios showed no significant difference between these patients (PD and PSP) (Table 4).

Additionally, we evaluated the uptake patterns in putamen and caudate nuclei by calculating the disproportionate hemispheric radiotracer uptake in each nucleus.

First, if any decreased uptake was seen in a nucleus, the contralateral side was assessed for decreased uptake, if none was seen, the pattern was considered to be unilateral in that nucleus, and the hemispheric disproportionate decreased uptake was calculated by dividing the ratios in the right and left nuclei. Also, the same was performed

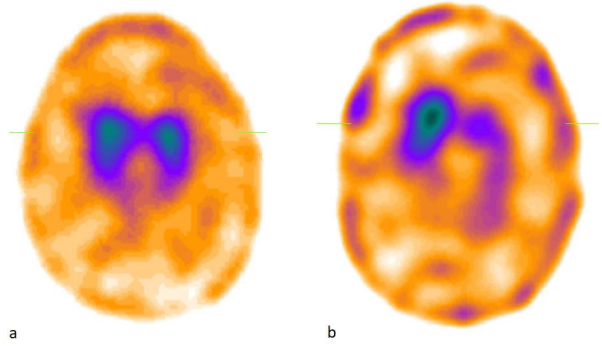

Figure 1. TRODAT SPECT images; (**a**) normal radiotracer uptake of basal ganglia, (**b**) abnormal radiotracer uptake of basal ganglia considered positive for parkinsonism.

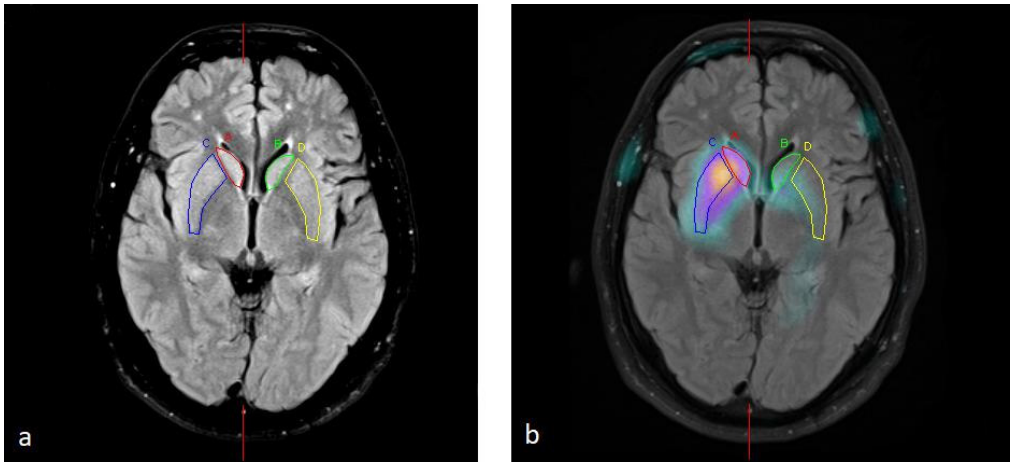

Figure 2. ROIs drawn above basal ganglia subregions in the same subject shown in **Figure 1b.** presenting with right tremor demonstrating prominent decreased radiotracer uptake of the left basal ganglia. (**a**) ROI on MRI images, (**b**) ROI on co-registered MRI/SPECT images; A, right caudate; B, left caudate; C, right putamen; D, left putamen.

Table 1. Demographic characteristics of subjects

	PD	PSP	ET	Control
Age (Mean ± SD)	52.42 ± 12.93	64.10 ± 5.30	41.10 ± 16.29	45.17 ± 5.74
Gender				
Male	70.8%	50%	66.7%	80%
Female	29.2%	50%	33.3%	20%
Tremor Side				
Left	16.7%	10%	33.3%	-
Right	16.7%	30%	33.3%	-
Head	8.3%	0	0	-
Bilateral	50%	60%	33.3%	-
Non-specific (tongue tremor)	8.3%	0	0	-

PD, Parkinson's disease; PSP, progressive supranuclear palsy; ET, essential tremor.

Table 2. Basal ganglia uptake ratios in SPECT images shown as median (percentile 25, percentile 75)

	PD	PSP	ET	Control	*P* value
Right BGUR	0.412 (0.264, 0.659)	0.312 (0.263, 0.366)	0.741 (0.698, 0.879)	0.869 (0.680, 0.911)	<0.001*
Left BGUR	0.334 (.273, 0.626)	0.245 (0.155, 0.438)	0.815 (0.795, 0.900)	0.896 (0.748, 0.987)	<0.001*

BGUR, basal ganglia uptake ratio; PD, Parkinson's disease; PSP, progressive supranuclear palsy; ET, essential tremor.

Table 3. Pairwise comparison of basal ganglia uptake ratios on TRODAT-SPECT images

Sample1-Sample2	Mean rank (Standard Error)	*P* value
PSP-PD	Right: 1.081 (5.486)	1.000
	Left: 1.645 (5.487)	6.000
PSP-ET	Right: -3.202 (7.527)	0.008*
	Left: -3.529 (7.528)	0.003*
PSP-CL	Right: 3.728 (6.519)	0.001*
	Left: 4.126 (6.519)	<0.001*
PD-ET	Right: -2.730 (6.653)	0.038*
	Left: -2.636 (6.653)	0.050*
PD-CL	Right: 3.348 (5.486)	0.005*
	Left: 3.258 (5.487)	0.007*
ET-CL	Right: 0.027 (7.527)	1.000
	Left: 0.044 (7.528)	1.000

Significance values have been adjusted by the Bonferroni correction for multiple tests.
BGUR, basal ganglia uptake ratio; PSP, progressive supranuclear palsy; PD, Parkinson's disease; ET, essential tremor; CL, control.

if the contralateral nuclei showed decreased uptake. Ultimately the hemispheric ratios of putamen and caudate nuclei were weighed up against each other. This revealed that out of 24 PD patients, 21 showed decreased uptake in both the caudate and the putamen nuclei bilaterally, which 8 of these patients showed greater decrease in putamen, 5 with greater decrease in caudate and 8 of them with symmetrical and equal loss of uptake in caudate and putamen nuclei. The other 3 PD patients also showed equal decreased uptake in both the putamen and caudate nuclei but unilaterally.

In comparison, in the PSP group all patients showed bilateral decreased uptake in both putamen and caudate nuclei, with 6 patients showing equal severity of loss of uptake, 3 with greater loss in putamen, and only one patient with greater loss in caudate.

Finally, to evaluate the accuracy of the semi-quantitative data in regard to the differences between the groups shown in previous analysis (Figures 3 and 4) and the fact that essential tremor shows a different pathophysiology than involvement of basal ganglia, also considering the limitations of sample size, we combined the PD and PSP group as the pathologic group and subsequently the ET and the control group as the non-pathologic (normal) group (Figure 5). The findings were significant ($P<0.001$) and ROC curve analysis was done to determine a cut-off BGUR mean value for the differentiation of ET/control (the normal group) from PD/PSP (the pathologic group) (Figure 6). The maximum AUC was obtained at the cut-off of 0.53 with the 76.47% sensitivity and 100% specificity. In this manner, at the cut-off point of .67 we can achieve a higher sensitivity of 88.2% but a specificity of 87.5% (Table 5).

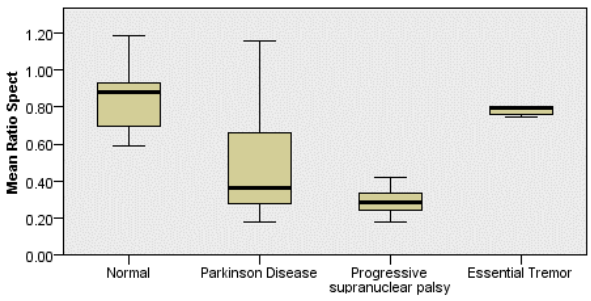

Figure 3. The distribution of the basal ganglia uptake ratios in TRODAT-SPECT images between groups.

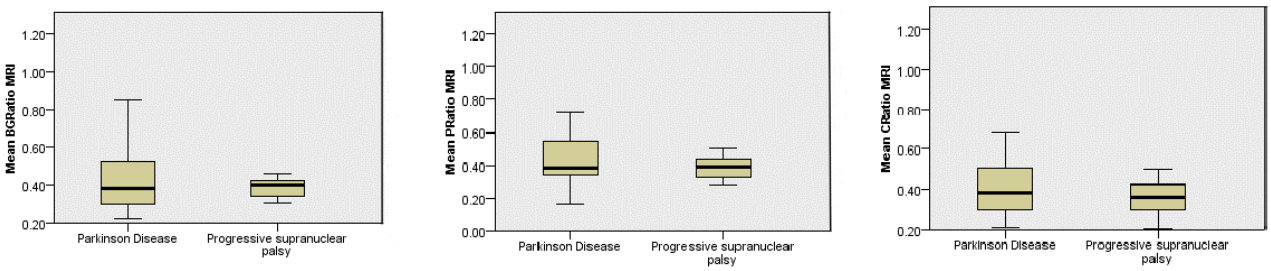

Figure 4. The distribution of basal ganglia, putamen and caudate uptake ratios between Parkinson's Disease and Progressive Supranuclear Palsy in co-registered MRI/SPECT images.

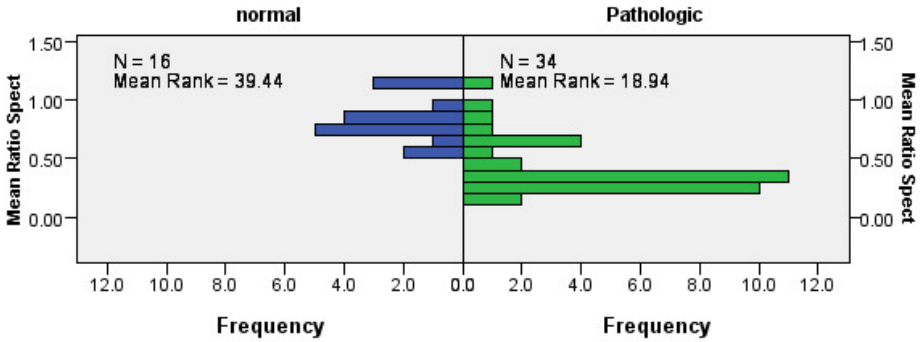

Figure 5. Comparing mean uptake ratios in pathologic and non-pathologic patients. N, sample number.

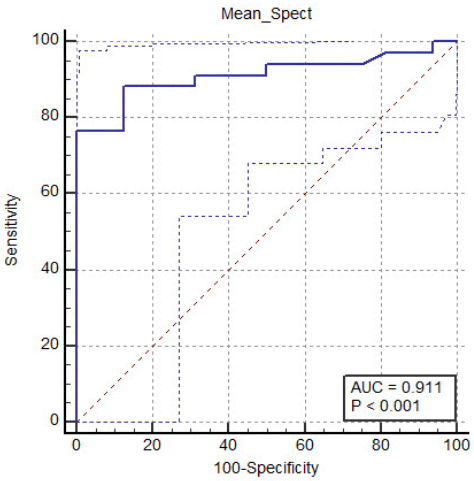

Figure 6. Receiver operating characteristics (ROC) curves of mean TRODAT-SPECT uptake ratios in differentiation of parkinsonian syndromes with pathology of basal ganglia from the subjects without pathology of basal ganglia. AUC, area under the ROC curve.

Discussion

PD is the second known cause of neurodegenerative disorders along with ET and PSP that leads to a series of early motor symptoms such as tremor.[29] And because treatment choices are different for variant etiologies, discriminating these parkinsonian-like syndromes from PD is beneficial for both patients and clinicians.

This study was mainly performed for the investigation of the diagnostic value of ^{99m}Tc-TRODAT-1 SPECT in differentiation of parkinsonism and also the benefit of co-registration on anatomic images.

In this study SPECT imaging was able to diagnose basal ganglia dysfunction with 76.4% sensitivity and 100% specificity at a cut-off point of 0.53 for the mean basal ganglia ratio. In another study, drug-induced parkinsonism and essential tremor were differentiated from other ASPs with a sensitivity of 80% and specificity of 83.3% at a cut-off point of 0.50.[22] Likewise, in a study, ^{99m}Tc-TRODAT-1 SPECT could differentiate PD from healthy subjects with a sensitivity and specificity of 0.98% and 0.88% respectively.[5] Weng et al evaluated age specific binding ratios in PD and healthy subjects; they showed the sensitivity of 98.6%, 94.4% and specificity of 100% in both the contralateral and ipsilateral striatum uptakes, respectively, at the cut-off of 0.59 and 0.63.[30]

In comparison of PSP with PD in our study, the findings in SPECT or MRI/SPECT showed no significant differences; compared to a study which was done recently that did differentiate non-parkinsonian syndromes from PD; this was performed with evaluating TRODAT SPECT binding ratios and MRI volumetry.[23] Although, the non-parkinsonian syndromes are not pathologically specified in the latter study.

In another study, semi-quantitative analysis of ^{123}I-FP-CIT uptake ratios showed markedly decreased uptake in APSs compared to early PD or PD in a study, but it was not possible to separate APS patients from PD patients on an individual basis,[31] and other studies showed controversial results.[32-34]

Table 4. Uptake ratios in co-registered MRI/SPECT images in Parkinson's disease and progressive supranuclear palsy shown as median (percentile 25, percentile 75)

	Right BGUR	Left BGUR	Right PUR	Left PUR	Right CUR	Left CUR
PD	0.399 (0.318, 0.575)	0.398 (0.253, 0.539)	0.403 (0.278, 0.567)	0.422 (0.353, 0.559)	0.389 (0.334, 0.573)	0.391 (0.294, 0.516)
PSP	0.393 (0.347, 0.411)	0.408 (.261, .497)	0.343 (0.316, 0.429)	0.401 (0.345, 0.543)	0.380 (0.289, 0.425)	0.325 (0.291, 0.473)
P value	0.705	0.850	0.406	0.705	0.364	0.385

BGUR, basal ganglia uptake ratio; PUR, putamen uptake ratio; CUR, caudate uptake ratio; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

Table 5. Accuracy of TRODAT-SPECT in diagnosing parkinsonian syndromes with pathology in basal ganglia from the subjects without pathology in basal ganglia

Criterion	Sensitivity	95% CI	Specificity	95% CI
<0.18	0.00	0.0-10.3	100.00	79.4-100.0
≤0.53	76.47	58.8-89.3	100.00	79.4-100.0
≤0.59	76.47	58.8-89.3	87.50	61.7-98.4
≤0.67	88.24	72.5-96.7	87.50	61.7-98.4
≤0.76	88.24	72.5-96.7	68.75	41.3-89.0
≤0.78	91.18	76.3-98.1	68.75	41.3-89.0
≤0.8	91.18	76.3-98.1	50.00	24.7-75.3
≤0.82	94.12	80.3-99.3	50.00	24.7-75.3
≤0.89	94.12	80.3-99.3	25.00	7.3-52.4
≤0.93	97.06	84.7-99.9	18.75	4.0-45.6
≤1.13	97.06	84.7-99.9	6.25	0.2-30.2
≤1.16	100.00	89.7-100.0	6.25	0.2-30.2

Furthermore, evaluation of putamen and caudate uptake ratios did not show significant differences between PD and PSP in our study. The study of Davidsson et al. showed significant decreased putamen to caudate uptake ratio in PD compared to APS. In the same study visual grading of uptake patterns revealed that APS showed equal degeneration of dopaminergic system in putamen and caudate nuclei; in contrary, PD patients expressed neuronal loss specially in putamen.[31] Another PET scan study done with 18F-FP-CIT, was able to differentiate PD from PSP and MSA by the greater loss of uptake of the anterior caudate nucleus in PSP and the prominent decreased striatal uptake in ventral putamen in MSA, with an acceptable sensitivity for both but a lesser specificity for ventral putamen in MSA.[35] Berding et al also had compared striatal uptake ratios between MSA and PD, they concluded that in MSA patients, with asymmetric symptoms, reduced uptake is predominant in the contralateral putamen, while the PD patients had shown the least impairment in the ipsilateral caudate.[33] Although these results show benefits of functional and anatomical imaging in differentiation of parkinsonism, still, more studies need to be done.

In our study, assessment of nuclei uptake patterns in PD, affirmed that putamen and caudate are involved mostly bilaterally (87%); which 38% of these had predominant putamen involvement and 23.8% predominant caudate involvement; and only in PD unilateral involvement was seen, which all showed equal striatal dysfunction in both nuclei. However, in PSP patients, 33% had predominant putamen dysfunction and only 11% caudate involvement, and 60% had equal involvement of putamen and caudate, which all were involved bilaterally. ^{123}I-FP-CIT DAT-SCAN imaging between APS and PD was performed and 75% of PD patients had visually predominant dopamine depletion in putamen, while most APS patients (56%) had visually severe dopamine depletion both in putamen and in caudate nucleus.[36] Consistent with our study, Fallahi et al also evaluated the uptake patterns visually; almost all APS patients in the latter study showed bilateral decreased uptake ratios, and only one showed greater unilateral involvement.[22]

Conclusion

^{99m}Tc-TRODAT-1 SPECT is specific and sensitive enough to be used in practice for diagnosing basal ganglia dysfunction. It showed a sensitivity of 76.4% and a specificity of 100% at a BGUR cut-off of .53. However, neither ^{99m}Tc-TRODAT-1 SPECT nor co-registration with MRI were significant for the differentiation between PSP from PD as a subgroup of APS in our study. But, subregional evaluation of the basal ganglia allows for characterization of striatal uptake patterns in APS, as our study showed unilateral involvement of basal ganglia was only seen in PD. Still, studies with a greater sample size must be done for further evaluation of striatal uptake patterns in APS.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

This study was confirmed by Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1397.164).

Author's Contributions

All authors contributed equally.

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References

1. Samii A, Nutt JG, Ransom BR. Parkinson's disease. Lancet. 2004;363(9423):1783-93. doi: 10.1016/s0140-6736(04)16305-8.
2. Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb Perspect Med. 2012;2(8):a009258. doi: 10.1101/cshperspect.a009258.

3. Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. N Engl J Med. 2003;348(14):1356-64. doi: 10.1056/NEJM2003ra020003.
4. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591-601. doi: 10.1002/mds.26424.
5. Huang WS, Lee MS, Lin JC, Chen CY, Yang YW, Lin SZ, et al. Usefulness of brain [99mTc]-TRODAT-1 SPET for the evaluation of Parkinson's disease. Eur J Nucl Med Mol Imaging. 2004;31(2):155-61. doi: 10.1007/s00259-003-1331-x.
6. Hwang WJ, Yao WJ, Wey SP, Ting G. Reproducibility of [99mTc]-TRODAT-1 SPECT measurement of dopamine transporters in Parkinson's disease. J Nucl Med. 2004;45(2):207-13.
7. Rajput AH, Rozdilsky B, Rajput A. Accuracy of clinical diagnosis in parkinsonism--a prospective study. Can J Neurol Sci. 1991;18(3):275-8. doi: 10.1017/s0317167100031814.
8. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55(3):181-4. doi: 10.1136/jnnp.55.3.181.
9. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology. 2001;57(8):1497-9. doi: 10.1212/wnl.57.8.1497.
10. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain. 2002;125(Pt 4):861-70. doi: 10.1093/brain/awf080.
11. Vlaar A. 3.106 Additional value of SPECT imaging in comparison with clinical diagnosis in 248 patients with parkinsonism. Parkinsonism Relat Disord. 2007;13 Suppl 2:S154. doi: 10.1016/s1353-8020(08)70814-9.
12. Prodoehl J, Li H, Planetta PJ, Goetz CG, Shannon KM, Tangonan R, et al. Diffusion tensor imaging of Parkinson's disease, atypical parkinsonism, and essential tremor. Mov Disord. 2013;28(13):1816-22. doi: 10.1002/mds.25491.
13. Passamonti L, Cerasa A, Quattrone A. Neuroimaging of essential tremor: what is the evidence for cerebellar involvement? Tremor Other Hyperkinet Mov (N Y). 2012;2:02-67-421-3. doi: 10.7916/d8f76b8g.
14. Badiavas K, Molyvda E, Iakovou I, Tsolaki M, Psarrakos K, Karatzas N. SPECT imaging evaluation in movement disorders: far beyond visual assessment. Eur J Nucl Med Mol Imaging. 2011;38(4):764-73. doi: 10.1007/s00259-010-1664-1.
15. Brooks DJ. Technology insight: imaging neurodegeneration in Parkinson's disease. Nat Clin Pract Neurol. 2008;4(5):267-77. doi: 10.1038/ncpneuro0773.
16. Berg D, Siefker C, Becker G. Echogenicity of the substantia nigra in Parkinson's disease and its relation to clinical findings. J Neurol. 2001;248(8):684-9. doi: 10.1007/s004150170114.
17. Rao SS, Hofmann LA, Shakil A. Parkinson's disease: diagnosis and treatment. Am Fam Physician. 2006;74(12):2046-54.
18. Utiumi MA, Felício AC, Borges CR, Braatz VL, Rezende SA, Munhoz RP, et al. Dopamine transporter imaging in clinically unclear cases of parkinsonism and the importance of scans without evidence of dopaminergic deficit (SWEDDs). Arq Neuropsiquiatr. 2012;70(9):667-73. doi: 10.1590/s0004-282x2012000900004.
19. Huang WS, Chiang YH, Lin JC, Chou YH, Cheng CY, Liu RS. Crossover study of [99mTc]-TRODAT-1 SPECT and 18F-FDOPA PET in Parkinson's disease patients. J Nucl Med. 2003;44(7):999-1005.
20. Lee JD, Huang CH, Weng YH, Lin KJ, Chen CT. An automatic MRI/SPECT registration algorithm using image intensity and anatomical feature as matching characters: application on the evaluation of Parkinson's disease. Nucl Med Biol. 2007;34(4):447-57. doi: 10.1016/j.nucmedbio.2007.02.008.
21. Dresel SH, Kung MP, Plössl K, Meegalla SK, Kung HF. Pharmacological effects of dopaminergic drugs on in vivo binding of [99mTc]TRODAT-1 to the central dopamine transporters in rats. Eur J Nucl Med. 1998;25(1):31-9. doi: 10.1007/s002590050191.
22. Fallahi B, Esmaeili A, Beiki D, Oveisgharan S, Noorollahi-Moghaddam H, Erfani M, et al. Evaluation of [99mTc]-TRODAT-1 SPECT in the diagnosis of Parkinson's disease versus other progressive movement disorders. Ann Nucl Med. 2016;30(2):153-62. doi: 10.1007/s12149-015-1042-y.
23. Hossein-Tehrani MR, Ghaedian T, Hooshmandi E, Kalhor L, Abolhasani Foroughi A, Ostovan VR. Brain TRODAT-SPECT versus MRI morphometry in distinguishing early mild Parkinson's disease from other extrapyramidal syndromes. J Neuroimaging. 2020;30(5):683-9. doi: 10.1111/jon.12740 .
24. Tzen KY, Lu CS, Yen TC, Wey SP, Ting G. Differential diagnosis of Parkinson's disease and vascular parkinsonism by [99mTc]-TRODAT-1. J Nucl Med. 2001;42(3):408-13.
25. Sasannezhad P, Juibary AG, Sadri K, Sadeghi R, Sabour M, Dabbagh Kakhki VR, et al. [99mTc]-TRODAT-1 SPECT imaging in early and late onset Parkinson's disease. Asia Ocean J Nucl Med Biol. 2017;5(2):114-9. doi: 10.22038/aojnmb.2017.8844.
26. Chou YH, Lin CH, Yen RF. Analysis of [99mTc]-TRODAT-1 SPECT binding to dopamine and serotonin transporters in patients with multiple system atrophy and Parkinson's disease. J Nucl Med. 2019;60(Suppl 1):424.
27. Tuite PJ, Mangia S, Michaeli S. Magnetic resonance imaging (MRI) in Parkinson's disease. J Alzheimers Dis Parkinsonism. 2013;Suppl 1:001. doi: 10.4172/2161-0460.s1-001.
28. Erfani M, Shafiei M, Charkhlooie G, Goudarzi M. Development of a freeze-dried radiopharmaceutical kit for dopamine transporters imaging. Iran J Nucl Med. 2015;23(1):15-20.
29. Zhang L, Liu J. The role of neuroimaging in the diagnosis of Parkinson's disease. Int J Integr Med. 2013;1:1-5.
30. Weng YH, Yen TC, Chen MC, Kao PF, Tzen KY, Chen RS, et al. Sensitivity and specificity of [99mTc]-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. J Nucl Med. 2004;45(3):393-401.
31. Davidsson A, Georgiopoulos C, Dizdar N, Granerus G, Zachrisson H. Comparison between visual assessment of dopaminergic degeneration pattern and semi-quantitative ratio calculations in patients with Parkinson's disease and atypical parkinsonian syndromes using DaTSCAN® SPECT. Ann Nucl Med. 2014;28(9):851-9. doi: 10.1007/s12149-014-0878-x.
32. Kim YJ, Ichise M, Ballinger JR, Vines D, Erami SS, Tatschida T, et al. Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA, and PSP. Mov Disord. 2002;17(2):303-12. doi: 10.1002/mds.10042.
33. Berding G, Brücke T, Odin P, Brooks DJ, Kolbe H, Gielow P, et al. [123I]beta-CIT SPECT imaging of dopamine and serotonin transporters in Parkinson's disease and multiple system atrophy. Nuklearmedizin. 2003;42(1):31-8.
34. Swanson RL, Newberg AB, Acton PD, Siderowf A, Wintering N, Alavi A, et al. Differences in [99mTc]TRODAT-1 SPECT binding to dopamine transporters in patients with multiple system atrophy and Parkinson's disease. Eur J Nucl Med Mol Imaging. 2005;32(3):302-7. doi: 10.1007/s00259-004-1667-x.
35. Oh M, Kim JS, Kim JY, Shin KH, Park SH, Kim HO, et al. Subregional patterns of preferential striatal dopamine transporter loss differ in Parkinson disease, progressive supranuclear palsy, and multiple-system atrophy. J Nucl Med. 2012;53(3):399-406. doi: 10.2967/jnumed.111.095224.
36. Georgiopoulos C, Davidsson A, Engström M, Larsson EM, Zachrisson H, Dizdar N. The diagnostic value of dopamine transporter imaging and olfactory testing in patients with parkinsonian syndromes. J Neurol. 2015;262(9):2154-63. doi: 10.1007/s00415-015-7830-4.