ORIGINAL ARTICLE

Diagnostic Evaluation of Technetium-99 metastable TRODAT-1 Single Photon Emission Computed Tomography-Computed Tomography in the Differential Diagnosis of Parkinsonism in Hospital Kuala Lumpur: A preliminary experience

Kamalia Kamarulzaman, MMed (Nuc Med) (USM)[1], Nadiah Abd Razak, MMed (Nuc Med) (USM)[1], Ahmad Shahir Mawardi, MMed (Int Medicine) (UKM)[2], Siti Zarina Amir Hassan, MMed (Int Med) (UM)[1]

[1]Department of Nuclear Medicine Hospital Kuala Lumpur, [2]Department of Neurology Hospital Kuala Lumpur

ABSTRACT

Introduction: Parkinsonian syndrome encompasses a group of movement disorders characterized by symptoms such as tremor, rigidity, bradykinesia, and postural instability. While Idiopathic Parkinson's disease is the most common cause, several other etiologies can also result in parkinsonism. Identifying the specific type of Parkinsonian syndrome is essential due to its varying therapeutic and prognostic implications. This study aims to evaluate the role of Technetium-99 metastable TRODAT-1 Single Photon Emission Computed Tomography-Computed Tomography (Tc-99m TRODAT-1 SPECT-CT) in patients with parkinsonism.

Materials and Methods: The clinical data and scintigraphy findings of patients referred to the Department of Nuclear Medicine, Hospital Kuala Lumpur for Tc-99m TRODAT-1 SPECT-CT from July 2022 to July 2023 were retrospectively reviewed. Follow-up with primary team was conducted to determine the clinical implications and subsequent therapeutic management of the patients.

Results: Tc-99m TRODAT-1 SPECT-CT was performed on sixteen patients (10 females and 6 males) with a mean age of 55.2 years (range 26 to 75 years). Five patients exhibited normal scintigraphy findings, while eleven patients showed abnormal Tc-99m TRODAT-1 SPECT-CT results. The scintigraphy findings led to changes in therapeutic management for 81.3% of the patients. Additionally, 19% of the patients were referred for further evaluation with Fluorine-18 fluorodeoxyglucose PET to assist in diagnosing atypical Parkinsonian disease.

Conclusions: Tc-99m TRODAT-1 SPECT-CT is a readily available tool for assessing presynaptic dopamine transporters in patients with parkinsonism. This study demonstrated that Tc-99m TRODAT-1 SPECT-CT significantly impacts the diagnostic and therapeutic outcomes for patients with parkinsonism.

KEYWORDS:
Parkinsonian syndrome, parkinsonism, Parkinson's disease, Dopamine transporter, TRODAT

INTRODUCTION

Parkinsonian syndrome encompasses a variety of movement disorders characterized by symptoms such as tremors, rigidity, bradykinesia, and postural instability. The etiologies of parkinsonism can be broadly classified into neurodegenerative and non-neurodegenerative categories. Neurodegenerative causes, commonly linked to striatal dopaminergic deficiency, include Idiopathic Parkinson's Disease (IPD) and atypical Parkinson diseases such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), Lewy body dementia (LBD), and corticobasal degeneration (CBD).[1] In contrast, non-neurodegenerative causes include essential tremor (ET), drug-induced parkinsonism (resulting from dopamine receptor-blocking drugs or pallidal toxins), psychogenic or functional parkinsonism, vascular parkinsonism, adult-onset dystonic tremor, and normal pressure hydrocephalus.[1] The most prevalent cause of parkinsonism, IPD, is defined by the progressive loss of pre-synaptic dopaminergic neurons in the pars compacta of the substantia nigra.[2]

Among all the neurological diseases included in the Global Burden Disease, Injuries, and Risk Factors study, IPD has shown the fastest growth in prevalence, largely due to the aging population.[3] Statistically, Asia countries including Malaysia will gather more than 60% of the world's population age of at least 65 years old by the year 2030.[3] According to post-2000 records from the World Health Organization, the age-standardized incidence of IPD in the Western Pacific region, including Malaysia, ranges from 6.7 to 26.9 per 100,000 person-years.[3] Aging is associated with a decline in various components of the dopamine system, including dopamine-producing neurons in the substantia nigra, reduced D1/D2 receptor densities, and pre-synaptic DAT densities.[4] Studies indicate a nearly linear decline in striatal DAT binding by 46% between ages 18 and 88 years.[4] Conversely, Mozley et al. observed a nonlinear aging effect on DAT scans, with the most significant striatal loss occurring before age 40.[5]

Formerly, few studies have demonstrated approximately 75% of accuracy in diagnosing IPD clinically when compared to autopsy.[6] This accuracy may rise to 90% after evaluating

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Corresponding Author: Nadiah Abd Razak
Email: nadiah.abdrazak@yahoo.com

treatment response during follow-up.[7] Accurate diagnosis of various Parkinsonian syndromes is crucial due to differing treatment strategies and prognoses. This has increased the need for non-invasive diagnostic methods such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), or positron emission tomography (PET). Although MRI is useful for detecting anatomical and structural abnormalities, it has limited value in early-stage diagnosis as it does not reveal specific findings until the later stages of the disease.[8-10] This can delay diagnosis and treatment especially in cases of clinically uncertain parkinsonism. Studies have shown that 60% to 80% of presynaptic dopaminergic neurons are lost before parkinsonism symptoms manifest.[2,11] Therefore, SPECT and PET using various radiotracers offer early-stage recognition and diagnosis of parkinsonism.[12]

A systematic review found that DAT scans have 98% to 100% sensitivity and specificity in detecting nigrostriatal cell loss in IPD and clinically uncertain parkinsonism.[13] Kraemmer J et al. emphasized the validity of DAT imaging as a live marker of nigrostriatal dopaminergic degeneration, showing a high correlation between striatal DAT binding and post-mortem substantia nigra counts.[14] This is supported by numerous studies reporting a close relationship between DAT concentrations and striatal dopamine levels.[15]

Nuclear medicine imaging with SPECT and PET assesses the dopaminergic neurotransmitter system at both pre- and post-synaptic levels. Post-synaptic dopaminergic using SPECT or PET imaging can differentiate IPD from atypical Parkinson diseases.[1-2,16-21] While post-synaptic D2-receptor imaging with SPECT is not routinely performed due to limited radiotracer availability, F-18 fluorodeoxyglucose (FDG) PET imaging, which has higher diagnostic accuracy, has taken over this role.[22-25] Pre-synaptic dopaminergic imaging evaluates striatal dopaminergic deficiency in neurodegenerative diseases. The dopamine transporter (DAT) proteins that are accountable for the reuptake of dopamine are found at the pre-synaptic membrane of the dopaminergic neurons in the synaptic cleft. Several studies have described a close relationship between DAT concentrations and striatal dopamine levels.[26-28] Therefore, a DAT scan reflecting the degree of pre-synaptic dopaminergic neuron loss can serve as a diagnostic biomarker for parkinsonism.[1-2] Several tropane-based radiotracers like Iodine-123 FP-CIT (I123-ioflupane) and Technetium-99m TRODAT-1 (Tc-99m TRODAT-1) can assess DAT expression levels in the striatum using SPECT. Currently, no PET radiotracers for DAT imaging are commercially available.[1] Few studies have demonstrated that SPECT-based DAT imaging is a reliable alternative to PET for evaluating IPD patients.[29]

In clinical practice, IPD is distinguished from other parkinsonism causes using clinical features and assessment criteria, such as the Movement Disorder Society clinical diagnostic criteria for Parkinson's Disease (MDS-PD).[30] Tc-99m TRODAT-1 SPECT-CT imaging benefits IPD patients with atypical or vague parkinsonism findings that do not meet the typical IPD diagnostic criteria. It is also indicated for patients treated as IPD but showing unsatisfactory therapy response or for early-stage disease with mild parkinsonism.[31-32] Additionally, Tc-99m TRODAT-1 SPECT-CT can exclude non-neurodegenerative causes of parkinsonism, like ET or drug-induced parkinsonism, from neurodegenerative etiologies.

Qualitative visual interpretation of DAT SPECT images is performed in three orthogonal planes with trans-axial slices reformatted parallel to the line connecting the anterior and posterior commissures using the rainbow color scale. Various studies have shown that high accuracy in DAT SPECT interpretation can be achieved through visual interpretation by an experienced reader.[33] While qualitative visual interpretation is the primary approach, quantitative image analysis provides more objective readings. Studies have shown that adding quantitative assessment improves the diagnostic performance of Tc-99m TRODAT-1 SPECT-CT[17].

One advantage of using Tc-99m TRODAT-1 is its labelling with widely available sodium pertechnetate (Tc04-). It has rapid pharmacokinetics and is more cost-effective compared to cyclotron-produced I123-ioflupane.[20-21] Given the limited access to PET and increasing awareness of dopaminergic functional studies among clinicians, our center has decided to fully utilize our SPECT machine with Technetium-99m TRODAT-1 Single Photon Emission Computed Tomography-Computed Tomography (Tc-99m TRODAT-1 SPECT-CT). Our study, conducted at Hospital Kuala Lumpur, is the first dopaminergic scintigraphy study in Malaysia. We aim to share the clinical associations, practical aspects, and scintigraphy findings of Tc-99m TRODAT-1 SPECT-CT imaging as a diagnostic tool for parkinsonism and its clinical implications for patient management.

MATERIALS AND METHODS

Patient selection

This retrospective study, approved by the Malaysian Ministry of Health Medical Research Ethics Committee (MREC approval number: NMRR-20-1008-54807), adhered to the Declaration of Helsinki guidelines for human research. We analyzed clinical data and scintigraphy results from patients referred to the Department of Nuclear Medicine, Hospital Kuala Lumpur, for Tc-99m TRODAT-1 SPECT-CT scans from July 2022 to July 2023. Inclusion criteria encompassed patients exhibiting parkinsonism symptoms who successfully completed the Tc-99m TRODAT-1 SPECT-CT scan. Patients with MRI-confirmed vascular parkinsonism and those with poor image quality due to severe motion artifacts were excluded. Our records indicated 16 patients who underwent the Tc-99m TRODAT-1 SPECT-CT, all of whom were included in the study.

Patient preparation

Fasting was not required for the Tc-99m TRODAT-1 SPECT-CT. However, one patient with severe tremors received 2.5 mg intravenous Midazolam ten minutes before image acquisition to mitigate motion artifacts. Standard anti-Parkinsonian medications (L-DOPA, dopamine agonists, monoamine oxidase B inhibitors, N-methyl-D-aspartate receptor blockers, amantadine, and catechol-O-methyltransferase inhibitors) do not significantly affect DAT binding,[17] hence, these medications were not withheld. None of our patients were on drugs known to alter striatal DAT binding per European Association of Nuclear Medicine guidelines.[17]

Radiopharmaceutical
Tc-99m TRODAT-1 was prepared and quality-controlled using established methods. 5 mL of freshly eluted Tc04-containing 1480 MBq (max 1628 MBq) was added to a TRODAT-1 freeze-dried kit (GMS TRODAT-1 kit, Taiwan), shaken immediately, and heated in a tightly sealed heating block for 60 minutes at 121°C. Radiochemical purity was verified using instant Thin Layer Chromatography Paper method. [System 1: pre-cut Agilent iTLC SG 1.5 x 13 cm developed in NaCl 0.9% (O: 2 cm, SF: 12 cm, rf: 0); System 2: pre-cut Agilent iTLC SG 1.5 x 13 cm developed in acetone, dried, then developed in NaCl 0.9% (O: 2 cm, SF: 12 cm, rf: 1)]. The radiochemical purity of Tc-99m TRODAT-1 administered exceeded 90%, with a 4-hour post-reconstitution expiration time.

Image acquisition
Tc-99m TRODAT-1 SPECT-CT brain imaging was conducted four hours after intravenous injection of 740 MBq of Tc-99m TRODAT-1. Images were acquired using a dual-head parallel hole gamma camera with high-resolution low-energy collimators (Siemens Intervo Bold). Data were captured in a 128 x 128 matrix with 1.45 zoom through a 360° rotation (180° per head) in continuous mode (stop condition: Repeats/Phase: 10, Cycles/Repeat: 1, Time Per Cycle: 5 min, Number of Views: 64). Images were reconstructed using Filtered Back Projection with a ramp-Butterworth filter (cut-off: 0.40 cm, order: 10), and attenuation correction via CT was applied to better delineate anatomical structures. All patients' heads were secured to prevent motion artifacts.

Image analysis, data interpretation, and statistical analysis
Image processing was performed on a Siemens Intervo Bold workstation. Interpretation of striatal DAT binding involved both qualitative visual and quantitative analyses of the reconstructed Tc-99m TRODAT-1 SPECT-CT images. Qualitatively, normal basal ganglia showed good striatal-to-background ratio with symmetrical radiotracer uptake, while abnormal basal ganglia displayed reduced tracer uptake.[17]

Quantitative analysis used DAT Striatal analysis on Siemens Intervo Bold, employing a fully automated volume of interest (VOI) template to quantify distribution volume ratio (DVR) of the striatum, caudate, and putamen.[34] All regions were normalized to background activity from the occipital cortex. Boundaries of basal ganglia and occipital cortex were defined using brain CT on the automated template.[34]

Given the acquisition parameters' similarity, our quantitative analyses were compared with the age-specific normal database from Weng et al., who reported normal values as striatal binding ratio (SBR) rather than DVR.[35] Based on Fahmi et al., to utilise Weng et al. reference for normal value, each of patients' striatal subregion DVR value that was obtained from DAT Striatal analysis in Siemens Intervo Bold were minus with one (i.e., SBR= DVR-1).[34] However, for two patients (aged 26 and 37) no database comparison was available, as Weng et al.'s lower age limit was 50 years. Therefore, reporting for these patients was relied mainly on qualitative analysis.

The image analysis, data interpretation and statistical analysis were performed by an experienced nuclear neurology physician. Follow-up with primary teams determined clinical implications and subsequent patient management. Fisher's Exact Test examined the association of gender, age, and Parkinsonism symptoms with TRODAT imaging analysis and conclusions.

RESULTS

Table I summarizes the characteristics of patients referred for Tc-99m TRODAT-1 SPECT-CT, including age, gender, clinical symptoms, scintigraphy findings, conclusions, and follow-up clinical updates.

Of the 16 patients, 10 were female and 6 were male, with an average age of 55.2 years (range: 26-75 years). Fisher's Exact Test (Table II) revealed a significant difference in qualitative TRODAT and overall scan findings between patients with and without tremor but no significant differences between gender, age, bradykinesia, and rigidity symptoms. The primary referral reasons for Tc-99m TRODAT-1 SPECT-CT varied among the patients. Most (62.4%) were referred for diagnosing idiopathic Parkinson's disease (IPD) in atypical presentations. Four patients (25.0%) were referred to exclude drug-induced parkinsonism, one patient (6.3%) to differentiate IPD from essential tremor, and another (6.3%) to exclude functional parkinsonism.

Figure 1 illustrates that the percentage of striatal asymmetry in normal DAT binding patterns ranged from 1.39% to 6.16% (mean 3.02%). In contrast, the abnormal DAT binding pattern displayed a broader range of striatal asymmetry, from 0.52% to 20.62% (mean 7.90%).

Five patients (31.3%) exhibited normal DAT binding patterns on the Tc-99m TRODAT-1 SPECT-CT. Based on clinical history and normal scintigraphy findings, one patient was diagnosed with essential tremor (Figure 2(i)), three with drug-induced parkinsonism (Figure 2(ii)), and one with functional parkinsonism. The remaining 11 patients (68.7%) with abnormal DAT binding, as assessed qualitatively and quantitatively by Tc-99m TRODAT-1 SPECT-CT, were confirmed to have striatal dopaminergic deficiency (Figure 3(i)). Among the 11 abnormal scans, three patients (27.3%) showed bilateral striatal DAT binding reduction, while eight (72.7%) exhibited asymmetrical DAT loss contralateral to the symptomatic side. Correlating these findings with clinical histories, six patients were concluded to have IPD. Qualitative and quantitative interpretations were concordant in all scans except for two patients with drug-induced parkinsonism, who showed a fairly symmetrical DAT binding pattern with slightly lower caudate SVR values. These discrepancies could be attributed to motion artifacts or non-specific uptake in Tc-99m TRODAT-1 scans. Five patients were recommended for further FDG PET imaging to aid in diagnosing atypical Parkinson's disease. Two of these patients underwent additional brain neuroimaging with FDG PET and both were diagnosed with corticobasal degeneration (CBD).

Reviewing our Tc-99m TRODAT-1 SPECT-CT reports, 13 patients (81.3%) experienced changes in therapeutic

management during follow-up. Our findings confirmed IPD in the majority of our patients (37.5%), leading to optimized anti-Parkinsonian medications for better disease control. Three patients (18.8%) received new anti-psychotic drugs following a diagnosis of drug-induced parkinsonism. One patient (6.3%), diagnosed with essential tremor based on clinical history and normal scintigraphy findings, was started on beta-blockers. Another patient (6.3%) with normal scintigraphy findings and functional parkinsonism was referred to a neuropsychiatrist for neurorehabilitation, resulting in recovery after three weeks. Two patients (12.5%) diagnosed with CBD based on Tc-99m TRODAT-1 SPECT-CT and FDG PET findings were treated accordingly.

DISCUSSION

Diagnosing IPD relies heavily on clinical symptoms such as bradykinesia, rigidity, resting tremor, postural instability, and response to levodopa therapy. Differentiating IPD from other parkinsonian-like syndromes is crucial for determining treatment options. This study primarily investigated the value of Tc-99m TRODAT-1 SPECT-CT in differentiating parkinsonism. Evaluating striatal DAT binding on Tc-99m TRODAT-1 SPECT-CT involves both qualitative visual interpretation of reconstructed SPECT images and quantitative analysis of the SPECT data. Our study found reduced striatal DAT binding in 11 out of 16 patients. Most patients (8) with abnormal scintigraphy demonstrated unilateral reduction at the contralateral striatum, prominently at the contralateral putamen. The remaining three patients showed bilateral striatum uptake reduction, suggesting advanced disease. Visual analysis included assessing asymmetrical striatum and differential radiotracer uptake in striatal subregions. The normal striatum appears symmetrical with a comma shape, clearly visualized in an axial cut (Figure 2(i)). However, slight asymmetry in striatal or striatal subregions may occur in less than 6% of healthy individuals.[17]

Decreased pre-synaptic dopaminergic function appears as unilateral or bilateral radiotracer uptake reduction in the striatum with high background activity in DAT SPECT images. Contralateral reduction of tracer uptake in the dorsal putamen relative to the clinically affected side is a common early finding in IPD, often presenting as a prominent unilateral posterior-to-anterior gradient loss.[17] This pattern aligns with many studies suggesting that the contralateral putamen is the most accurate region for differentiating between IPD and healthy individuals or essential tremor.[15] In early-stage IPD, the contralateral striatum typically appears oval or circular on a Tc-99m TRODAT-1 SPECT-CT scan due to severe putamen involvement.[33] As the disease progresses, it affects the ipsilateral putamen, followed by the contralateral caudate nucleus, and subsequently the ipsilateral caudate nucleus.[17] Therefore, bilateral striatum uptake reduction may be observed in advanced IPD cases.[17]

Quantitative analysis evaluates each striatal subregion and the degree of striatal asymmetry, particularly in complex and borderline cases.[17] We conducted quantitative analysis using a fully automated template on VOI analysis to quantify DVR of various striatal subregions, including the striatum, caudate and putamen. All these subregions were then normalized to the occipital cortex.[34] Our quantitative analyses were compared with a normal database provided by Weng et al., which proposed age-specific normal ranges of SBR for each striatal subregion.[35] However, for our two patients (aged 26 and 37), no database comparison was made due to the lower age limit of 50 years in Weng et al.'s study. Reporting for these patients was based primarily on qualitative analysis and subsequent follow-up with the primary team.

Weng et al. evaluated 78 consecutive IPD patients and 40 age-matched healthy subjects, finding high sensitivity and specificity of Tc-99m TRODAT-1 SPECT-CT in measuring DAT loss in IPD patients.[35] The study also highlighted an age-related decline in striatal binding in the healthy group.[35] Based on the similar parameter of image acquisition, Weng et al.'s age-specific normal range of SBR for each striatal subregion served as a reference for our patients with DAT-related disease to estimate DAT loss.[35] All our analyzed data for each striatal subregion were in DVR, converted to SBR before interpretation.

Hwang WJ et al. found a mean striatal asymmetry index of 12.62 ± 11.32 in IPD patients.[36] The normal TRODAT scan in our study showed a lower mean striatal asymmetry (3.02%) compared to the abnormal scan (7.90%). The range of striatal asymmetry in abnormal studies (0.52% to 20.62%) was significantly broader than in normal scans (1.39% to 6.16%). The lowest striatal asymmetry in abnormal scans (0.52%) was even lower than in normal scans (1.39%), indicating advanced disease. Higher striatal asymmetry reflects a greater decrease in contralateral striatal DAT binding, consistent with IPD. This highlights Tc-99m TRODAT-1 SPECT-CT's ability to distinguish IPD patients from other parkinsonian-like syndromes, except in advanced IPD.

Overall, there was concordance between qualitative and quantitative results. All substriatal values in normal and abnormal results fell within or below the reference range, respectively. However, two cases showed discrepancies between qualitative and quantitative analyses, likely due to motion artifacts or non-specific uptake in Tc-99m TRODAT scans.[35] Thus, quantitative analysis should be interpreted alongside visual analysis by an experienced reader.

In our study, five patients exhibited normal striatal DAT bindings, including one patient with essential tremor, three patients with drug-induced parkinsonism, and one patient with functional parkinsonism. These findings align with numerous recent studies demonstrating that Tc-99m TRODAT-1 SPECT-CT imaging serves as a marker for distinguishing IPD patients from healthy individuals or those with essential tremor.[15] Tc-99m TRODAT-1 SPECT-CT findings are typically normal in healthy individuals and in cases of non-neurodegenerative parkinsonism such as essential tremor (ET), psychogenic or functional parkinsonism, and drug-induced parkinsonism.[33] Consequently, these conditions can be differentiated from neurodegenerative Parkinsonian syndrome, which shows abnormal DAT imaging results. Tc-99m TRODAT-1 SPECT-CT images also exhibit high

Table I: Characteristics of patients referred for Tc-99m TRODAT-1 SPECT-CT, including age, gender, clinical symptoms, scintigraphy findings, conclusions, and follow-up clinical updates

No	Age (year)	Gender	Clinical symptoms	Qualitative analysis	Quantitative analysis Striatal volume ratio (SVR)				Striatal Asymmetry (%)	Conclusion of TRODAT reporting	Post scan input from the referring Neurologist
					Caudate		Putamen				
					Left	Right	Left	Right			
1	55	Male	Schizophrenia on Olanzapine. Bilateral hand tremors (right > left) associated with hand tremor.	Bilateral striatum shows normal and symmetrical DAT binding.	1.3 N	1.22 N	1.14 N	1.34 N	1.68	Normal DAT binding pattern. The clinical tremor is likely secondary to drug induced Parkinsonism.	Drug induced Parkinsonism. Change the antipsychotic treatment.
2	72	Female	Schizophrenia on intramuscular Paliperidone injection. Bilateral lower limb weakness and bilateral upper and lower limb tremors.	Bilateral striatum shows normal and symmetrical DAT binding.	0.8 AB	0.81 AB	0.9 N	0.83 N	1.39	Normal DAT binding pattern.	Drug induced Parkinsonism. Change the antipsychotic treatment.
3	52	Female	Bradykinesia, resting tremor and rigidity of the limbs.	Asymmetrical severely reduced DAT binding of bilateral posterior putamen (severe on the right) and right caudate.	0.87 AB	0.48 AB	0.36 AB	0.19 AB	20.62	Abnormal DAT binding pattern. In correlation with clinical history, this findings is suggestive of IPD.	IPD. Optimisation of medication.
4	51	Male	Rigidity and resting tremor of right upper limb and bradykinesia.	Severely reduced DAT binding of bilateral caudate and putamen.	0.59 AB	0.51 AB	0.33 AB	0.48 AB	1.31	Abnormal DAT binding pattern. In correlation with clinical history, this findings is suggestive of IPD.	IPD. Optimisation of medication.
5	54	Male	Resting tremors over left upper and lower limb.	Asymmetrical reduced DAT binding of bilateral posterior putamen (severe on the right) and right caudate.	1.08 AB	0.8 AB	0.61 AB	0.4 AB	14.43	Abnormal DAT binding. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest for FDG PET if clinically indicated.	IPD. Patient defaulted treatment
6	56	Female	Presented with fall, imbalance while walking, weakness and rigidity of right upper and lower limb with micrographia. TRO atypical Parkinsonism.	Asymmetrical reduced DAT binding of bilateral posterior putamen (severe on the left) and left caudate.	0.43 AB	0.56 AB	0.19 AB	0.21 AB	6.70	Abnormal DAT binding. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest FDG PET TRO atypical Parkinson Disease.	To exclude atypical Parkinson disease. For FDG PET CT.

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No	Age (year)	Gender	Clinical symptoms	Qualitative analysis	Quantitative analysis Striatal volume ratio (SVR)				Striatal Asymmetry (%)	Conclusion of TRODAT reporting	Post scan input from the referring Neurologist
					Caudate		Putamen				
					Left	Right	Left	Right			
7	60	Male	Paroxysmal head tremor, which emerge during high concentration activity or stressful situation	Bilateral striatum shows normal and symmetrical DAT binding.	1.38 N	1.28 N	1.1 N	1.09 N	2.46	Normal DAT binding pattern.	Essential tremor. Started on beta blocker.
8	26	Female	Unsteady gate, fall, slurred speech, occasional urinary incontinence, vertical gaze palsy, dysphagia and bradykinesia. TRO atypical Parkinsonism.	Asymmetrical reduced DAT binding of bilateral caudate and bilateral putamen.	0.33 AB	0.44 AB	0.26 AB	0.29 AB	5.65	Abnormal DAT binding pattern. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest FDG PET TRO atypical Parkinson Disease.	To exclude atypical Parkinson disease. For FDG PET CT.
9	68	Female	Right sided hemiaprexia, severe dysarthria, emotional disability and dysphagia. TRO atypical Parkinsonism.	Asymmetrical reduced DAT binding of bilateral putamen (severe on the left) and left caudate.	0.67 AB	1.01 AB	0.19 AB	0.45 AB	19.00	Abnormal DAT binding pattern. FDG PET shows features of corticobasal degeneration.	Further evaluation with FDG PET CT confirmed the diagnosis of CBD.
10	69	Female	Initially presented with essential tremor. Symptom worsened with gait instability and bradykinesia.	Asymmetrical reduced DAT binding uptake of the bilateral posterior putamen, with significant reduction on the right.	0.72 AB	0.63 AB	0.42 AB	0.43 AB	3.52	Abnormal DAT binding pattern. In correlation with clinical history, this could likely suggest IPD.	IPD. Optimisation of medication.
11	37	Female	Bilateral lower limb tremor, unable to walk normally, slow speech and occipital headache. TRO functional parkinsonism.	Bilateral striatum shows normal and symmetrical DAT binding.	1.68 N	1.74 N	1.32 N	1.49 N	3.39	Normal DAT binding pattern. In correlation with clinical history, these findings are suggestive of functional Parkinsonism more likely than IPD.	Referred for Neurorehabilitation. Patient improved well.
12	42	Male	Bilateral rigidity, bradykinesia and axial rigidity associated with constipation and urinary urgency.	Reduced DAT binding of bilateral caudate and bilateral putamen.	0.57 AB	0.58 AB	0.29 AB	0.26 AB	0.52 AB	Abnormal DAT binding pattern. In correlation with clinical history, this finding is suggestive of parkinsonism syndrome. However, unable to differentiate between IPD or atypical PD. Suggest FDG PET TRO atypical Parkinson Disease.	Further evaluation with FDG PET CT confirmed the diagnosis of CBD.

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No	Age (year)	Gender	Clinical symptoms	Qualitative analysis	Quantitative analysis Striatal volume ratio (SVR)				Striatal Asymmetry (%)	Conclusion of TRODAT reporting	Post scan input from the referring Neurologist
					Caudate		Putamen				
					Left	Right	Left	Right			
13	45	Male	Bradykinesia and cogwheel rigidity of bilateral upper limb.	Asymmetrical reduced DAT binding of bilateral caudate and putamen (severe on the right).	0.73 AB	0.56 AB	0.59 AB	0.55 AB	6.80	Abnormal DAT binding pattern.	IPD. Optimisation of medication.
14	75	Female	Schizophrenia (more than 30 years) with depression) on Paliperidone and T. Artane. Pill rolling tremor, bradykinesia, jaw tremor and cogwheel rigidity.	Bilateral striatum shows normal and symmetrical DAT binding.	0.84 AB	0.63 AB	0.73 N	0.75 N	6.16	Fairly symmetrical DAT binding pattern. Scan findings is suggestive of drug-induced Parkinsonism.	Drug induced Parkinsonism. Change the antipsychotic treatment and continue PD medication.
15	52	Female	Initially treated with IPD. Also presented with multiple falls due to imbalance and difficulty to initiate movements. Patient did not respond to treatment. TRO atypical parkinsonism.	Reduced DAT binding of bilateral caudate and bilateral putamen.	0.23 AB	0.23 AB	0.11 AB	0.04 AB	1.50	Abnormal DAT binding pattern indicating basal ganglia dysfunction. However, unable to differentiate between IPD or atypical PD. Suggest for FDG PET.	To exclude atypical Parkinson disease. For FDG PET CT.
16	69	Female	Bipolar disorder on Epilim and Olanzapine. Bilateral hand tremor (right more than left).	Asymmetrical reduced DAT binding of left putamen.	0.96 AB	0.92 AB	0.54 AB	0.91 N	6.80	Abnormal DAT binding pattern.	IPD. Optimisation of medication.

N: Normal
AB: Abnormal
TRO: To rule out

Table II: Association of gender, age and symptoms of Parkinsonism with TRODAT reporting

	Qualitative assessment of TRODAT		p-value	Quantitative assessment of TRODAT		p-value	Conclusion of TRODAT reporting		p-value
	Normal	Abnormal		Normal	Abnormal		Normal	Abnormal	
Gender									
Female	3	7	1.0000	1	9	0.5179	3	7	1.0000
Male	2	4		2	4		2	4	
Age									
≤ 50	1	3	1.0000	1	3	1.0000	1	3	1.0000
> 50	4	8		2	10		4	8	
Tremors									
Yes	5	4	0.0337*	3	6	0.2125	5	4	0.0337*
No	0	7		0	7		0	7	
Bradykinesia									
Yes	2	7	0.5962	1	8	0.5500	2	7	0.5962
No	3	4		2	5		3	4	
Rigidity									
Yes	1	5	0.5879	0	6	0.2500	1	5	0.5879
No	4	6		3	7		4	6	

Fishers' Exact Test (p-value <0.05 indicated a significant difference)

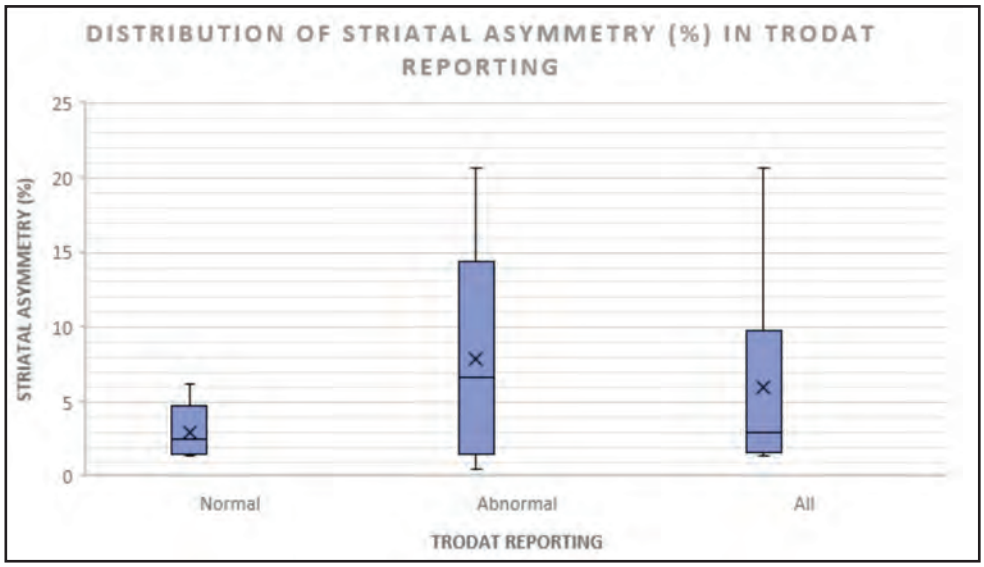

Fig. 1: Distribution of striatal asymmetry (%) in TRODAT reporting

sensitivity and negative predictive values in the early stages of IPD, which often presents with mild parkinsonism.[33] Both the Unified Parkinson's Disease Rating Scale and Hoehn and Yahr stage scores, which assess the degree of motor impairment, have shown a strong correlation between the level of TRODAT-1 uptake and IPD severity, though this correlation diminishes once it reaches saturation in the later stages of the disease.[15,33] In advanced IPD cases, reduced tracer uptake is observed in all striatal subregions.[17] Interestingly, in IPD patients, the downregulation of DAT expression in remaining neurons leads to an overestimation of the true extent of neurodegeneration in the striatum on Tc-99m TRODAT-1 SPECT-CT imaging. This downregulation functions as an adaptive mechanism to preserve synaptic dopamine levels.[33]

Accurate differentiation of IPD from atypical Parkinsonian syndrome is crucial, as it impacts prognosis and treatment strategies. A study by Aghdam et al. found no significant differences in differentiating IPD from atypical Parkinsonian syndrome using either Tc-99m TRODAT-1 SPECT or its co-registration with MRI.[37] Conversely, another study utilizing Tc-99m TRODAT-1 SPECT with MRI volumetry was able to differentiate non-parkinsonian syndromes from IPD, although the non-parkinsonian syndromes were not pathologically verified.[38] Generally, FDG PET brain imaging has become the standard for distinguishing IPD from atypical Parkinsonism syndromes.[22-25] Five of our patients with abnormal scintigraphy findings were recommended for further evaluation for atypical Parkinsonian syndrome due to clinical presentations atypical for IPD. Only two patients consented to FDG PET, both demonstrating typical patterns of corticobasal degeneration (CBD) on FDG findings. In CBD, marked asymmetrical striatal involvement is observed in both the caudate nucleus and putamen on the Tc-99m TRODAT-1 SPECT study, which can be more pronounced on

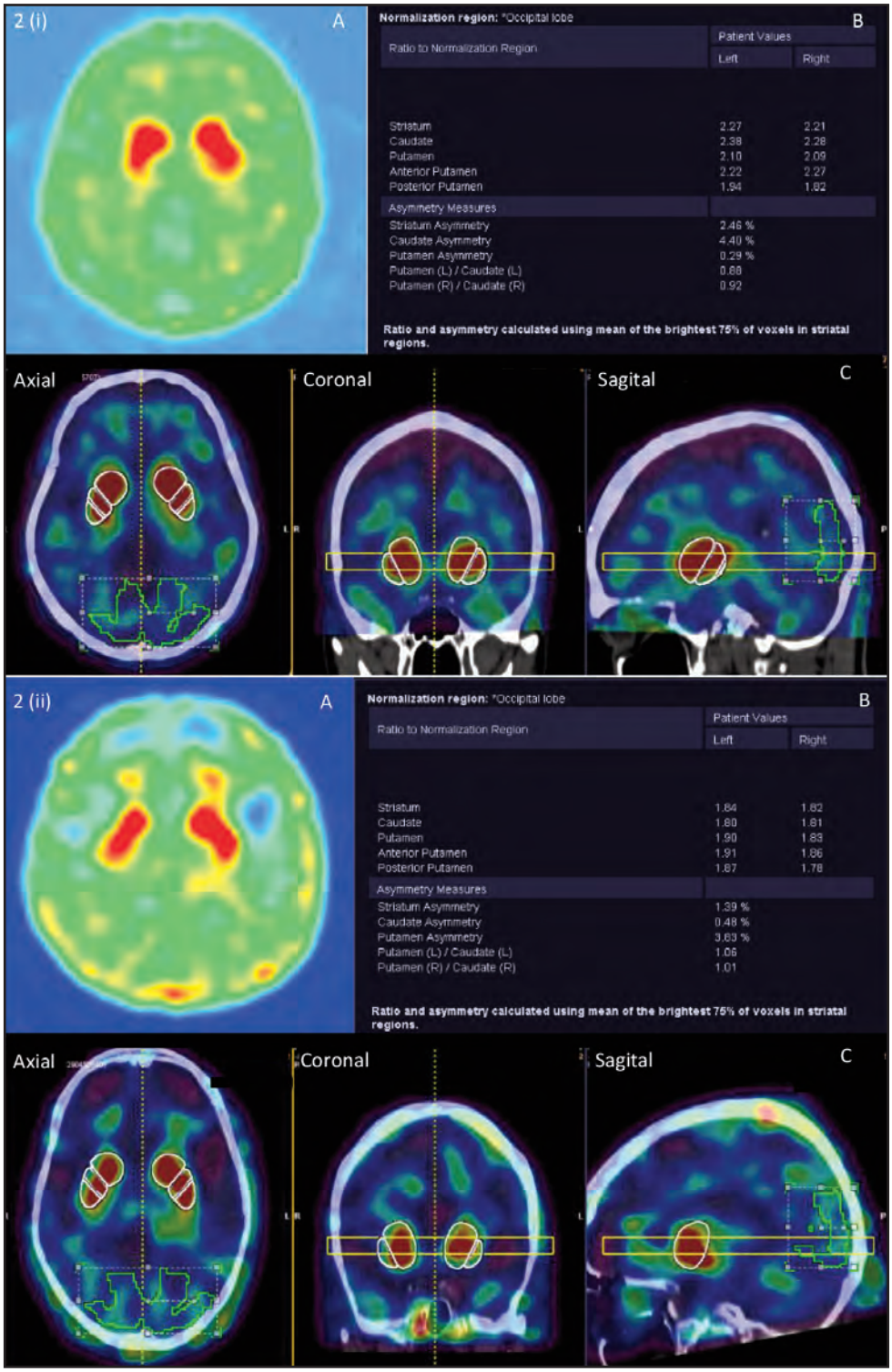

Fig. 2: (i). Tc-99m TRODAT-1 SPECT CT images of a 60-year-old man, presented with paroxysmal head tremors for 3 years with suspected essential tremor. The patient had an inconsistent response towards Benzhexol. (A) Transaxial TRODAT-1 SPECT-CT scan showed symmetrical and normal DAT striatal binding. Both striata have comma shapes and sharp borders. (B) and (C) Semiquantitative analysis based on automated VOI was in normal ranges. This finding excludes the presence of a striatal dopaminergic deficiency and is consistent with essential tremor

(ii). Tc-99m TRODAT-1 SPECT CT images of a 72-year-old female, known case of schizophrenia on 3-monthly Paliperidone injection, presented with bilateral hands and lower limb tremors as well as bilateral lower limb weakness. (A) Transaxial TRODAT-1 SPECT-CT scan showed symmetrical and normal DAT striatal binding. Both striata have comma shapes and sharp borders. (B) and (C) Semiquantitative analysis based on automated VOI was in normal ranges. This scan finding excludes the presence of a striatal dopaminergic deficiency and is consistent with drug-induced parkinsonism secondary to Paliperidone

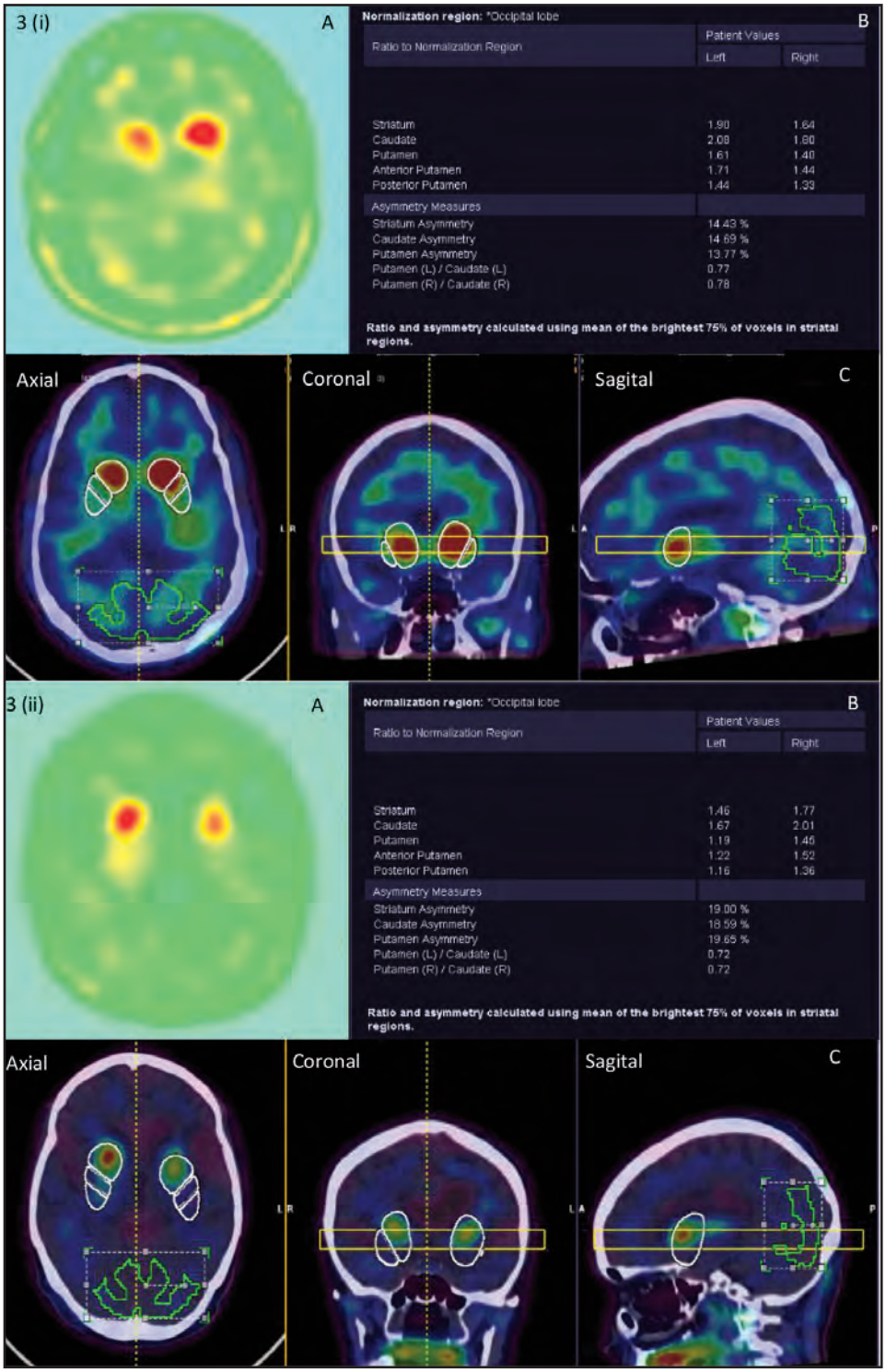

Fig. 3: (i). Tc-99m TRODAT-1 SPECT CT images of a 54-year-old male, presented with left leg cramping (predominantly at foot, ankle, and calf region), left hand resting tremor and left foot tremor. (A) Transaxial TRODAT-1 SPECT-CT scan showed reduced DAT binding of bilateral putamen and right caudate. Both striatum appear oval. (B) and (C) Specific binding ratios calculated from both putamen were significantly lower than the patient's age group. The striatal asymmetry index was 14.43%. These findings indicate the severe degree of nigrostriatal dopaminergic neuron loss and the pattern of involvement is suggestive of Idiopathic Parkinson's Disease

(ii). 68 year 68-year-old female presented with right-sided hemiaprexia, severe dysarthria, emotional disability, and dysphagia. (A) Transaxial TRODAT-1 SPECT-CT scan showed marked asymmetrical reduced DAT binding of bilateral putamen and left caudate. (B) and (C) Specific binding ratios calculated from both putamen and left caudate were significantly lower than the patient's age group. The striatal asymmetry index was 19%. Subsequent FDG PET CT as in Figure 3(iii)

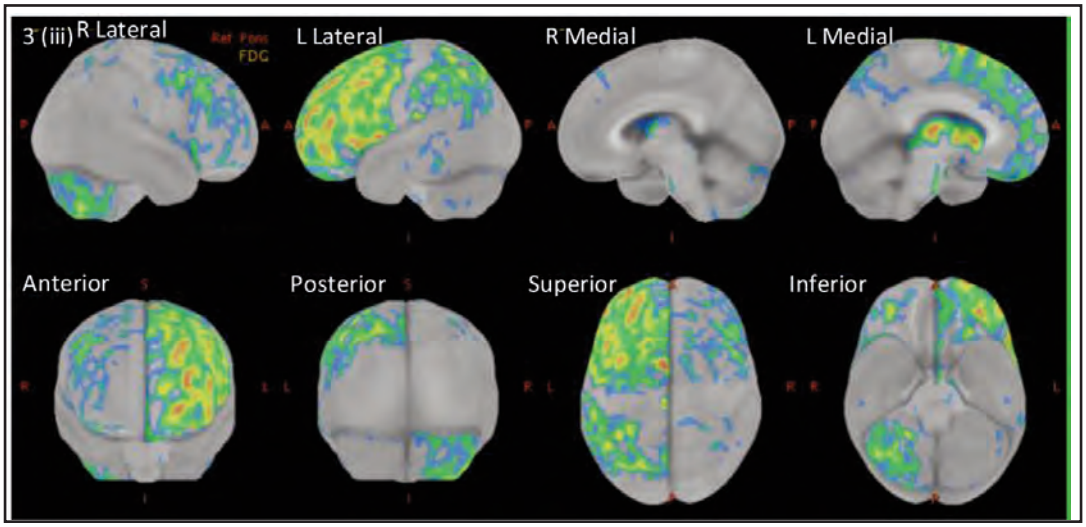

Fig. 3: (iii) Subsequent FDG PET-CT shows asymmetrical pattern of FDG hypermetabolism involving both frontoparietal cortices, more on the left

the side opposite to the clinically affected side (Figure 3(ii)).[33] This asymmetrical pattern of FDG hypometabolism was observed in both patients who underwent subsequent FDG PET CT scans (Figure 3(iii)).

However, a normal pattern of TRODAT uptake may also occur in patients with clinical corticobasal syndrome (CBS), likely due to underlying etiologies other than CBD, such as Alzheimer's disease or frontotemporal dementia. Patients with Lewy Body Dementia typically show early involvement of the caudate nuclei, leading to a less pronounced putamen-to-caudate gradient on TRODAT SPECT.[33] Similarly, early involvement of the anterior striatum is observed in the Parkinsonian subtype of multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) compared to IPD.[33] The Parkinsonian subtype of MSA has less DAT function than the cerebellar subtype of MSA.[33] Although atypical Parkinsonian syndromes generally cause symmetrical involvement of the striatum compared to IPD, TRODAT-1 SPECT imaging alone may not sufficiently differentiate between different types of atypical Parkinsonian syndromes.[33]

Interestingly, in our study, one patient was diagnosed with neurodegenerative parkinsonian syndrome at the age of 23. Although rare in the young population, less than 5% of IPD cases present before age 50, termed early-onset IPD. Early-onset IPD is subdivided into juvenile PD (JPD), with onset before 21, and young-onset PD (YOPD), with onset between 21 and 40.[39-40] Due to atypical symptoms and abnormal imaging findings, this patient was referred for further FDG PET imaging, but patient defaulted.

All scintigraphy findings were communicated to our referring teams, and patients were followed up in subsequent clinic reviews after the Tc-99m TRODAT-1 SPECT-CT scan. Based on post-scan clinical updates, we observed a high percentage (81%) of changes in medical treatment following the Tc-99m TRODAT-1 SPECT-CT scan. This finding aligns with studies by Arjona M et al. and Catafau et al., which reported treatment changes of 75% and 72%, respectively.[13] Similarly, a study by Mirpour S et al. reported changes in management, including initiating new dopaminergic treatment, optimizing medication, and discontinuing dopaminergic drugs.[38] In our study, for abnormal scan findings, neurologists optimized anti-Parkinsonian drugs or requested further FDG PET-CT imaging to exclude atypical Parkinson's disease. For normal scan findings, neurologists excluded neurodegenerative causes of parkinsonism and treated patients accordingly. For instance, patients with essential tremors were prescribed beta blockers, and drugs causing parkinsonism in patients diagnosed with antipsychotic-induced parkinsonism were withheld. These findings underscore the important role of Tc-99m TRODAT-1 SPECT-CT scans in guiding physicians toward accurate clinical diagnoses of various parkinsonian syndromes and appropriate treatment choices. Additionally, Tc-99m TRODAT-1 SPECT-CT findings may lead to referrals for further FDG PET imaging for specific diagnoses of parkinsonian syndromes.

Our study had a few limitations. First, our sample size was small, and all patients were from a single institution. There was no established database for age-specific normal ranges for striatal binding ratios in our population, so we used the normal range from Weng et al. to interpret our quantitative data. However, this database is limited to a lower age limit of 50 and could not be utilized for early-onset parkinsonian syndrome. Lastly, our study lacked a control group to prove the clinical utility of this scan in influencing clinical decision-making.

CONCLUSION

Tc-99m TRODAT-1 SPECT-CT is a widely accessible tool for evaluating presynaptic dopamine transporters in parkinsonism patients. Despite some overlap in disease patterns between idiopathic Parkinson's disease (IPD) and

atypical Parkinsonian syndromes, normal Tc-99m TRODAT-1 SPECT-CT findings can effectively exclude non-neurodegenerative conditions like essential tremor (ET), drug-induced parkinsonism, and functional parkinsonism. For more precise differentiation of Parkinsonian syndromes, further imaging with FDG PET is recommended. Our study highlights the need for age-specific normal ranges for striatal binding ratios, underscoring the importance of further research in this area. This would enhance the diagnostic accuracy of Tc-99m TRODAT-1 SPECT-CT, particularly in diverse populations. Future research should focus on larger, multi-center studies to validate these findings and establish comprehensive normative data.

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