

Clinical and [¹⁸F]dopa PET findings in early Parkinson's disease

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Abstract

Twenty seven patients with recent onset (mean symptom duration 22 (SD 14) months, Hoehn and Yahr score 1.8 (SD 0.7)) Parkinson's disease were studied with [¹⁸F]dopa PET. There was a correlation between putamen influx (Ki) and clinical rating, but not symptom duration. In 11 patients with hemi-Parkinson's disease of recent onset there were significant differences between normal (mean 0.0123 (SD 0.0023)), asymptomatic (mean 0.0099 (0.0020)) and symptomatic (mean 0.0070 (0.014)) putamen Kis. This suggests that Parkinson's disease has a widely variable rate of progression, and is most compatible with a short preclinical period. Symptom onset was estimated at a putamen Ki of between 57% and 80% of normal. Most ipsilateral putamen Ki values in early asymmetric Parkinson's disease fell within the normal range. The implication is that either the disease is not established in the ipsilateral putamen or that the technique is insufficiently sensitive to detect it. Discriminant analysis completely separated the normal and Parkinson's disease cohorts, but when a discriminant function from a previous study was used predictively four of the 27 patients with Parkinson's disease were incorrectly classified as normal.

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Postmortem data from patients with very recent onset idiopathic Parkinson's disease are lacking and the belief that cell loss may be greater than 50% at presentation is based on extrapolation from patients with disease of several years duration.¹ [¹⁸F]dopa PET enables the study of presynaptic dopaminergic terminal function in the striatum in Parkinson's disease, but there are no previous quantitative PET studies close to the onset of symptoms.

Postmortem data in humans² and primates treated with MPTP³ have suggested a direct correlation between PET measurements of striatal [¹⁸F]dopa uptake and nigral cell count. If there is a 50% reduction in nigral cell count at presentation, then striatal [¹⁸F]dopa uptake should be similarly reduced. It has been suggested that [¹⁸F]dopa PET might be used to

identify those with preclinical Parkinson's disease.⁴ For such an application PET measurements of striatal dopa uptake must be significantly reduced, and distinct from the normal range at clinical presentation.

It has been argued that the preclinical period may be as long as 20 years.⁵ Patients with unilateral symptoms develop bilateral symptomatology after a mean of 6.1 years from onset.⁶ If the preclinical period is more prolonged than this, then [¹⁸F]dopa PET should identify the presence of bilateral disease in patients with unilateral symptoms. There are no previous [¹⁸F]dopa PET studies on a large group of patients with Parkinson's disease with purely unilateral symptoms.

Studies showing a correlation between clinical stage and [¹⁸F]dopa PET measurements of striatal function have included patients with a wide range of disease severity and duration.^{7,8} We wished to assess the value of this technique as an objective measure of disease severity early in the disease. We have shown that application of discriminant analysis to [¹⁸F]dopa PET data distinguishes normality from Parkinson's disease⁹ in a group of patients with mean Hoehn and Yahr score 2.7 (SD 1.0). Complete discrimination at onset of disease and predictive use of a derived discriminant function to classify new subjects as normal or having Parkinson's disease would be of greater clinical value.

We have performed [¹⁸F]dopa PET in a group of 27 patients with idiopathic Parkinson's disease early in the course of their illness (mean Hoehn and Yahr score 1.8, mean duration 22 months). A subgroup of 11 with purely unilateral disease were identified and studied separately. Our aim was to investigate, close to the time of presentation, the extent to which striatal [¹⁸F]dopa uptake is reduced in Parkinson's disease and its relation to duration, laterality, and severity of symptoms and signs. We hoped to gain insight into the nature of the disease process, and to evaluate the ability of [¹⁸F]dopa PET to discriminate Parkinson's disease from normality at the earliest clinical stage.

Patients and methods

Twenty seven patients (20 men, seven women, age 59 (SD 11)) fulfilling the brain bank criteria for prospective diagnosis of Parkinson's disease¹⁰ were assessed by history, examination, and [¹⁸F]dopa PET as soon as possible after onset of symptoms (mean 22 (SD 14) months)

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and at least 12 hours after stopping medication. Their illness was clinically staged with the unified Parkinson's disease rating scale (UPDRS),¹¹ Hoehn and Yahr¹² rating scales, and the following timed motor tests: (a) upper limb pronation/supination (20 times); (b) upper limb movement between two points 30 cm apart (10 times); (c) finger dexterity: opposing the thumb to each finger through 10 cycles.

A group of normal unrelated controls (n = 16, mean age 63 (SD 13)) were recruited and scanned over the same period. Patients were deemed to have unilateral Parkinson's disease if they scored zero on one side for UPDRS and if all timed tests for this limb fell within 1 SD of the mean time for that from a larger group (including most of the scanned controls) of normal subjects (n = 23, mean age 63 (SD 12)).

All subjects gave written informed consent before PET. Permission to perform these studies was obtained from the ethics committee of the Hammersmith Hospital, London, United Kingdom, and from the Administration of Radioactive Substances Advisory Committee, United Kingdom.

All subjects were given carbidopa—100 mg one hour before and 50 mg five minutes before scanning. When available we introduced the catechyl-o-methyl transferase inhibitor entacapone¹³ (Orion Farnos pharmaceuticals) and 14 of the 27 patients with Parkinson's disease and eight of the 16 normal subjects were given 400 mg and two other normal subjects were given 800 mg entacapone orally one hour before scanning. PET was performed using the CTI 931/08/12 tomograph (CTI, Knoxville, TN) with a protocol of 31 time frames over 93 minutes. [¹⁸F]dopa (80–180 MBq) in 10 ml normal saline solution was infused intravenously over 30 seconds. A radial arterial line gave plasma counts and samples for metabolite analysis using alumina extraction.¹⁴

Data analysis was performed with ANA-

LYZE (ANALYZE 7.0, Mayo Foundation, Baltimore, MD¹⁵) image analysis software. Region of interest analysis was performed with a standard template as previously described.⁴ [¹⁸F]dopa uptake (Ki) was calculated for each of right and left caudate and putamen using the MTGA approach of Patlak and Blasberg,¹⁶ with metabolite corrected plasma counts as input function. Results from right and left were also averaged to give mean results for putamen and caudate. As the results obtained for the control group in this study and previous work from this unit¹³ show that entacapone does not significantly change striatal Ki values when calculated using metabolite corrected plasma count as input function the findings of normal and Parkinson's disease groups scanned with and without entacapone were combined to increase the power of the study. Discriminant function analysis was carried out with statistical software (SPSS version 4.0, SPSS UK Ltd, Surrey, England).

Results

CLINICAL

Clinical assessment of the 27 patients showed a mean Hoehn and Yahr score of 1.8 (SD 0.7), mean total UPDRS 24.2 (SD 11.5), and mean motor UPDRS 15.1 (SD 7.5). There was no significant correlation between time since estimated symptom onset and severity of disease (rated by Hoehn and Yahr score, total, or motor UPDRS). Of the 27 patients with Parkinson's disease 19 had rest tremor, 10 had predominantly right sided symptoms, six predominantly left sided, and the remaining 11 had bilateral symptomatology. Eleven (mean UPDRS 18 (SD 8), mean duration of symp-

Table 1 Comparison of results in controls and patients scanned with and without entacapone

With entacapone	Normal (n = 10)	PD (n = 14)
Mean putamen Ki	0.0121 (0.0028)	0.0065 (0.0017)
Mean caudate Ki	0.0127 (0.0033)	0.0104 (0.0026)
Without entacapone	Normal (n = 6)	PD (n = 13)
Mean putamen Ki	0.0126 (0.0011)	0.0087 (0.0024)
Mean caudate Ki	0.0131 (0.0023)	0.0123 (0.0027)
Combined groups	Normal (n = 16)	PD (n = 27)
Mean putamen Ki	0.0123 (0.0023)	0.0075 (0.0023)
Mean caudate Ki	0.0129 (0.0029)	0.0113 (0.0028)

Values are means (SD).

Table 2 Comparison of duration and severity of disease in patients treated with and without selegiline, and with and without tremor

	No	UPDRS	Months since onset	Mean putamen Ki (min ⁻¹)
Selegiline	8	23 (12)	25.9 (14)	0.0086 (0.0023)
No selegiline	19	25 (12)	19.8 (14)	0.0071 (0.0022)
Tremor	19	22 (10)	21.4 (13.7)	0.0079 (0.0021)
No tremor	8	30 (13)	22.1 (15.1)	0.0066 (0.0027)

Values are means (SD).

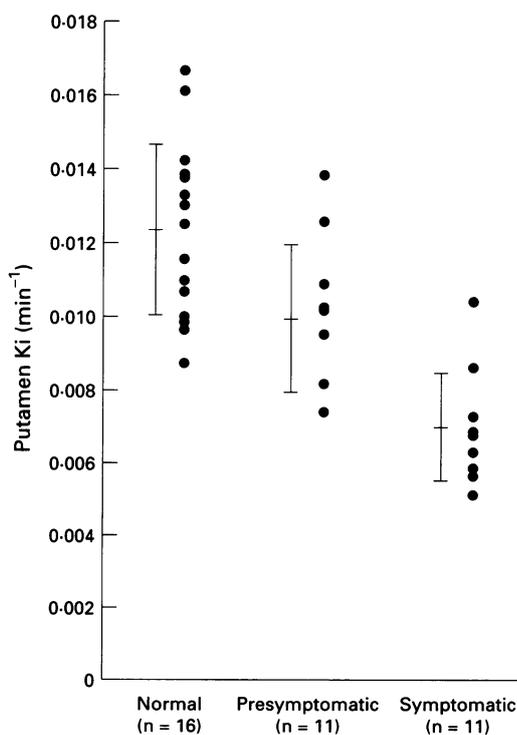


Figure 1 Putamen Ki in the normal, presymptomatic, and early symptomatic putamen. Bars are SD.

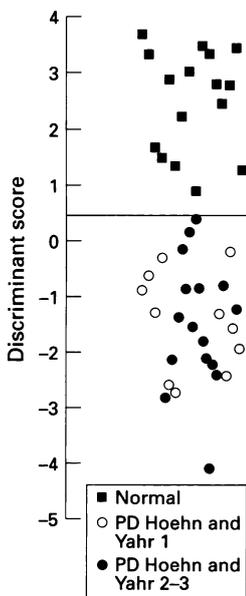


Figure 2 Application of discriminant analysis to 16 normal subjects and 27 patients with Parkinson's disease.

toms 24 (16) months) of the 27 fulfilled our clinical criteria for unilateral disease.

[¹⁸F]DOPA PET

There was no significant difference in mean caudate and putamen Ki values between the two groups of normal subjects scanned with and without entacapone (table 1). There were no significant differences in mean putamen Ki, clinical disease duration, or UPDRS score between those patients with Parkinson's disease taking selegiline and those not. The Parkinson's disease group with tremor showed a trend towards lower mean putamen Ki and higher UPDRS score at similar duration of clinical disease to those without tremor but the differences did not reach significance (table 2).

Correlation was found between both total and motor UPDRS and mean putamen Ki (total UPDRS *v* mean putamen Ki, $r = -0.41$ $P < 0.05$, motor UPDRS *v* mean putamen Ki, $r = -0.39$ $P < 0.05$, Spearman rank correlation) and between sided motor UPDRS and contralateral putamen Ki ($r = -0.49$, $P < 0.005$). No correlation was identified between [¹⁸F]dopa uptake in the contralateral putamen and performance time in any of the three timed tests.

In each of the 11 patients with clinically unilateral Parkinson's disease, identified as above, the putamen Ki contralateral to the affected limb was lower than that of the ipsilateral putamen. There was a significant difference ($P < 0.05$, Mann-Whitney *U* test) between the mean putamen Ki of the normal group (0.0123 (SD 0.0023)) and the mean putamen Ki ipsilateral to the affected limb (0.0099 (SD 0.0020)). There was also a significant difference ($P < 0.005$, Mann-Whitney *U* test) between the mean putamen Ki ipsilateral and contralateral (0.0070 (SD 0.014)) to the affected limbs. Figure 1 shows the individual results for the putamen ipsilateral and contralateral to the affected limb.

A discriminant function completely separated the normal and Parkinson's disease [¹⁸F]dopa PET results. Figure 2 shows the discriminant scores and separation of the groups. There was a significant correlation ($r = -0.49$, $P = 0.01$, Spearman rank correlation) between discriminant score and total UPDRS score. There was no significant difference between the discriminant scores of those with unilateral and those with bilateral symptomatology. When the discriminant function from a previous study⁹ was applied to this group four patients with Parkinson's disease were incorrectly assigned to the normal group.

Discussion

The extent of disease at the onset of clinical symptomatology is an issue crucial to understanding the disease process in Parkinson's disease. When this group of 27 patients with early Parkinson's disease was considered the mean putamen Ki was 62% of normal but this group contains patients of varying disease severity and duration. The 11 patients with unilateral symptomatology represent the earli-

est clinical stage of the disease. If the right and left putamen deteriorate and produce clinical signs independently then this group allows us to study both early clinical disease in the putamen contralateral to the affected limb and pre-clinical disease in the putamen contralateral to the unaffected limb. Our estimate for the mean threshold putamen [¹⁸F]dopa uptake, at which symptoms develop, is between 57% and 80% of normal (as this group had symptoms for a mean of two years before scanning the true threshold is unlikely to be as low as 57%). The results from the putamen contralateral to the symptomatic limb lay between 41% and 89% of the normal mean, with only two results lying within 2 SDs. By contrast [¹⁸F]dopa uptake measured in the presymptomatic putamen ranged between 60% and 127% of the normal mean, nine of the 11 results lying within 2 SDs.

We have previously used [¹⁸F]dopa PET to try to identify preclinical disease in at risk relatives,¹⁷ but only one of these to date has gone on to develop unequivocal Parkinson's disease. The means and SDs from the normal and presymptomatic groups presented here allow assessment of the implication of a single putamen result (assuming a normal distribution around the mean in each). Below a putamen Ki of 0.0077 min^{-1} (two SDs below the normal mean) lie 2.5% of normal putamen results; only 15% of presymptomatic putamen results in our unilateral Parkinson's disease group would fall below this point. Hence most subjects with genuine preclinical disease are likely to have putamen Ki results within 2 SDs of the normal mean. Either they do not have the disease or it is not identifiable with this technique. The incidence of incidental Lewy body disease (suggested to be the pathological precursor of Parkinson's disease) has been estimated at 3.8% in the sixth decade rising to 12.8% in the ninth decade.¹⁰ Consequently a putamen Ki with a value falling two SDs below the normal mean in a subject from the general population is still more likely to be normal than to represent preclinical disease.

If putamen Ki is proportional to nigral cell count² then our study suggests that at symptom presentation in unilateral Parkinson's disease the cell count on the preclinical side is still in the normal range in most patients classified as Hoehn and Yahr score 1. We are not aware of postmortem data from patients with very recent onset of disease. Bernheimer *et al*¹ first identified severe dopamine depletion at symptom onset in Parkinson's disease but the average duration of disease in their patients with idiopathic parkinsonism was 9.3 (SD 5.7) years. Several postmortem studies¹⁸⁻²⁰ found nigral cell counts reduced by between 60% and 70% in Parkinson's disease but only considered patients with severe disease. Our findings are in keeping with the calculations of Fearnley and Lees²¹ who studied a group of patients with a more recent onset of symptoms (although only two patients, each Hoehn and Yahr grade 3, had disease onset of less than five years). They computed a short preclinical period (4.7 years), an age adjusted total nigral

cell count of 69% at presentation, and an exponential deterioration in cell count. Given the expected progression from unilateral to bilateral disease in a mean six years,⁶ putamen Ki values for the asymptomatic side would be expected to be much closer to those measured for the symptomatic side if the preclinical period were more prolonged.

Of course [¹⁸F]dopa uptake is not a measure of nigrostriatal cell count, but of presynaptic dopaminergic terminal function. It is possible that a depleted cell pool is able to compensate by upregulation of putamen dopa decarboxylase activity, maintaining both clinical normality and [¹⁸F]dopa uptake. Such a mechanism could explain the lack of an aging effect on normal striatal function reported in some PET studies^{22 23} and would make our conclusion about a short preclinical period for Parkinson's disease less secure.

We were able to show an inverse correlation between UPDRS scores and putamen [¹⁸F]dopa uptake but there was no correlation between performance on our quantitative tests and [¹⁸F]dopa uptake in the contralateral putamen (even when a subgroup taking selegiline was excluded). Decline in motor performance is probably related to fall in [¹⁸F]dopa uptake from the premorbid value in each person rather than any absolute value and the spread of measured [¹⁸F]dopa uptake in normal subjects is wide. There was no significant correlation between putamen [¹⁸F]dopa uptake and duration of symptoms. This is not surprising given the lack of correlation between duration of symptoms and clinical rating, and is compatible with the lack of correlation between duration of disease and severity of nigral cell loss previously reported.¹

To test discriminant analysis at the earliest stages of disease we applied it to this group of patients and normal subjects. The groups were again completely separated and discrimination was equally effective for patients with unilateral and bilateral symptomatology. We then applied the discriminant function obtained by Sawle *et al.*⁹ Four of the 27 patients were misclassified, emphasising that discriminant analysis is of greater value as a descriptive than a predictive test.

This study shows an apparent wide difference in side to side putamen [¹⁸F]dopa uptake in unilateral Parkinson's disease, with ipsilateral putamen function often normal. This suggests a relatively short preclinical period. Either true preclinical disease is difficult to detect with this technique (and subjects previously suspected as having preclinical disease may simply represent the lower end of a wide normal range) or the ipsilateral putamen is unaffected at this stage. Morphological and biochemical data from patients with recent onset unilateral disease are required to determine whether the preservation of function that

we find in the asymptomatic putamen is due to absence of disease, biochemical compensation, or insensitivity of the technique.

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