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*Original Article*

# The sensitivity and specificity of F-DOPA PET in a movement disorder clinic

Nevein Ibrahim[1], Joanna Kusmirek[1], Aaron F Struck[1,2], John M Floberg[3,4], Scott B Perlman[1], Catherine Gallagher[2], Lance T Hall[1]

*[1]Department of Radiology, University of Wisconsin School of Medicine and Public Health, USA; [2]Department of Neurology, William S. Middleton VA Hospital, USA; [3]Department of Medical Physics, University of Wisconsin, USA; [4]Transitional Year Residency Program, Hennepin County Medical Center, USA*

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**Abstract:** Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disorder. Early PD may present a diagnostic challenge with broad differential diagnoses that are not associated with nigral degeneration or striatal dopamine deficiency. Therefore, the early clinical diagnosis alone may not be accurate and this reinforces the importance of functional imaging targeting the pathophysiology of the disease process. $^{18}$F-DOPA L-6-[$^{18}$F] fluoro-3,4-dihydroxyphenylalnine ($^{18}$F-DOPA) is a positron emission tomography (PET) agent that measures the uptake of dopamine precursors for assessment of presynaptic dopaminergic integrity and has been shown to accurately reflect the monoaminergic disturbances in PD. In this study, we aim to illustrate our local experience to determine the accuracy of $^{18}$F-DOPA PET for diagnosis of PD. We studied a total of 27 patients. A retrospective analysis was carried out for all patients that underwent $^{18}$F-DOPA PET brain scan for motor symptoms suspicious for PD between 2001-2008. Both qualitative and semi-quantitative analyses of the scans were performed. The patient's medical records were then assessed for length of follow-up, response to levodopa, clinical course of illness, and laterality of symptoms at time of $^{18}$F-DOPA PET. The eventual diagnosis by the referring neurologist, movement disorder specialist, was used as the reference standard for further analysis. Of the 28 scans, we found that one was a false negative, 20 were true positives, and 7 were true negatives. The resultant values are Sensitivity 95.4% (95% CI: 100%-75.3%), Specificity 100% (95% CI: 100%-59.0%), PPV 100% (95% CI 100%-80.7%), and NPV 87.5% (95% CI: 99.5%-50.5%).

**Keywords:** $^{18}$F-DOPA, flouorodopa, Parkinson's disease, PET

## Introduction

Idiopathic Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease [1]. The cardinal pathological features of PD are the formation of proteinaceous intraneuronal Lewy body inclusions and progressive loss of the dopaminergic neurons, particularly targeting the substantia nigra pars compacta (SNc), which results in striatal dopamine deficiency [2, 3]. Early PD may present a diagnostic challenge with broad differential diagnoses that are not associated with nigral degeneration or striatal dopamine deficiency. In addition, atypical parkinsonian disorders associated with striatal dopamine deficiency but with non-Lewy body pathologies such as multiple-system atrophy, progressive supranuclear palsy, and corticobasal degeneration [2] might be difficult to differentiate from early PD [4]. A recent study using neuropathologic findings of PD as a gold standard to confirm the clinical diagnosis demonstrated that the accuracy of the clinical diagnosis of PD in not clearly responsive subjects is only 26% and rises to 53% in early PD responsive to medication (<5 year duration) and >85% of longer duration, medication-responsive PD. In addition, they reported that a clinical diagnosis of PD identifies patients who will have pathologically confirmed PD with a sensitivity of 88% and specificity of 68% [5]. Therefore, the clinical diagnosis alone is not accurate enough especially in the early stages of the disease and this reinforces the importance of the functional imaging aiming at the pathophysiology of the disease process [3].

L-6-[$^{18}$F] fluoro-3,4-dihydroxyphenylalnine ($^{18}$F-DOPA) is a positron emission tomography (PET) agent that measures the uptake of dopamine precursors for assessment of presynaptic dopaminergic integrity [3] and has been shown to accurately reflect the monoaminergic disturbances in PD. Small clinical trials have demonstrated high sensitivity and specificity for $^{18}$F-DOPA PET, but little data exists about $^{18}$F-DOPA PET's diagnostic accuracy in an ambulatory movement disorders clinic population.

This retrospective study illustrates our local experience to determine the diagnostic accuracy of $^{18}$F-DOPA PET in differentiating early Parkinson's disease from other similar non-Parkinson's disorders in a movement disorders clinic population using long-term clinical outcomes as a reference standard.

## Materials and methods

### *Subjects*

Institutional Review Board (IRB) approved the use of human subjects for this study and a patient consent requirement was waived. A query of a departmental database was carried out for all patients that underwent $^{18}$F-DOPA PET brain scan for motor symptoms suspicious for PD between 2001 and 2008. To be eligible in this study, the patient had to have adequate post-scan clinical follow-up and a diagnosis that states whether the patient has PD or not. This was assessed by retrospective electronic chart review. The PET scan was done as a part of clinical evaluation.

### *Procedures and techniques*

A standard protocol was used for $^{18}$F-DOPA PET scans at our institution. All subjects were prepared prior to the scan as follows: patients were instructed to adhere to a low protein diet for 24 hours and fast after midnight. A small amount of water with medications was allowed. All the medications that could interfere with $^{18}$F-DOPA uptake were held and the patients were called prior to the scan to verify the changes in their medication schedule. Patients were premedicated with 200 mg of carbidopa orally 1 hour prior to the injection of 5-10 mCi of $^{18}$F-DOPA. The patients rested comfortably with no strenuous movement in a calm environment during the uptake time. The time of injection and scanning was recorded. Imaging started 110 minutes post injection. The patients were positioned in a scanner with help of a head holder. The PET images were obtained using a GE Advance scanner. Three experienced nuclear medicine physicians (all with 20-30 years of clinical experience) evaluated the $^{18}$F-DOPA PET scans. The readers were aware of initial clinical data and other imaging results that were available at the time of the PET scan acquisition. Clinical interpretation was based on both a qualitative and semi-quantitative analyses. The qualitative interpretation was based on a visual assessment of $^{18}$F-DOPA uptake in the basal ganglia. The semi-quantitative interpretation was based on region of interest (ROI) analysis of the caudate nucleus, the anterior, middle, and posterior putamen, and the occipital cortex [6]. $^{18}$F-DOPA uptake in these ROI's was measured and ratios of the caudate, the anterior, mid, and posterior putamen to the occipital cortex were calculated for each side according to Otsuka et al. [7]. Caudate-putamen index (CPI) was also calculated by a formula based on difference in the uptakes in the caudate and putamen divided by the caudate uptake using uptake in the occipital lobe as background correction [7].

### *Definitions and criteria*

A scan was considered positive for PD when visual assessment revealed a relative decrease in $^{18}$F-DOPA uptake in the basal ganglia (unilateral or bilateral) in a pattern typical for PD (i.e. asymmetric reduction of $^{18}$F-DOPA uptake in the posterior greater than anterior putamen).

Semi-quantitative analysis was used to support the qualitative analysis or the final interpretation when qualitative analysis was indeterminate in differentiating PD from non-PD conditions.

### *Data collection and validation*

Each patient's medical records were assessed for length of follow-up, response to levodopa, clinical course of illness, and laterality of symptoms at time of $^{18}$F-DOPA PET.

Demographic data were also collected. The eventual long-term diagnosis by the referring Neurologist was used as the reference standard for further analysis.

**Table 1.** Demographic data and symptomatology

| | Non-Parkinson's disease | Parkinson's disease | *p*-value |
|---|---|---|---|
| | Median (range) | Median (range) | Wilcoxon |
| Age at dx (years) | 45 (41-61) | 47.5 (29-76) | 0.934 |
| Age at Scan (years) | 47 (43-67) | 50 (33-78) | 0.821 |
| Follow-up (years) | 4 (2-8) | 5 (3-9) | 0.197 |
| | Proportion with (%) | Proportion with (%) | Fisher's Test |
| Sex (male) | 3/7 (42.9%) | 15/20 (75.0%) | 0.175 |
| % with Depression | 5/7 (71.4%) | 5/20 (25.0%) | 0.065 |
| Lateral findings | 6/7 (85.7%) | 15/19 (78.9%) | 1.000 |
| Bradykinesia | 5/7 (71.4%) | 11/18 (61.1%) | 1.000 |
| Tremor | 4/7 (57.1%) | 20/20 (100%) | 0.012 |
| Gait | 4/6 (66.7%) | 4/20 (20.0%) | 0.051 |
| Rigidity | 3/7 (42.9%) | 13/19 (68.4%) | 0.369 |
| Behavioral and/or Cognitive defect | 3/5 (60.0%) | 8/20 (40.0%) | 0.623 |
| Response to Levodopa | 4/4 (100.0%) | 16/18 (88.9%) | 1.000 |

**Table 2.** Results of imaging versus final diagnosis per clinical assessment

| | Scan (+) | Scan (-) | Total |
|---|---|---|---|
| PD | 20 | 1 | 21 |
| No PD | 0 | 7 | 7 |
| Total | 20 | 8 | 28 |

*Statistical tests*

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were then calculated as simple ratios and confidence intervals were generated. The confidence interval was calculated using the adjusted-Wald 95% confidence interval (CI) method [8].

## Results

Twenty-nine patients were found in the initial query, and 2 were excluded (1 uncertain diagnosis, 1 inadequate follow-up). Twenty-seven patients (28 scans) remained with 18 males (67%) and 9 females (33%). All the patients had a clinical follow-up of at least 2 years, however the median length of follow-up was 5.4 years (range: 2-9 years). The median age at scan time was 50.6 years (range: 33-78). The patients' basic demographic data and symptomatology along with statistical analysis are listed in (**Table 1**).

Of the 28 scans, the combined qualitative and semi-quantitative assessment was indicative of PD in 20 scans (consistent with dopamine deficiency in the basal ganglia) while the remaining 8 scans were read as negative for PD. Examples of negative and positive $^{18}$F DOPA PET scans are shown as **Figures 1** and **2** respectively. Analysis of the patients' data showed that 20 patients were finally diagnosed with PD and 7 patients were diagnosed with other conditions (**Table 2**). These conditions included: mixed tremor (1 patient), corticobasal syndrome (1 patient), hemidystonia (1 patient), and psychogenic PD (4 patients). There was 1 false negative scan, 20 were true positives, and 7 were true negatives. There were no false positives.

The resultant values are: sensitivity 95.4% (95% CI: 100%-75.3%), specificity 100% (95% CI: 100%-59.0%), PPV 100% (95% CI 100% -80.7%), and NPV 87.5% (95% CI: 99.5%-50.5%).

## Discussion

The cardinal symptoms of PD include bradykinesia, rigidity and rest tremor; however, multiple additional motor and non-motor symptoms are present as well.

Several neurologic diseases can present with similar clinical features including multiple system atrophy (MSA) with three main subtypes: MSA-P (parkinsonian subtype), MSA-C (cerebellar subtype), and MSA-A (autonomic subtype), progressive supranuclear palsy (PSP, Steele-

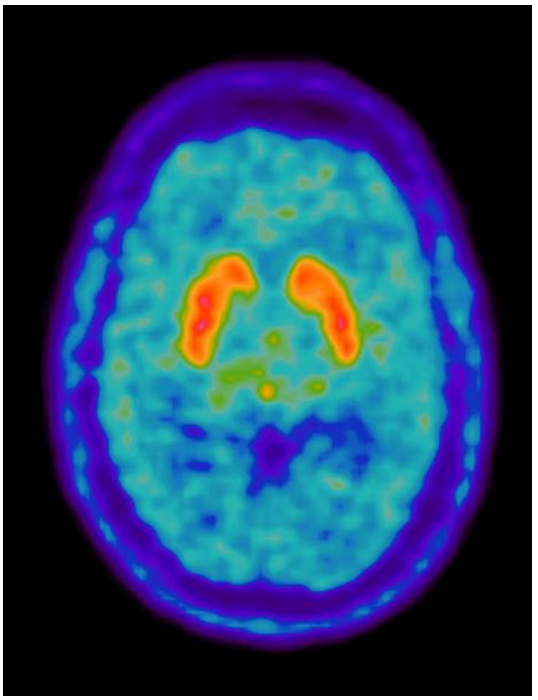

**Figure 1.** Negative $^{18}$F-DOPA PET scan in a patient suspected of having PD. The image shows uniform uptake within the bilateral caudate and putamen in a pattern of normal physiological uptake.

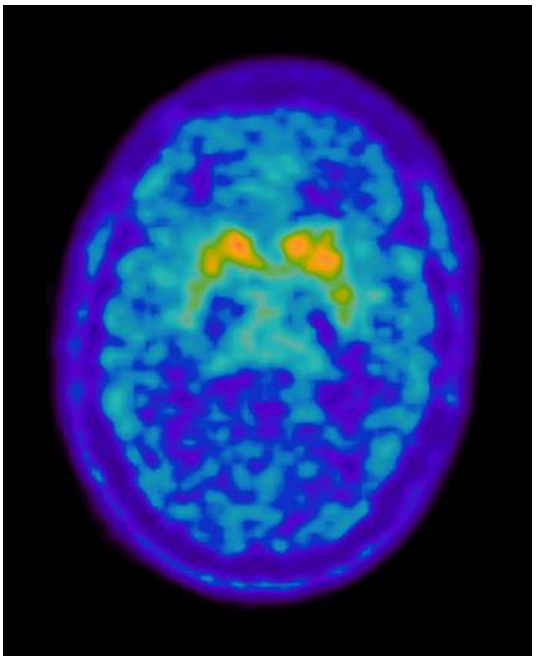

**Figure 2.** Positive $^{18}$F-DOPA PET scan in a patient suspected of having PD. The image demonstrates decreased $^{18}$F-DOPA uptake within the bilateral posterior greater than anterior putamen consistent with PD.

Richardson-Olszewski syndrome), corticobasal degeneration (CBD) or dementia with Lewy bodies (DLB) [9]. Another important entity is parkinsonism secondary to other diseases or exogenous agents such as neuroleptics. Some conditions such as vascular parkinsonism can be excluded by standard imaging (CT and MRI) however PD remains a clinical diagnosis.

The parkinson-like syndromes frequently respond poorly to levodopa and progress faster. Therefore, a potential way to diagnose PD would be using the response to dopaminergic medications ("levodopa challenge"). However, the results are not completely specific due to partial response to levodopa in other conditions and placebo effect [10]. Some responsiveness to levodopa is not uncommon in early MSA or PSP or even vascular parkinsonism making a proper diagnosis very challenging [11]. In our study group, anti-Parkinson medications were started in 25 out of 27 subjects. A good clinical response was observed in all of the patients except for 2, who were finally diagnosed with idiopathic PD. Two patients with psychogenic parkinsonism, patients with dystonia and mixed tremor, and a CBD patient, all had initial good response to medications.

Therefore, functional imaging aiming at the pathophysiology of the disease process is of particular value in certain situations, e.g. atypical features, mild symptoms, or early age of onset.

There are multiple methods for functional imaging of dopamine deficiency [2]:

1. Presynaptic dopamine reuptake transporter (DAT) imaging with PET (e.g., $^{11}$C-2-carbomethoxy-3-(4-$^{18}$F-fluorophenyl) tropane ($^{11}$C-CFT)) and SPECT (e.g., $^{123}$I-beta 2 beta-carbomethoxy-3 beta-(4-iodophenyl) tropane ($^{123}$I-beta-CIT) or $^{123}$I-N-3-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) tropane ($^{123}$I-FP-CIT) (DaTSCAN)).

2. $^{18}$F-DOPA PET as a marker of terminal dopa decarboxylase activity.

3. Vesicular monoamine transporter (VMAT2) availability with $^{11}$C- or $^{18}$F-dihydrotetrabenazine PET.

4. Postsynaptic D2 dopamine receptor imaging with $^{123}$I-iodobenzamide ($^{123}$I-IBZM or $^{11}$C-raclopride).

$^{18}$F-DOPA is a PET agent that measures the uptake of a dopamine precursor for assessment of presynaptic dopaminergic integrity. The uptake of $^{18}$F-DOPA in the striatal nuclei reflects both the density of catecholaminergic terminals and the activity of the aromatic amino acid decarboxylase (AADC), the enzyme responsible for the conversion of $^{18}$F-DOPA to $^{18}$F-dopamine. Measurements of $^{18}$F-DOPA uptake in the striatum of patients with PD will therefore be influenced by the number of remaining dopaminergic cells [3]. $^{18}$F-DOPA has been shown to accurately reflect the monoaminergic disturbances in PD, and can be useful in situations where clinical uncertainty exists for patients with Parkinson like movement disorders. Our study indicates that $^{18}$F-DOPA PET is an accurate tool for the diagnosis of PD in heterogeneous patient population followed in a movement disorders clinic. These results are in agreement with other published studies that show that functional imaging is highly sensitive and specific and may be valuable in PD diagnosis [12, 13]. The previously reported sensitivities and specificities for $^{18}$F-DOPA PET were 90%-100% and 91% respectively [14]. $^{123}$I-FP-CIT imaging was also shown to have sensitivity and specificity of over 90% [15].

It has been shown previously that $^{18}$F-DOPA uptake in the putamen correlates with clinical severity of the PD as measured by Unified Parkinson's Disease rating scale (UPDRS) [16, 17]. Several studies reported a correlation between $^{18}$F-DOPA uptake in putamen and severity of bradykinesia and rigidity for both PET and SPECT modalities [18]. However, there is no such correlation for rest tremor, which suggests a role of the serotonergic system [18]. In addition, noradrenalin pathways have been associated with depression (2-6 times more common in PD, affecting 10-45% PD patients), which do not follow the course of other symptoms [2, 18].

Patients with hemiparkinsonism have the most pronounced decrease in uptake in the contralateral dorsal posterior putamen [19].

One of the disorders causing diagnostic problems in a movement disorder clinic is an adult-onset dystonic tremor. In these patients, clinical diagnosis can be very difficult or even impossible and functional imaging can spare the patient inappropriate pharmacotherapy and concern that they may be afflicted with Parkinson's disease [11, 20]. The clinical diagnosis for this entity has good sensitivity of >90%, however the specificity was reported as low as 30% [2].

Another valid indication is differentiating PD from a senile gait disorder and slowing associated with aging. Early imaging can prevent unnecessary drug therapy and avoid possible side effects of therapy such as psychosis.

In clinical settings, $^{18}$F-DOPA PET can be also helpful in excluding psychogenic movement disorders, the estimated prevalence of which may be 2-3% or even higher in movement disorders clinics [11]. Importantly, due to a good placebo effect in this patients group, a positive levodopa challenge can be misleading. In our study population, we observed very high frequency of this disorder (15%). This can be explained by the fact that only pre-selected patients were referred for $^{18}$F-DOPA PET. Clearly, in this patient population, a negative study can spare costs and possible complication of additional diagnostic tests and medications. Negative imaging findings supporting alternative diagnosis is a powerful tool in such circumstances. This facilitates physician-patient communication, gives a background for antiparkinsonian therapy withdrawal and also helps the patients to adjust to the alternative diagnosis and its implications.

An important problem, accounting for 24-35% of Parkinsonism and up to 50% of hospital admissions due to parkinson-like symptoms is a drug-induced Parkinsonism [11, 21]. The culprit medications include neuroleptics, certain ant-emetics and calcium channel blockers (flunarizine and cinnarizine - used in Europe). In a clinical practice, functional imaging can help establish a diagnosis in cases where drug-induced Parkinsonism is suspected and a reliable drug history is not available. It is also of a great value in patients with psychiatric diseases in whom stopping the medications is not safe (e.g. risk of suicide). On the other hand, these medications can unmask presymptomatic PD. In this scenario, a positive scan and clear temporal relationship to the drug therapy can lead to diagnosis. Functional imaging with

PET and SPECT can detect subclinical dopaminergic dysfunction in subjects at risk (patients' relatives, carries of genetic mutations, elderly with idiopathic hyposmia, and REM sleep behavior disorders) [2]. It has also been investigated as a tool for monitoring disease progression and effectiveness of the therapy [18]. However, the correlation between disease progression and decrease in $^{18}$F-DOPA uptake remains questionable. The conflicting data may be related to compensatory mechanisms and medication effect [3].

In up to 15% of cases clinically labeled as early PD, functional imaging does not support a diagnosis of PD [11, 22]. These patients with "scans without evidence of dopaminergic deficit" (SWEEDs) have been followed in several studies [22]. The majority of these patients will finally be diagnosed with parkinsonian-like disorders (especially dystonic tremor), not a true PD. However, patients with such findings have a good prognosis regardless of ultimate diagnosis [23]. In our study, there was only 1 patient with negative scan who finally was given a diagnosis of PD. This patient has been followed 4.5 years and did not show significant progression of the symptoms.

## Limitations

An obvious limitation for this study is a small sample size. However, our study included only a small percentage of the clinic patients, whose symptoms were atypical and the clinical diagnosis was difficult to establish. This is exactly the population targeted by dopamine imaging.

We considered clinical diagnosis a reference standard; however a definitive diagnosis of idiopathic PD requires histological demonstration of intraneuronal Lewy body inclusion in the substantia nigra compacta [2]. The pathological diagnosis is very impractical and clinical diagnosis has been used as a gold standard in multiple studies, which is in agreement with experts' opinions. Moreover, Lewy body inclusions on post-mortem examination can be seen in individuals without clinical evidence of PD (presumably pre-clinical cases). Another limitation of our study design is that the results of the scan possibly could have an influence on the final diagnosis of the patient, i.e., the movement disorder specialist was not blinded to the results of the $^{18}$F-DOPA scan. However, a long follow-up ensures that the clinical diagnosis is verified several times.

There are also certain general limitations of functional imaging in PD. One limitation is difficulty of definitively differentiating between PD and MSA [24]. However, there are studies showing that the typical gradient of loss of dopaminergic function in PD with relative sparing of the caudate head (rostro-caudal gradient) is not present in PSP and CBD [7].

Interestingly, $^{18}$F-FDG PET in conjunction with $^{18}$F-DOPA PET has been reported of value for differentiation of Parkinson-like disorders. In typical idiopathic PD, lentiform nucleus metabolism was described as preserved or raised, whereas in most atypical cases this was reduced [2]. Bilateral hypometabolism in the putamen is more typical for MSA, hypometabolism in the brainstem and the middle frontal cortex mass suggest PSP and unilateral striatal decrease in uptake has been implicated in CBD [11]. In addition, loss of cardiac sympathetic innervation present in PD may help the diagnosis. This is present in PD, but not MSA and PSP and can be detected with $^{18}$F-DOPA PET [2].

Another issue for functional imaging is quantification of the results. $^{18}$F-DOPA uptake can be quantified by ratio method, graphical method (Patlak analysis using influx constant, $K_i$), or compartmental model. $K_i$ is a slope of linear fitting between 2 time-activity curves: in striatum and in the blood. This requires dynamic imaging which result in prolonged scanning time and unavoidable patient's movements necessitating motion correction in some cases [25]. A good correlation was found between influx constants and ratios [25, 26]. The latter would be clinically preferred due to shorter scanning time, and less frequent motion artifact.

## Summary and future directions

Although PD remains a clinical diagnosis, many clinicians have started showing an interest in applying the new diagnostic tools including PET and SPECT imaging.

Our study supports this statement, showing that $^{18}$F-DOPA PET is very accurate for differentiating PD form other Parkinson-like entities in selected cases, in which a clinical diagnosis is challenging.

## Disclosure of conflict of interest

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**Address correspondence to:** Dr. Nevein Ibrahim, Department of Radiology, University of Wisconsin School of Medicine and Public Health, USA. E-mail: NIbrahim@uwhealth.org

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