REVISTA DE INVESTIGACIÓN CLÍNICA

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Rev Invest Clin. 2018;70:285-90 ORIGINAL ARTICLE

# Diagnostic Utility of [11C]DTBZ Positron Emission Tomography In Clinically Uncertain Parkinsonism: Experience of a Single Tertiary Center

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## ABSTRACT

**Background:** The use of single-photon emission computed tomography and positron emission tomography (PET) has proven to be helpful in differentiating Parkinson's disease (PD) from other movement disorders with a sensitivity of up to 95%. **Objective:** The objective of this study was to determine the accuracy of [11C]DTBZ PET imaging in patients with clinically uncertain parkinsonism from a tertiary referral center in Mexico City. **Materials and Methods:** Patients who underwent [11C]DTBZ PET brain scan due to clinically uncertain parkinsonism where divided into two groups: PD or non-PD. A scan was considered positive when visual assessment revealed a decrease in [11C]DTBZ uptake typical for PD; a scan was considered negative when visual assessment showed no decrease in [11C]DTBZ uptake or showed a decrease in tracer uptake in a non-PD pattern. Sensitivity, specificity, and positive and negative predictive values were calculated using a 2 × 2 table, with a 95% confidence interval. **Results:** A total of 39 patients were included in the study. 14 PET studies were deemed positive and 25 PET studies were deemed negative; 12 true positives and 23 true negatives were found. This yielded a sensitivity of 92.9% (95% CI, 66.1-99.8), specificity of 92% (95% CI, 74-99), PPV of 86.7% (95% CI, 63.1-96.1), and NPV of 95.8% (95% CI, 79.1-98.4). **Conclusions:** The [11C]DTBZ PET has an excellent accuracy for differentiating idiopathic PD from other disorders. (REV INVEST CLIN. 2018;70:285-90)

**Key words:** Positron emission tomography. [11C]DTBZ. Parkinsonism. Differential diagnosis.

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Received for publication: 25-06-2018
Accepted for publication: 23-08-2018
doi: 10.24875/RIC.18002644

## INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease. The cardinal motor features of PD are bradykinesia, rigidity, and rest tremor. PD differential diagnosis mainly includes other atypical parkinsonisms as well as essential tremor (ET). The complex clinical heterogeneity occasionally may difficult the clinical diagnosis. In fact, diagnostic accuracy ranges from 73.8% in general practitioners up to 83.9% in movement disorders specialists[1]. The use of molecular imaging probes for the brain has proven to be helpful in differentiating PD from other movement disorders. *In vivo* evaluation of the striatonigral dopaminergic system using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) has shown to be reliable in this matter, yielding a sensitivity of up to 95%[2-5]. Several radiotracers are currently available for assessing the presynaptic dopaminergic system. PET tracers include 3,4-dihy-droxy-6-[$^{18}$F]fluoro-L-phenylalanine ([$^{18}$F] DOPA) and [$^{11}$C]dihydrotetrabenazine ([$^{11}$C]DTBZ). SPECT tracers include [$^{123}$I]ioflupane (DaTSCAN™) and 99mTc-TRODAT-1, among others. To date, [$^{123}$I] ioflupane (DaTSCAN™), assessing the dopamine transporter (DAT), is the most studied radiotracer. On the other hand, the clinical utility of [$^{11}$C]DTBZ has been less studied for the parkinsonism diagnosis workout. [$^{11}$C]DTBZ targets the vesicular transporters of monoamines type 2 (VMAT2), making possible to visualize the nigrostriatal dopaminergic system while estimating in a qualitative and semi-quantitative way its integrity.

The objective of this study is to determine the accuracy of [$^{11}$C]DTBZ PET imaging in patients with clinically uncertain parkinsonism from a tertiary referral center in Mexico City.

## MATERIALS AND METHODS

### Subjects

Patients who underwent [$^{11}$C]DTBZ PET brain scan due to clinically uncertain parkinsonism from January 2014 to July 2017 were included in the study. All patients were seen at the movement disorders clinic of the National Institute of Neurology and Neurosurgery in Mexico City. Clinically, uncertain parkinsonism was defined as a patient with unequivocal parkinsonian syndrome, not meeting the currently accepted clinical criteria for PD[6], progressive supranuclear palsy (PSP)[7], multiple system atrophy (MSA)[8], or ET[9]. The study was approved by the local Ethics Committee and all participants gave full written consent.

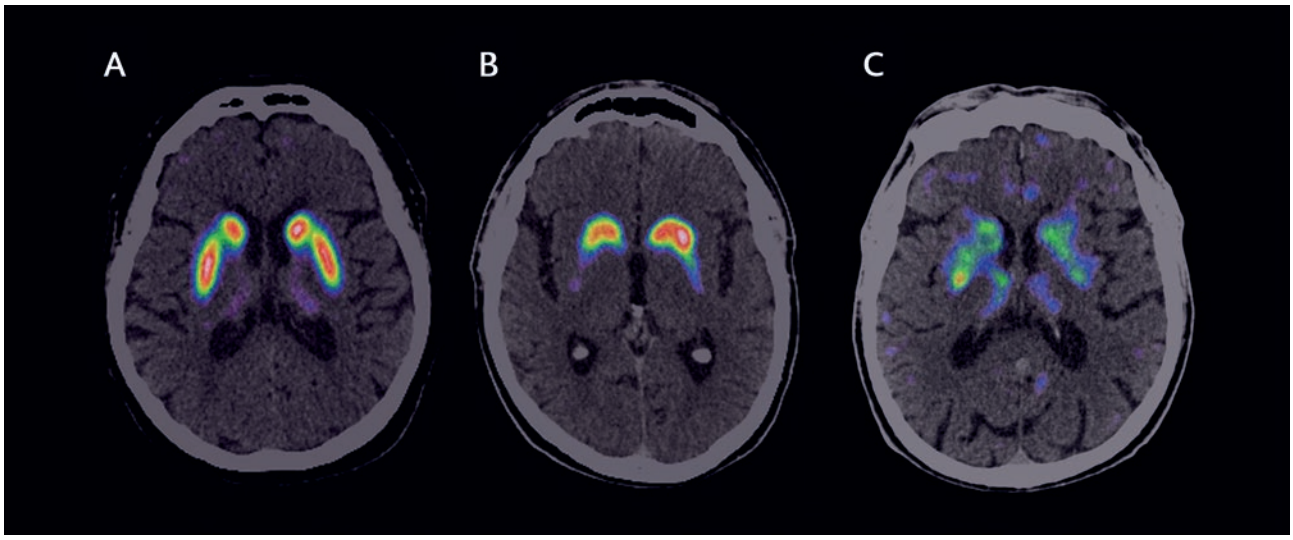
Clinical evaluation was performed by a movement disorders specialist. Motor evaluation was assessed using the Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS). All patients had at least one evaluation before PET imaging and at least one follow-up visit after 6 months of the PET imaging. Patients were divided into two groups according to the presumptive diagnosis: PD or non-PD. Patients were classified as presumptive PD if they failed to meet the criteria for clinically established or clinically probable PD according to the Movement Disorders Society - Clinical diagnostic criteria[6], but still had one supportive criterion and two "red flags" counterbalancing the supportive criteria, and did not meet any criterion for another parkinsonism. Levodopa response was recorded and taken under consideration when making a presumptive diagnosis of PD; nonetheless, it has been reported that levodopa response by itself has a sensitivity and specificity to predict clinical diagnosis of PD of 70.9% and 81.4%, respectively[10].

### Procedures

A standard protocol was used for [$^{11}$C]DTBZ PET. No patient was required to stop their usual antiparkinsonian medication before the study. The radiotracer was injected intravenously; the image acquisition started immediately and lasted for 45 min, acquiring five images of 1 min; followed by three images at 5 min, one image at 10 min, and finally, one image at 15 min. The imaging was obtained using a Siemens Biograph mCT64 PET/CT scanner. The head CT was performed for attenuation correction and anatomical reference. Images were reconstructed with iterative method and with a post-processing algorithm ultra-HD PET, giving a spatial clinical resolution of 4 mm. PET imaging was evaluated with and without fusion with CT image in a Siemens SyngoMMWP VE52A workstation.

Imaging interpretation was based on a visual qualitative analysis by two experienced nuclear medicine physicians blinded to the patient's presumptive

Figure 1. [11C]DTBZ PET images of actual patients included in the study. (a) Shows a Grade 5 pattern, normal uptake, (b) shows a Grade 3 "mixed" pattern; note asymmetry in tracer uptake, (c) shows a Grade 1 "burst striatum" pattern; note almost no tracer uptake on either side.




diagnosis. Imaging interpretation was based on a visual qualitative analysis using as reference the grading system described by Kahraman et al.[11]. Grade 5 is a normal study that shows a symmetric tracer uptake bilaterally in the putamen and caudate. Grade 4, known as an "eagle-wing" pattern, shows an almost normal, symmetrical tracer uptake with a discrete reduction in one or both putamina. Grade 3, referred to as a "mixed" pattern, shows an asymmetric tracer uptake with normal or almost normal uptake in the putamen of one hemisphere and reduced uptake in the contralateral putamen. Grade 2, "egg shape" pattern, shows bilateral reduction of tracer uptake with almost no or no uptake in the putamen and normal or almost normal uptake in the caudate on either side. Grade 1, known as a "burst striatum" pattern, shows severe bilateral reduction with almost no uptake in either the putamen or caudate; this pattern is indicative of severe dopaminergic deficit, and it is also highly indicative of atypical parkinsonian syndromes[11].

In addition, a scan was considered positive when visual assessment revealed a decrease in [11C]DTBZ uptake typical for PD, that is, asymmetric reduction in the posterior putamen more than the anterior putamen (Grade 2 through 4). A scan was considered negative when visual assessment showed no decrease in [11C]DTBZ uptake (Grade 5) or showed a decrease in tracer uptake in a non-PD pattern (Grade 1). Figure 1 for examples of Grades 5, 3 and 1.

## Statistical analysis

Data were expressed as means and standard deviations, or frequencies and percentages, as appropriate. Normality was tested for all variables. Comparison between quantitative variables was performed using Student's *t*-test or Mann–Whitney test as needed. Qualitative data were analyzed using Chi-square test or Fisher's test as needed. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS, version 17 (SPSS, Inc., Chicago, Illinois). Sensitivity, specificity, and positive and negative predictive values (PPV and NPV, respectively) were calculated using a 2 × 2 table; 95% confidence intervals (CI) were also calculated. Accuracy, i.e., overall probability that a patient is correctly classified, was also calculated. For the study purposes, the clinical presumptive diagnosis was considered as the gold standard.

## RESULTS

A total of 39 patients were included in the study, 22 (56.4%) women and 17 (43.6%) men. The mean age was 60.23 ± 15.48 years, with a mean parkinsonism duration of 5.41 ± 4.03 years. The mean time

Table 1. Comparison of main demographic and clinical characteristics.

| Variable | PD group (*n* = 14) | Non-PD group (*n* = 25) | *p* |
|---|---|---|---|
| Male gender | 7 (53.8) | 11 (44%) | 0.73 |
| Age (years) | 58.2 ± 12.2 | 61.4 ± 17.1 | 0.19 |
| Age of onset | 53.4 ± 15.1 | 53.9 ± 21.2 | 0.54 |
| Disease duration, y | 3.1 ± 3.5 | 6.7 ± 9.4 | 0.13 |
| Use of levodopa | 10 (71.4) | 6 (24%) | 0.01 |
| Levodopa dose | 430 ± 210.9 | 675 ± 472.8 | 0.54 |
| Partial levodopa response* | 10 (100) | 3 (12) | 0.04 |
| Use of DA | 8 (57.1) | 1 (4) | < 0.01 |
| LEDD | 379.4 ± 208.4 | 751.7 ± 613.3 | 0.18 |

*Partial response to levodopa was defined as an improvement of < 30% in the motor score of the MDS-UPDRS, or lack of unequivocal and marked on/off fluctuations. DA: dopamine agonist, LEDD: levodopa equivalent daily dose

between parkinsonism onset and the PET scan was 4.46 ± 3.89 years. The main clinical and demographic characteristics are shown in table 1.

Presumptive diagnosis before PET imaging was PD in 14 cases (35.9%) and non-PD in 25 cases (64.1%). The most common presumptive diagnosis in the non-PD group was ET in 12 cases (48%), followed by atypical parkinsonism (including MSA and PSP) in 4 cases (16%), dystonia-parkinsonism in 3 cases (12%), secondary parkinsonism (vascular and medication-induced parkinsonism) in 2 cases (8%), psychogenic movement disorder in 2 cases (8%), one case of spastic paraplegia (4%), and one case of neurodegeneration with brain iron accumulation. Bradykinesia and rigidity were the most common symptoms at the onset in the PD group (38.5%), followed by tremor in 18% and dystonia in 8%.

A total of 15 positive PET scans were obtained. Only one patient in the PD group had a negative scan. On the other hand, two patients from the non-PD group had a positive scan (one with suspected MSA and one with suspected ET). In patients with a positive PET imaging, the most common severity grading was 3 "mixed pattern," present in 7 PET scans (50%). No positive PET imaging was graded below 2.

These results yielded a sensitivity of 92.9% (95% CI, 66.1-99.8), specificity of 92% (95% CI, 74-99), PPV of 86.7% (95% CI, 63.1-96.1), and NPV of 95.8% (95% CI, 79.1-98.4). The overall accuracy was 92.3% (95% CI, 79.1-98.4).

## DISCUSSION

PD diagnosis may be elusive. Several diagnostic tools have been evaluated to discriminate between PD and other causes of parkinsonism. Both PET and SPECT molecular imaging of the brain can detect nigrostriatal cell loss. The most common SPECT radiotracer is [$^{123}$I]ioflupane, assessing DAT in presynaptic endings. On the other hand, the most widely used PET radiotracer is [$^{18}$F]DOPA PET, which assesses striatal levodopa decarboxylase activity, dopamine turnover, synthesis, and release. Both tracers have shown to correlate with motor disability and disease progression[12,13].

A recent systematic review reported a 98% sensitivity and 98% specificity of DAT SPECT imaging to detect nigrostriatal cell loss[14]. Moreover, it has been suggested that DAT SPECT imaging has a significant impact on clinical diagnosis even in tertiary movement disorder clinics. Studies have reported that 59-63% of cases with diagnostic uncertainty seen at a tertiary referral center who underwent DAT SPECT resulted in a change in clinical approach[15,16]. More recently, Graebner et al. reported their experience in 27 cases seen at a movement disorder center; they found that 88.9% of the cases resulted in changes on subsequent clinical decisions after the DAT SPECT imaging was performed[17].

Furthermore, Thiriez et al. demonstrated that the proper use of SPECT has an impact in the clinical utility. For instance, a change in management is seen in

up to 92% of those patients with an appropriate request in comparison to only 13% of patients with an inappropriate request[18]. As a consequence, it has been recommended that the major utility of DAT SPECT imaging is in distinguishing between nigrostriatal dopaminergic degeneration and non-nigrostriatal degeneration in patients displaying parkinsonism with diagnostic uncertainty[19].

Regarding [18F]DOPA PET, a study with 27 patients seen in a movement disorder clinic reported a 95.4% sensitivity, 100% specificity, 100% PPV, and 87.5% NPV[20]. Eshuis et al. compared [18F]DOPA PET with [123I]ioflupane SPECT and found that both scans are equally effective in distinguishing between patients with *de novo* and advanced PD[21]. Furthermore, both scans can discriminate patients with PD from healthy controls with sensitivity and specificity of 100% and 91% for [123I]ioflupane, and 90% and 96% for [18F]DOPA[22].

[11C]DTBZ is a specific ligand of the VMAT2, which is responsible for translocating monoamine neurotransmitters from the cytoplasm into vesicles. More than 95% of striatal VMAT2 transporters are associated with dopaminergic terminals[23], thus [11C]DTBZ reflects the storage ability of dopaminergic neurons. In addition, [11C]DTBZ also linearly reflects dopaminergic neurons' density since it is not influenced by the processes involved in the synthesis, turnover, and release of dopamine.

[11C]DTBZ PET scans have been less studied; nevertheless, reduction in striatal binding of this radiotracer has proven to correlate with disease duration and clinical asymmetry[24-26]. It has also been suggested that this radiotracer could be considered as an early biomarker of disease. In an MPTP non-human primate model of PD, it was shown that decreased VMAT2 binding precedes a DAT binding decline for as early as 2 months[27]. In addition, [11C]DTBZ is not affected by dopaminergic medications commonly used in PD[28]. In our study, [11C]DTBZ PET yielded a sensitivity of 92.9% and specificity of 92%, along with an accuracy of 92.3%. Only one patient in the presumptive PD group had a negative scan; this phenomenon is referred to as scan without evidence of dopaminergic deficit, or SWEDD, and presents in 5-15% of the cases. Some authors have suggested that SWEDDS may be the result of compensatory non-dopaminergic mechanism operating in early disease, but follow-up and reassessment are usually warranted in this case[29].

There are limitations in this study. First, a referral bias is present because patients are attending a tertiary center. In addition, only patients with diagnostic uncertainty were included in the study. Generalization to other settings is not possible and should be considered when interpreting our findings. Second, we chose to compare the results of only visual analysis of the PET scan instead of both visual and computer-aided quantitative analysis. Third, clinical presumptive diagnosis was used as the gold standard. PD definitive diagnosis requires histopathological confirmation, and at the time of the study, all subjects were alive. Furthermore, a 6-month follow-up period was required for all cases to reduce the possibility of further changes in the diagnosis.

The [11C]DTBZ PET has an excellent accuracy for differentiating idiopathic PD from other disorders when clinical uncertainty exists. When properly implemented by experienced neurologists in the movement disorders' field and performed, read, and reported by competent nuclear medicine physicians, it can help to determine the course of action in specific situations.

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