Analysis of the Effect of Dopamine Transporter Scan on the Diagnosis and Management in a Tertiary Neurology Center

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Abstract

Background and Purpose: The dopamine transporter scan or DaT scan is abnormal in presynaptic parkinsonism but normal in nondegenerative or postsynaptic parkinsonism. In this study, we tried to ascertain the impact of DaT scan on the diagnosis and clinical management and if the semiquantitative analysis of the DaT scans has any correlation with the clinical symptoms. **Methods:** The electronic and nonelectronic records of patients of Plymouth Hospital NHS Trust, United Kingdom, from 2011 to 2015 were studied to find the indication, outcome, and the impact of the scan on the management of patients. The DaT scan results were assessed visually and semiquantitatively by the Department of Nuclear Medicine. The available data were statistically analyzed with the help of Microsoft XL2010 and GraphPad software. **Results:** A total of 258 people had DaT scan. The scan results suggested an alternate diagnosis in 50.5% of clinically diagnosed patients with Parkinson disease. Similarly, DaT scan changed the diagnosis of 40% of patients with clinical diagnosis of vascular parkinsonism, 25% of clinically diagnosed drug-induced parkinsonism, and 54% of patients with possible Lewy body dementia. Visual assessment of the DaT scan revealed that more than 60% had grade 2 abnormalities. The distribution volume ratio, a semiquantitative tool for tracer uptake, was significantly less in the patients with akinetic-rigid subtype of Parkinson disease in comparison to a tremor predominant subtype. **Conclusions:** Dopamine transporter scan had a significant impact in diagnosis and management.

Keywords

dopamine, SPECT, transporter, presynaptic, degeneration, parkinsonism

Introduction

Dopamine transporter (DaT) is a presynaptic dopamine transporter. Dopamine transporter transports dopamine back to the presynaptic neuron from the synaptic cleft.¹⁻⁴ A radioiodine isotope I123 or Ioflupane has a high binding affinity for this presynaptic dopamine transporter, DaT. The dopamine transporter single-photon emission computed tomogram (DaT-SPECT or DaT) scan utilizes this ioflupane radioisotope to identify the degeneration of the presynaptic dopaminergic neurons. The degenerative parkinsonism is a presynaptic disorder, while nondegenerative parkinsonism is postsynaptic. It is estimated that at least 60% to 70% of the presynaptic dopaminergic neuronal degeneration is needed before any motor clinical symptoms like tremor, rigidity, or bradykinesia become obvious, though most of the nonmotor symptoms develop much later.^{1,2,5} The degenerative parkinsonism includes idiopathic Parkinson disease (PD), multiple

system atrophy, progressive supranuclear palsy, corticobasal degeneration, and dementia of Lewy body (DLB).^{1,2,3,4} The postsynaptic parkinsonism is drug-induced or vascular parkinsonism. The commercial name for this scan is DaT scan (GE healthcare, Chicago, Illinois). Dopamine transporter scan is positive or abnormal in presynaptic parkinsonism but normal in postsynaptic parkinsonism. Although DaT scan

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can distinguish the presynaptic from postsynaptic parkinsonism, it cannot distinguish among various subtypes of presynaptic parkinsonism.^{1,2,3,4} Dopamine transporter scan was introduced in Europe in 2000 while it was approved in the United States in 2011. Despite being available in Europe for nearly 2 decades, only a few large-scale studies on the impact of the combined visual and semiquantitative DaT scan on the clinical diagnosis and management are available. In this study, we tried to ascertain the effect of DaT scan, using visual and semiquantitative approach, on the diagnosis and management of patients and if the semiquantitative analysis of the DaT scan bears any correlation with the clinical symptoms.

Material and Methods

This is a retrospective observational cohort study conducted at the Department of Neurology and Nuclear Medicine of the Plymouth Hospital NHS Trust, United Kingdom. Institutional ethics committee approval was obtained for this study. The electronic and nonelectronic records of patients from 2011 to 2015 were studied to collect data such as the indication for the scan, the outcome, and the impact of the scan on the management. Modified Hoehn and Yahr (H & Y) clinical staging was used to assess the clinical progression and functional status of the patients with IPD. According to the modified H and Y scale, stage 1 suggests unilateral clinical involvement, stage 2 means bilateral involvement without the impairment of the balance, stage 3 means bilateral clinical signs and symptoms of parkinsonism with postural instability, stage 4 is severe disability though still able to walk and stand unsupported, and stage 5 suggests bedridden or wheelchair bound unless aided.⁵

The DaT scan results were assessed visually and semiquantitatively by the Department of Nuclear Medicine of the Plymouth Hospital NHS Trust. Each scan was reviewed by 2 nuclear medicine specialists independently before the final report. The European Association of Nuclear Medicine protocol was adopted for the DaT scan in our hospital. The images were obtained with a standard Gamma camera 3 hours after 185 megabecquerel (MBq) contrast 123-Ioflupane injection.

As per the visual assessment method, grade 1 abnormality appears like a “full-stop with a disappearing comma” (asymmetrical loss of putaminal tail), grade 2 shows “two full-stops” (bilateral loss of putaminal tail), and grade 3 shows “disappearing full stops” (partial to complete loss of caudate and putaminal signal).⁴

The 123-Ioflupane tracer uptake of the DaT scans was measured with a combined visual and semiquantitative approach. The distribution volume ratio (DVR) was adopted as the indicator for semiquantitative uptake.⁶

The 123-Ioflupane SPECT image of each individual patient was stereotactically normalized into the anatomical space of the Montreal Neurological Institute (MNI) using the normalization tool of the Statistical Parametric Mapping software

package SPM (version SPM8, Wellcome Trust Centre for Neuroimaging, Institute of Neurology, UCL, London, United Kingdom).

The stereotactically normalized 123-Ioflupane uptake image was scaled to the 75th percentile of the voxel intensities in the whole brain without striata as reference region. The intensity value of each voxel was divided by the 75th percentile of the voxel intensities calculated in the reference region. The voxel intensity of the scaled SPECT image is representative of the DVR. The DVR is a semiquantitative measure of the local DaT availability.

The DVRs in caudate and putamen were derived by the “hottest voxel analysis” in large predefined region of interest (ROIs) for left/right caudate and left/right putamen in the MNI space. The number of hottest voxels to be averaged was fixed to a total volume of 10 mL for the putamen and 5 mL for the caudate nucleus. The DVR of the whole striatum was obtained by averaging over the 15 mL hottest voxels in the union of the caudate and the putamen ROI.

This DVR value was used to ascertain if there was any statistically significant correlation with the clinical symptoms like tremor. The available data were statistically analyzed with the help of Microsoft XL2010 and GraphPad software (©2018 GraphPad Software, Inc <https://www.graphpad.com/quickcalcs/ttest1.cfm>). A *P* value of less than .05 was deemed to be statistically significant.

Results and Data Analysis

A total of 258 people underwent dopamine transporters (DaT) scan between 2011 and 2015 (Table 1). The mean age of patients was 71.65 years. The duration of symptoms like tremor, rigidity, bradykinesia, or postural imbalance before the performance of DaT scan was 4.35 years $\pm$ 2.1 years (mean $\pm$ 2 standard deviation). The records revealed that out of clinically diagnosed 190 patients with PD, 60 patients had tremor-predominant PD, 48 had rigidity predominant PD, and rest had mixed subtype. The DaT scans in our hospital were requested by geriatricians, general neurologists, movement disorders neurologists, and neurology residents. Geriatricians requested 25% of the scans, general neurologists 45%, movement disorders neurologists 28%, and residents requested 2% of the scans.

The UK Brain Bank clinical criteria were adopted for the clinical diagnosis of idiopathic Parkinson disease (IPD).⁷ A total of 190 patients had the DaT scan to confirm the clinical suspicion of IPD (Table 2). However, 96 (50.5%) of the DaT scan results changed the initial clinical diagnosis, that is, the scan result suggested an alternate diagnosis than IPD. Similarly, DaT scan changed the clinical diagnosis of 40% of patients when requested to distinguish IPD from vascular parkinsonism. The scan revealed that 4 patients with ongoing treatment for essential tremor (ET) had PD. Similarly, DaT scan revealed that 2 drug-induced parkinsonism patients had degenerative parkinsonism. Four patients had undiagnosed

Table 1. Demographics and Clinical Status of Patients Undergoing Dopamine Transporters (DaT) Scan.

Parameters for Dopamine Transporters Scan	Total Number
Total patients	258
Male	135
Female	123
Age in years (Mean $\pm$ 2 SD)	71.65 $\pm$ 16.02
Duration of symptoms in years before DaT scan (Mean $\pm$ 2 SD)	4.35 $\pm$ 2.16 years
Number of patients diagnosed as idiopathic Parkinson Disease (PD)	190
Modified H & Y stage (median) for patients with PD	1.5
Idiopathic Parkinson disease (clinically tremor predominant)	60
Idiopathic Parkinson disease (clinically akinetic rigid or PIGD subtype)	48
Idiopathic Parkinson disease (clinically mixed symptoms)	82

Abbreviations: DaT, dopamine transporter; H & Y, Hoehn and Yahr; PIGD, postural instability/gait disorders; SD, standard deviation.

ataxia, myoclonus, and apraxia suspicious of atypical parkinsonism without any obvious clinical features of parkinsonism like rigidity, tremor, or bradykinesia. Dopamine transporter scan was performed to rule out dopaminergic degeneration as clinical features of parkinsonism appear much later during the clinical course of the disease.

Almost 47.6% of 258 scans performed were abnormal/positive (Table 3). A total of 7 DaT scan revealed equivocal results and 2 could not undergo full scan owing to claustrophobia. The 123 patients had positive scans of which 58 patients showed bilaterally abnormal uptake of the Ioflupane and 21 patients had abnormal Ioflupane uptake unilaterally. However, the report did not mention the symmetry of uptake in 34 patients with an abnormal scan. The visual analysis of the scan showed 78 (63.4% of all positive scans) had grade 2 abnormality and 12 (9.75%) had grade 3 abnormal uptake. Four of the 7 patients with equivocal DaT scan were rescanned after 14 to 18 months. However, only 1 showed the clearly abnormal result on repeat imaging.

The voxel intensity of the scaled SPECT image reflects the DVR as a semiquantitative measure for local DaT availability. The patients' records were reassessed after the scan reports. Out of the clearly abnormal DaT scans with clinical features consistent with IPD, 45 had tremor predominant presentation, 40 had the akinetic-rigid type of presentation, and 20 had mixed symptoms (Table 4). The DVR was calculated for 45 tremor-predominant and 40 akinetic-rigid/nontremor predominant patients with PD. The clinical features of hemiparkinsonism like tremor, rigidity, or bradykinesia of any side (right or left) arise due to the degeneration of the contralateral basal ganglia pathologies. The more diseased side of the akinetic-rigid subtype (basal ganglia contralateral to the side with more obvious rigidity and parkinsonism) showed a statistically

significant reduction in the DVR value (2-tailed *P* value of .0031 and 95% confidence interval of 0.062328-0.297672) in comparison to the diseased side (basal ganglia contralateral to the side with more obvious rest tremor) of the tremor predominant patients with PD. Similarly, the analysis showed a statistically significant reduction (2-tailed *P* value of .0072 and 95% confidence interval of 0.047-0.29) in the DaT uptake of the basal ganglia contralateral to the less symptomatic/asymptomatic side of the akinetic-rigid subtype when compared to the less symptomatic/asymptomatic side of the tremor predominant subtype. However, a sex-matched correlation analysis was not done.

Discussion

The DaT scan can have significant impact on the diagnosis and management in movement disorders clinics. Our cohort had a mean age of 71.6 years during the DaT scan. The scan suggested an alternate diagnosis than in 50.5% of clinically diagnosed patients with PD, 40% of patients with clinical diagnosis of vascular parkinsonism, 25% of clinically diagnosed drug-induced parkinsonism, and 54% of patients with possible Lewy body dementia (LBD). The DVR, a semiquantitative tool for tracer uptake, was significantly less in both right and left basal ganglia in our cohort with the akinetic-rigid subtype of patients with PD in comparison to the DVR value of the right and left basal ganglia of the tremor predominant subtype.

This study is one of the largest single center-based retrospective studies since the DaT scan became commercially available. Previously, Oravivattanukul et al studied 175 DaT scans from a single US center.⁸ Kupsch et al published a large multicenter study where DaT scan was performed in 122 patients.⁹ Recently, Mirpour et al published a study of 173 patients who had DaT scan from the United States.¹⁰

Our cohort had a shorter interval between the onset of symptoms of parkinsonism and having the scan (mean duration of 4.35 years). Sadasivan and Friedman found that the duration of clinical symptoms before the DaT scan performed varied between 3 months and 30 years.¹¹ Another study reported a mean interval of 2.54 years between the onset of symptoms and the performance of the scan.⁹ Our PD cohort had a median modified H & Y stage of 1.5, whereas Kupsch et al also reported the modified H & Y score below 2 in 73% of patients with PD.

Almost 73% of scans were requested to confirm the clinical diagnosis of degenerative parkinsonism, 7% to rule out ET and 8.5% to distinguish LBD from non-LBD in our study. Previously, Oravivattanukul et al found that 40% of scans were requested to establish degenerative parkinsonism, 8% to rule out essential or dystonic tremor but none to distinguish the LBD from non-LBD. They reported 42% of patients with the clinically uncertain condition had positive DaT scan compared to 40% in our series. However, they had a much higher number of scans done for clinically uncertain diagnosis

Table 2. Impact of DaT Scan Results on Diagnosis and Management of Patients.

Indications for DaT scan	No of Cases	Change in Diagnosis After DaT Scan	Change in Treatment (Drug Stopped)	Change in Treatment (New Drug Started)
To confirm the clinical diagnosis of idiopathic Parkinson disease (IPD) (early/equivocal signs)	190	96	Levodopa-40, MAOI-30, Dopamine agonist-5	Levodopa-45, MAOI-10, Dopamine agonist-25
Vascular parkinsonism from degenerative parkinsonism	5	2	Levodopa stopped-1	Levodopa + Rasagiline-1 (same patient)
Clinical essential tremor (ET) from PD	18	4	Propranolol-2	4 (Rasagiline 2, levodopa 2)
Clinically drug induced parkinsonism (DPD)–(DPD) from degenerative parkinsonism	8 (Valproate-4, Lithium-2, Metoclopramide-1, Risperidone-1)	2	Metoclopramide-1, valproate-1	New levodopa-1
Clinically dystonia–dystonia from Young onset PD from	2	0	0	Levodopa in 2
Functional tremor from IPD	1	0	0	0
Supportive for Parkinson Plus syndrome: (Multisystem Atrophy, Progressive Supranuclear palsy, Corticobasal diseases, Lewy body dementia)	4 (MSA-2, CBD-2)	1	0	0
Probable Lewy body dementia (LBD) from non-LBD dementia	22	12	0	Levodopa 5
Progression of IPD	1	0		
Diagnosis Uncertain	5	2		Levodopa-1

Abbreviations: CBD, corticobasal degeneration; IPD, idiopathic Parkinson disease; MAOI, monoamine oxidase inhibitor; MSA, multiple system atrophy.

(26% compared to 2% in our cohort). Gayed et al observed 64% of clinically uncertain patients with PD had abnormal DaT scan in their study.¹²

In a meta-analysis, Brigo et al reported that the sensitivity and specificity of DaT scan in distinguishing DLB from non-DLB dementia reached nearly 80%, though our study supported the clinical diagnosis of the DLB in 54.5% of patients.¹³ Van der Zande et al reported 7 patients with clinical diagnosis of probable LBD who had normal DaT scan at the outset.¹⁴ Five of those had abnormal DaT scans when repeated after 2 years of the initial scan. However, none of our probable patients with LBD with initially normal DaT scan outcomes were rescanned. There are very few studies who analyzed the accuracy of DaT scan against the neuropathological diagnosis of DLB. A recent Cochrane database review reported only one study which used neuropathological reference standard to ascertain the accuracy of DaT scan in the diagnosis of the DLB. The study concluded that the DaT scan was more accurate for the diagnosis of DLB than clinical parameters when correlated with the neuropathological findings.¹⁵

Twenty-two patients were found to have clinical features consistent with degenerative parkinsonism, though the DaT scan revealed that 40.9% of these patients did not have degenerative parkinsonism. Our cohort revealed that DaT imaging changed the diagnosis of 96 (50.5%) of all 196 clinically diagnosed patients with PD. Kupsch et al reported a 50% change in diagnosis and management in their study post-DaT scan. A study from an Irish teaching hospital revealed

normal DaT scan in 16% of clinically diagnosed patients with PD.¹⁶

Dopamine transporter scan altered the diagnosis of 22% of clinical patients with ET in our cohort. Sadasivan reported a change in the diagnosis of ET in 20% of their patients' post-scan like ours. However, another study of 83 patients from the United States revealed a change in the diagnosis of 72% of all patients with ET post-DaT scan. All of these scans were requested either by the general neurologists or by the movement disorders neurologists in this US-based study. However, such a high proportion of positive DaT scan in ET was probably due to a selection bias.

Oravivattanakul et al found that approximately 50% of patients diagnosed as psychogenic disorders had abnormal DaT scan, though we had no such observation during our analysis. However, the exact reason for the DaT scan to be abnormal in such a high proportion of clinically diagnosed "psychogenic disorders" was not clear from the study. The possible reasons are the limited understanding of the clinical presentations of psychogenic disorders or the higher prevalence of psychogenic symptoms in neurological disorders.

The scan outcome altered the diagnosis of drug-induced parkinsonism in 8% of the patients reported by Sadasivan et al. However, our cohort had 25% wrong diagnosis of drug-induced parkinsonism. Bega et al also reported almost 25% abnormal scan of drug-induced parkinsonism (5 of 18).¹⁷ Oravivattanakul et al found abnormal DaT scan in 35% of nondegenerative parkinsonism. We found abnormal DaT scan

Table 3. Dopamine Transporters Scan (DaT) Scan Result on Visual Assessment.

DaT Result	Number	Bilateral Abnormal Uptake		Unilateral Abnormal Uptake		Not Mentioned About Symmetry Though Abnormal Uptake	Degree or Grade of Tracer Uptake Abnormality on Visual Assessment			
		Asymmetrical	Symmetrical	Right	Left		1	2	3	Unspecified
Positive/abnormal	123	40	28	11	10	34	31	78	12	2
Negative/normal	126	0		0		0			0	
Equivocal	7									
Static DaT scan	2									

Table 4. Semiquantitative Analysis of Positive DaT Scan.

Distribution Volume Ratio (DVR; Marker of Tracer Uptake)	Tremor Predominant PD	Akinetic Rigid Subtype of PD	P Value (<.05 Was Significant)
Number of cases	45	40	
DVR value of the more diseased basal ganglia (mean + standard deviation)	1.98 (0.2565)	1.8 (0.289)	.0031
DVR value of the contralateral side/less diseased side (mean + standard deviation)	2.17 (0.283)	2 (0.285)	.0072

Abbreviations: DVR, distribution volume ratio; PD, Parkinson disease.

in 40% of our vascular parkinsonism patients. Bega et al found abnormal DaT result in 58% of vascular parkinsonism patients. The same authors reported DaT scans being performed for myoclonus or upon patients' request, though we did not have such scan requests. However, 6 of our patients had scans to assess the degree of dopaminergic neurodegeneration. Although Van Dyck et al demonstrated that patients with PD showed a nigrostriatal loss of 5% per year in comparison to 8% per decade in a normal individual, the role of DaT scan in monitoring the progression of PD or neurodegeneration is unclear and currently not recommended.¹⁸

The Nuclear Medicine department of our hospital adopted the combined approach of visual and semiquantitative analysis of the ROI normalized to reference brain to analyze the DaT scans. Although previous studies by Acton et al revealed that one approach is not superior to the other, Söderlund et al concluded that a combined visual and semiquantitative analysis created more reproducible clinical reporting.^{19,20} Albert et al found that 5 of 9 scans with the equivocal result on visual analysis had clearly normal result on additional semiquantitative analysis.²¹ The semiquantitative analysis in our cohort revealed a statistically significant reduction in DVR value (a measurement of DaT uptake) contralateral to the predominantly symptomatic side in akinetic rigid subtype patients with PD when compared to the tremor dominant subtype.

Similarly, Rossi et al demonstrated significantly higher FP-CIT uptake in contralateral putamen and a higher but not statistically significant uptake in all the other striatal regions in patients with tremor dominant when compared to akinetic rigid subtype patients with PD.²²

Almost 63% of our abnormal scans revealed grade 2 abnormal uptake and 10% showed grade 3 abnormal tracer uptake on visual analysis. Nissen et al reported grade 2 abnormal uptake in 64% and grade 3 abnormal uptake in 12%.²³ An Irish study reported grade 2 abnormality in almost 81% of patients. Only 2 of our 7 patients with equivocal DaT scan result showed a positive result on rescanning. Recently, Apostolova et al revealed that almost 72% equivocal scans showed no clear abnormality and only 20% showed a clear abnormality on follow-up scan after a mean duration of 22 months.²⁴ The authors concluded that the likelihood of abnormal result during repeat imaging of initially uncertain scan is very low in people below 60 years old. However, Tolosa et al reported that 87% of their DaT scans with inconclusive results turned positive when rescanned after 2 years.²⁵

The strength of this study is the large cohort and the combined approach of visual and semiquantitative analysis of the scans, correlation of reports with morphological brain imaging when necessary and making necessary adjustments during reporting to minimize the effect of dystonia or abnormal neck posturing. Previously, inaccurate interpretation of the DaT scan was reported in the presence of brain infarct, space-occupying lesion or even neck dystonia. However, the retrospective approach and single center-based analysis made our study susceptible to selection bias. We were unable to repeat scans in all patients with previously equivocal results because of the high cost of the scans. Moreover, correlation between the DVR value and clinical symptoms in our patients were not sex matched, though age groups were comparable. Age and sex can influence the uptake of DaT in striatum.²⁶ Although DaT scan has high specificity and sensitivity, false-positive and false-negative DaT scans are well recognized in the literature. We demonstrated that DVR value, a maker of semiquantitative DaT uptake, was significantly lower in age-matched akinetic rigid subtype of IPD. However, its prognostic value in PD is uncertain and needs further exploration. The futures studies need to assess what factors are considered

important before requesting the DaT scan by clinicians like geriatricians, resident, general neurologists, and movement disorders neurologists. Moreover, multicenter studies are needed to compare the accuracy among visual, semiquantitative, quantitative, or combined approach of DaT scan among the age- and sex-matched subgroups.

Conclusions

A combined visual and semiquantitative analysis of the DaT scan has a significant impact on the diagnosis and management of patients in neurology clinics. The akinetic-rigid subtype of PD shows more dopaminergic depletion than a tremor-predominant PD in DaT scan. The future studies need to be larger in size, prospective, and multicentric.

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Author Contributions

Shakya Bhattacharjee: study concept and design, acquisition of data, analysis and interpretation of data, study supervision, review of literature, critical revision of the manuscript for intellectual content; Vijayashankar Paramanandam: review of literature, critical revision of the manuscript for intellectual content; Atrayee Bhattacharya: Statistical analysis.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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