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ORIGINAL RESEARCH ARTICLE

[^{99m}Tc]Tc-TRODAT-1 scan diagnostic accuracy for differentiation of dementia of Lewy body from Alzheimer's disease

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ABSTRACT

Introduction: Dopamine transporter (DAT) receptors are reduced in the striatum in dementia of Lewy body (DLB) but normal in Alzheimer's disease (AD). We assessed the diagnostic accuracy of TRODAT-1 imaging to differentiate patients with DLB from AD.

Methods: Patients with DLB or AD underwent SPECT TRODAT imaging by [^{99m}Tc]Tc-TRODAT-1. Visual interpretation and quantification analyses were done. The activity of the right and left caudate nucleus (CN), putamen (P), striatum (S) as a whole, background (BG), and occipital area (OC) were calculated in addition to the ratio of right and left CN/OC, P/OC, and S/BG. Absolute right and left value difference of the striatum (ΔS), putamen (ΔP), and caudate (ΔCN) to OC or BG were also calculated. The diagnostic accuracy of the visual and quantitative method were compared between patients with AD and LBD. The area under the ROC curve (AUC) was analyzed.

Results: Twenty-five patients (15 DLB and 10 AD) were included. Scans were visually interpreted as DLB, AD, and non-diagnostic in 11, 13, and one patients, respectively. Sensitivity, specificity, and accuracy of the scan were 57.1% (28.9-82.3), 70% (34.8-93.3), and 62.5% (40.6-81.2), respectively. CN/OC, P/OC, and S/BG in the left, right, and bilaterally were statistically same between two groups. The AUC of ΔCN/OC was 70.7%. The optimal cut-off value for ΔCN/BG to diagnose DLB was 6.6% with a sensitivity, specificity, and accuracy, of 86.7%, 50%, and 72.0%, respectively.

Conclusion: The [^{99m}Tc]Tc-TRODAT-1 imaging has limited diagnostic accuracy for discrimination of DLB and AD patients.

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INTRODUCTION

Dopamine transporter (DAT) scan has proven its efficacy for the diagnosis of patients with neuronal degeneration in the striatum leading to Parkinsonism [1]. By the use of this imaging, Parkinsonism can be differentiated from essential tremor, dystonia, and drug-induced Parkinsonism [2]. For DAT scan, the activity of dopamine transporter at presynaptic neuron in the striatum is imaged using tropane derivatives [3].

Dementia of the Lewy body (DLB) shares many aspects of Parkinson's disease including degeneration of striatum presynaptic neurons and the presence of intracellular inclusion bodies [4, 5]. DAT scan can be used for discrimination of DLB from Alzheimer's disease (AD) in which degeneration occurs in the neurons out of substantia nigra and its dendrites in the striatum [6, 7]. Consequently, DLB with abnormal uptake at striatum could be differentiated from AD with a normal scan. Globally, [^{123}I]I-Ioflupane is used for DAT scan with documented diagnostic accuracy [8]. In Iran because of unavailability of this radiopharmaceutical, a different derivative of tropane, TRODAT-1, has been developed and used for DAT imaging. The scan is used in practice for the diagnosis of Parkinsonism, but the diagnostic accuracy and performance for discrimination of DLB from AD is not well determined; in the current study, we intended to investigate the diagnostic accuracy of [^{99m}Tc]Tc-TRODAT-1 scan for this clinical dilemma.

METHODS

Patients were referred from the department of neurology (2 psychiatry and general referral university hospitals) for DAT imaging. The diagnosis of DLB or AD was clinically evident at the time of imaging or then approved during the follow-up period of 17 months. Imaging was done using a TRODAT-1 kit (Pars Isotope, Tehran, Iran) and freshly eluted ^{99m}Tc from ^{99}Mo/^{99m}Tc generator (Pars Isotope, Tehran, Iran). Imaging was done by a dual-head gamma camera (AnyScan, Mediso, Budapest, Hungary) using a head holder and the following specifications: 360^{o} rotation, low energy conventional collimation, 128*128 matrix size, 30 second projection time, and 16 stops. The following specifications were employed for the process of the images filter back projection with Butterworth pre-filter, background and noise subtraction, and cut off equal to 0.45. Attenuation correction was done using the Chang method [9] which is a mathematical method to correct the attenuation of the brain for the water coefficient of attenuation (i.e. 0.1). At the time of imaging, visual interpretation was done with access to the clinical data, except for the final diagnosis. The report was sent to the neurologist. At the end of study, the images were visually interpreted for research purpose with 1 cm slices at axial, coronal, and sagittal as well as a 4 cm axial composite slice. The researcher was blind to the clinical data. For quantification, two sets of the region of interests (ROIs) were designed over the composite image (Figure 1) as follows: 3 ROIs over the right and left striatum (S) and occipital cortex as background (BG) and 5 ROIs over right and left caudate nucleus (CN) and putamen (P), and one over all occipital area (OC).

Diagnostic accuracy of the [^{99m}Tc]Tc-TRODAT-1 scan for discrimination of DLB and AD was assessed using cross-tabulation in SPSS software (v23, Chicago, IL). Visual interpretation, both diagnostic and research intended, were used. Ratios of right and left CN/OC, P/OC, and S/BG were calculated. Furthermore, accumulated uptake in the right and left striatum to BG (bilateral S/BG) and the absolute value of the difference of left and right uptake in the S, P, and CN were calculated. These last indices were considered as the indicators of asymmetry (i.e. ΔS/BG, ΔP/OC, and ΔCN/OC). These ratios were compared between patients with DLB and AD employing an independent sample T-test. ROC curves were analyzed and areas under the ROC curves (AUC) were calculated. For calculation of the optimal thresholds, the shortest distance on the ROC curve to point (0, 1) or closest to (0, 1) criteria was employed according to the least value of $\sqrt{(1-sensitivity)^2+(1-specificity)^2}$.

RESULTS

Twenty-five patients aged 62 ± 12 years were included (10 AD and 15 DLB). The duration of disease/symptoms was 6.0 ± 6.5 years. Visual hallucination was present in 14 (56%), bradykinesia in 5 (20%), and rigidity or postural instability in 15 (60%) patients. Four (40%) and 5 (33.3%) patients were female in AD and DLB groups, respectively. Visual hallucination, bradykinesia, and rigidity were respectively presented in 9 (60%), 3 (20%), and 10 (66.7%) DLB patients. No statistical predilection was detected between the prevalence of symptoms in DLB or AD. Scans were visually interpreted at diagnostic and research settling as abnormal in 13 (52%) and 11 (44%), respectively. A scan was interpreted indeterminate/non-diagnostic at the research setting (4%). The diagnostic performance of the visual interpretation of the [^{99m}Tc]Tc-TRODAT-1 scan is summarized in Table 1.

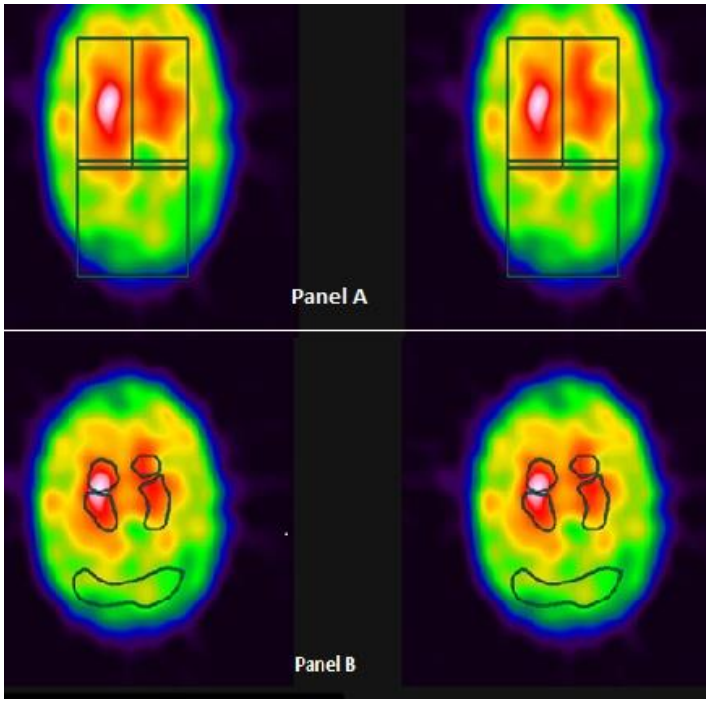

Figure 1. The [^{99m}Tc]Tc-TRODAT-1 uptake in the basal ganglia; 2 sets of the region of interests (ROIs) were designed over the composite image: 3 ROIs over the right and left striatum and occipital cortex as background (panel A), and 5 ROIs over right and left caudate nucleus, putamen, and occipital area (panel B).

The ratio of CN/OC, P/OC, and S/BG in the left, right, and bilaterally were similar between patients with DLB or AD. No evidence of quantitative asymmetry was detected based on the ratio of absolute difference of P, CN, and S to background i.e. occipital lobe (Table 2). AUCs were not generally higher than the accuracy of visual interpretation. Exceptionally, the AUC of ΔCN/OC was 70.7%. The optimal cut-off value for ΔCN/OC based on the shortest distance to point (0, 1) criteria was 6.6%. Based on this cut-off point, 72.0% of scans could be interpreted correctly (p=0.04; Table 1).

Table 1. Diagnostic performance of [^{99m}Tc]Tc-TRODAT-1 scan for classification of dementia of Lewy body (DLB) and Alzheimer's disease (AD)

		Sensitivity	Specificity	PPV	NPV	Accuracy
Visual interpretation	Diagnostic purpose†	66.7 (38.4-88.2)	70.0 (34.8-93.3)	76.9 (54.8-90.2)	58.3 (38.1-76.1)	68.0 (46.5-85.1)
	Research intended‡	57.1 (28.9-82.3)m	70.0 (34.8- 93.3)	72.7 (48.3-88.4)	53.9 (36.0-70.7)	62.5 (40.6-81.2)
Quantification	ΔCN/OC >6.6%	86.7 (59.5-98.3)	50.0 (18.7-81.3)	72.2 (57.6-83.3)	71.4 (37.4-91.3)	72.0 (50.6-87.9)

† The interpreter had access to examination and history except the neurologist's final diagnosis.
‡ The interpreter was blind to the clinical data
PPV: Positive predictive value; NPV: Negative predictive value; ΔCN/OC: The absolute value of right and left caudate uptake difference /background uptake (i.e. occipital lobe)

Table 2. Quantification data of the ratios of the uptake of [^{99m}Tc]Tc-TRODAT-1 in the caudate nucleus, putamen, and striatum (right and left) with an absolute difference of the uptake in the right and left

Quantification data	AD	DLB	Total	AUC	P-Value
Right striatum/BG	1.4 (0.1)	1.4 (0.2)	1.4 (0.2)	52.7 (29.4-75.9)	0.9
Left striatum/BG	1 (0)	1 (0)	1 (0)	50 (26.4-73.6)	0.8
Right caudate/BG	1.7 (0.3)	1.7 (0.3)	1.7 (0.3)	51.3 (27.0-75.7)	0.7
Left caudate/BG	1.6 (0.2)	1.7 (0.3)	1.6 (0.2)	56.7 (33.5-79.8)	0.6
Right putamen/BG	1.5 (0.2)	1.6 (0.3)	1.6 (0.2)	62 (39.2-84.8)	0.4
Left putamen/BG	1.5 (0.1)	1.6 (0.3)	1.5 (0.2)	57.3 (34.8-79.9)	0.8
Bilateral striatum/BG	2.8 (0.2)	2.8 (0.3)	2.8 (0.3)	54 (31.0-77.0)	0.7
Striatum difference /BG	0 (0)	0.1 (0)	0.1 (0)	66.7 (43.0-90.3)	0.2
Putamen difference /BG	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	62 (39.2-84.8)	0.3
Caudate difference /BG	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	70.7 (48.9.-92.4)	0.1

AD: Alzheimer's disease; DLB: Dementia of Lewy body; BG: Occipital lobe uptake; AUC: The area under the curve

DISCUSSION

The diagnosis and differentiation of AD and DLB are mainly clinical; however, there are circumstances that diagnostic assistance from imaging remarkably contributes to patients' wellbeing. Certain medications for the treatment of AD may aggravate the symptoms of a patient with DLB misdiagnosed as having AD [10]. The role of the DAT scan could be highlighted in confusing clinical scenarios. It should be considered that different tracers, imaging, and quantification methods may provide different diagnostic results, particularly in terms of sensitivity, specificity, and accuracy. The accuracy of commonly employed tracer, [^{123}I]I-Ioflupane, has been well documented worldwide in different neurological entities including differentiation of AD and DLB [8]. In Iran, TRODAT-1 has been developed with a privilege to the use of more available and less expensive isotope, ^{99m}Tc [11]. In the current study, we documented that for differentiation of AD and DLB, the accuracy of TRODAT-1 imaging is not perfect; however, due to acceptable specificity, the absence of normal uptake in the basal ganglia substantially increases the possibility of DLB [12]. The results also denoted that quantification data indicating asymmetry of the uptake in the caudate nucleus may provide better accuracy for discrimination of AD and DLB [13, 14].

Different derivatives of tropane or any other biologically active agent may present different kinetics and bio-affinity to their active site. Functional imaging based on biological active radiotracers should be scrutinized when different derivatives of a single tracer are used. TRODAT-1 has been commercially produced in Iran and Brazil [15, 16]. While there is no theoretical evidence denoting substantial differences between the functional aspects of more commonly used radiotracer, [^{123}I]I-Ioflupane, and [^{99m}Tc]Tc-TRODAT-1; it is prudent to consider this tracer cautiously in particular clinical scenarios. [^{99m}Tc]Tc-TRODAT-1 has the advantage of using ^{99m}Tc instead of ^{123}I which is a cyclotron product, hence less expensive. Particularly, ^{123}I might have limited availability when cyclotrons are preferably set to produce more necessary radioisotopes such as ^{18}F [17]. While the main application of DAT scan is to diagnose Parkinsonism, discrimination of DLB and AD could be valuable. The diagnostic accuracy of [^{123}I]I-Ioflupane for such discrimination was reportedly 57.5-59.3% [18, 19]. In the current study, we reported the comparable figure of 62.5% or 68.0% for accuracy, whether the history of the patient was concealed or available.

Quantification has been widely used for analyses of DAT scans. In the current study, the usual basal ganglia to background indices were similar between patients with AD or DLB. Because the asymmetric reduction of striatal uptake has been a millstone for abnormal DAT imaging [20], we developed an index based on the difference of the right and left basal ganglia uptakes adjusted for the occipital uptake as background. The absolute value of this ratio was used because right or left basal ganglia may become the prominent side in abnormal DAT scans. Employing this absolute value (i.e. ΔCN/OC), diagnostic accuracy could be enhanced up to 70%. The caudate nucleus asymmetry index (i.e. ΔCN/OC) had an accuracy of 72.0% at >6.6% with a considerable sensitivity of 86.7%. Interestingly, the visual interpretation provided acceptable specificity, and the cut-off point of ΔCN/OC at 6.6% provided good sensitivity. Consequently, interpretations based on visual readings and cut-off values should be used wisely according to the clinical scenario in question.

This study suffers certain shortcoming; above all the sample size was small. Consecutively, the confidence limits are wide and possible correlations might not be properly found. Furthermore, diagnosis of dementia was clinically established, however, the final impression of the neurologist after trial and error with available medications is the only currently applicable standard.

CONCLUSION

The [^{99m}Tc]Tc-TRODAT-1 imaging with an accuracy of 62.5% to 72% does not seem to be of much value for discrimination of AD and LBD patients in general. However, the scan may assist neurologists in uncertain clinical situations. Visual interpretation and quantification provide comparable and rather similar specificity and sensitivity.

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