Nonlinear Progression of Parkinson Disease as Determined by Serial Positron Emission Tomographic Imaging of Striatal Fluorodopa F 18 Activity

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Background: The investigation of disease progression provides important information on the dynamics of cell death in Parkinson disease (PD).

Objective: To determine the progression of dopaminergic impairment in PD with the use of positron emission tomography (PET).

Design: Longitudinal prospective cohort study with a follow-up period of 64.5±22.6 months (mean±SD).

Setting: University hospital.

Patients: A consecutive sample of patients with PD (N=31; age at symptom onset, 53.6±11.3 years) with a wide range of symptom duration and severity at the time of study entry.

Interventions: Investigation by serial fluorodopa F 18 ([18F]fluorodopa) PET as a marker for striatal dopaminergic function.

Main Outcome Measures: Changes in caudate and putaminal [18F]fluorodopa influx constant (K,) values.

Results: In patients with PD, the decline rate of putaminal [18F]fluorodopa K, correlated inversely with disease duration before study inclusion (r=-0.46, P=.01) and positively with baseline K, values (r=0.44, P=.01), indicating a negative exponential loss of dopaminergic neurons. Annual disease progression rates ranged from 4.4% in the caudate nucleus to 6.3% in the putamen. A mean preclinical period of 5.6±3.2 years was calculated with symptom onset at a putaminal K, threshold of 69% from controls. Assuming nonlinear progression kinetics, the required sample size to prove neuroprotection with the use of [18F]fluorodopa PET was found to increase strongly with the preceding symptom duration of study subjects.

Conclusion: These data suggest that the neurodegenerative process in PD follows a negative exponential course and slows down with increasing symptom duration, contradicting the long-latency hypothesis of PD.

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METHODS

STUDY SUBJECTS AND CLINICAL MEASUREMENTS

We investigated a total of 31 patients with PD with a wide range of symptom duration and severity at the time of study inclusion (Table 1) and 16 healthy controls free of neurologic dis-
eases and medication with central nervous system action (10 men and 6 women; mean ± SD age, 54 ± 12 years). Parkinson disease was diagnosed according to the UK brain bank criteria. Disease severity was assessed by the Unified Parkinson’s Disease Rating Scale (UPDRS) and the Hoehn and Yahr scale. At follow-up, patients were subdivided into clinical PD subtypes according to the degree to which resting and action tremor items accounted for the total UPDRS stage 3 score: tremor dominant (tremor items accounted for >75% of the total UPDRS stage 3 score; n = 4), equivalence (25%-75%; n = 15), and akinetic-rigid type (<25%; n = 12). Patients with PD were treated with antiparkinsonian medication in various combinations. The study protocol was approved by the local ethics committee, and all study subjects gave their written informed consent to participate in the study.

PET DATA ACQUISITION

The PET scans were performed with 1 of 2 scanners (ECAT EXACT HR or ECAT EXACT; Siemens CTI, Knoxville, Tenn) according to previously described standard procedures. In each patient, one baseline scan and one follow-up scan were undertaken on the same PET camera with a mean ± SD interval of 64.5 ± 22.6 months (Table 1). All antiparkinsonian medication was withdrawn at least 12 hours before PET imaging.

PET DATA ANALYSIS

Data analysis was performed on workstations (SUN Sparc 2; Sun Microsystems, Santa Clara, Calif). For each subject, both PET scans were exactly coregistered with standard software (MPITool; Advanced Tomovision, Erlfstadt, Germany) and analyzed at the same time according to a standardized protocol by one rater (R.H.) blinded for the presence of baseline or follow-up PET data. In striatal regions of interest, [18F]fluorodopa influx constants (Kᵢ, min⁻¹) were calculated as described previously, according to the graphical Patlak and Blasberg analysis approach.  

CALCULATION OF DISEASE PROGRESSION AND PRECLINICAL PERIOD

Within each region of interest, the annual decline of [18F]fluorodopa Kᵢ over the entire study period was given by the difference of baseline minus follow-up PET data divided by the duration of the individual PET follow-up period. To consider nonlinear decline of [18F]fluorodopa Kᵢ over time, data analysis was based on logarithmic (log₁₀ Kᵢ) values. For each individual and each region of interest, the rate constant of the decline of [18F]fluorodopa uptake was determined as the slope of log₁₀ (Kᵢ) values vs time. Annual progression rates were then expressed as percentages of baseline Kᵢ values. The duration of the preclinical disease period was estimated from the mean putaminal progression rate constant by comparison of the average putaminal log₁₀ Kᵢ in patients with PD at study entry with the reference value of controls. The presymptomatic period was then estimated by subtraction of the average time from symptom onset from the duration of the preclinical period.

STATISTICS

All analyses were performed with the statistical software package SPSS 10.0 for Windows (SPSS Inc UK Ltd, Surrey, England). Unpaired Student t test and univariate analysis of variance with post hoc Bonferroni correction were used to compare metric between-group variables. Intraindividual differences in [18F]fluorodopa Kᵢ values of both PET scans were evaluated by paired Student t test. In addition, correlation analysis was performed with Spearman rank correlation. Statistical significance was accepted at the level of P < .05. Power analysis with a type I error rate of 0.05 and a power of 80% was performed to calculate the required sample sizes in serial [18F]fluorodopa PET studies to demonstrate a 30% neuroprotective effect of a putative agent. We assumed that patients with PD were included in a parallel group–designed trial either 1 or 10 years after symptom onset with a PET follow-up of either 1 or 5 years. We further assumed that a therapy under investigation would protect patients from 30% of this progression. Data variance was measured by means of the standard deviations of individual predicted changes after 1 and 5 years.

RESULTS

The mean [18F]fluorodopa Kᵢ values of patients with PD were significantly reduced vs those of healthy controls in all regions of interest except from baseline values in the ipsilateral caudate (Table 2). All mean striatal Kᵢ values decreased significantly during the scan-to-scan interval (Table 2). In line with a negative exponential decline of [18F]fluorodopa uptake over time, symptom duration before study inclusion correlated inversely with the annual decline of [18F]fluorodopa Kᵢ in the contralateral putamen (r = −0.46, P > .01). The annual loss of putaminal [18F]fluorodopa uptake significantly increased with the baseline [18F]fluorodopa Kᵢ in the ipsilateral (r = 0.52, P < .003) and contralateral (r = 0.44, P = .01) putamen (Figure 1).

Annual baseline progression rates, as calculated by logarithmic transformation, are given in Table 3. Patients with tremor-dominant PD had significantly lower progression rates in the ipsilateral caudate nucleus than those with the equivalence PD subtype (0.6% ± 1.9% vs 5.8% ± 3.7%; P = .02). However, putaminal progression rates were not significantly different between clinical PD subtypes (Table 3). The duration of the preclinical disease period was 5.6 ± 3.2 years, with symptom onset at a putamen Kᵢ threshold of 69% from controls (Figure 2).
**Table 2. Fluorodopa F 18 K Values and Percentage Reductions From the Control Subjects’ Mean in 31 Patients With PD**

<table>
<thead>
<tr>
<th>Time of Fluorodopa F 18 PET Scan*</th>
<th>Baseline</th>
<th>Follow-up†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kᵢ, min⁻¹‡</td>
<td>% Reduction vs Controls§</td>
</tr>
<tr>
<td>Caudate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>0.0115 (0.0021)</td>
<td>8.0 (16.9)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>0.0111 (0.0020)</td>
<td>10.6 (16.6)</td>
</tr>
<tr>
<td>Putamen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>0.0084 (0.0024)</td>
<td>33.4 (19.2)</td>
</tr>
<tr>
<td>Contralateral</td>
<td>0.0066 (0.0018)</td>
<td>47.7 (14.2)</td>
</tr>
</tbody>
</table>

Abbreviations: Kᵢ, influx constant; PD, Parkinson disease; PET, positron emission tomography.

*Values are mean (SD).
†All [¹⁸F]fluorodopa Kᵢ values obtained at the time of follow-up PET were significantly lower than baseline PET values (P < .001; paired t test).
‡All [¹⁸F]fluorodopa Kᵢ values in the Parkinson disease group were significantly lower (P < .001) than those of controls except for baseline ipsilateral caudate (P = .09) and baseline contralateral caudate (P = .02) (unpaired t test).
§[¹⁸F]fluorodopa Kᵢ values in healthy controls averaged for both hemispheres (n = 16): caudate, 0.0125 (0.0015), and putamen, 0.0126 (0.0013).

Figure 1. Significant correlation of the baseline fluorodopa F 18 influx constant (Kᵢ) values with the subsequent annual decline of radiotracer uptake in the contralateral putamen in 31 patients with Parkinson disease (r = 0.44, P = .01; Spearman rank correlation). PET indicates positron emission tomography.

In line with a negative exponential decline of putaminal dopaminergic capacity over time, power analysis showed that the required sample size to demonstrate a significant neuroprotective effect by means of [¹⁸F]fluorodopa PET strongly decreases with the length of the follow-up period and increases with the patients’ symptom duration at the time of study inclusion (Table 4).

This study demonstrates a striatal annual PD disease progression ranging from 4.0% to 6.6% of the baseline regional [¹⁸F]fluorodopa uptake. These data are comparable with those from the largest PET progression study in PD published so far, by Morrish et al, who found an annual baseline PD progression of 8.9% for the putamen and 3.5% for the caudate with the use of the same graphical Patlak and Blasberg plot approach. Moreover, we detected a significantly lower caudate disease progression in tremor-dominant PD, which is in agreement with the often-reported clinical impression of a slower deterioration of disease severity and widely preserved cognitive functions in these patients. It is also in line with a previous anatomic study demonstrating a lower nigral neuronal density in akinetic-rigid compared with tremor-dominant patients.

In our PET series, a relatively large patient sample with a wide range of symptom duration and severity was investigated during a follow-up period longer than that reported in many other imaging studies on PD progression. Moreover, we used the sensitive Kᵢ analysis approach for determination of disease progression. Presumably, these favorable conditions allowed us to describe significant determinants of PD progression that had not yet been observed in previous PET studies, namely a decrease of progression rates with symptom duration and an increase with the number of available intact dopamine nerve terminals within the putamen. Therefore, we propose a negative exponential loss of dopaminergic cells over time in line with previous anatomic, biochemical, and functional imaging studies using single-photon emission computed tomography with iodine 123–labeled β-carboxymethoxy-3-β-(4-iodophenyl) tropane (β-CIT). In this context, confounding pharmacologic effects of antiparkinsonian drugs on imaging progression data have to be considered. To avoid a systematic bias, we stopped medication at least 12 hours before each PET scan, although no significant short-term effects of levodopa and dopamine agonists on radiotracer binding have been demonstrated in previous [¹⁸F]fluorodopa PET and dopamine transporter single-photon emission computed tomographic studies. However, a long-term acceleration or slowing of disease progression by dopaminergic drugs cannot be ruled out. Therefore, this question will be the subject of a future study in our PD cohort.

Previous studies estimated the duration of the presymptomatic period in PD to vary from 4.7 to 50 years. Our data suggest that early PD disease progression is not linear but exponentially negative and that the preclinical disease period lasts approximately 6 years with a loss...
Annual Disease Progression From Baseline, %

<table>
<thead>
<tr>
<th>Caudate</th>
<th>Total PD Group</th>
<th>TR Type</th>
<th>EQ Type</th>
<th>Total PD Group</th>
<th>TR Type</th>
<th>EQ Type</th>
<th>Total PD Group</th>
<th>TR Type</th>
<th>EQ Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral</td>
<td>0.00047 (0.00045)</td>
<td>0.00086* (0.00042)</td>
<td>0.00086 (0.00041)</td>
<td>0.00048 (0.00045)</td>
<td>4.4 (4.2)</td>
<td>0.6* (1.9)</td>
<td>5.8 (3.7)</td>
<td>4.3 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>0.00051 (0.00044)</td>
<td>0.00064 (0.00037)</td>
<td>0.00046 (0.00054)</td>
<td>5.1 (4.1)</td>
<td>1.3 (1.1)</td>
<td>6.5 (3.8)</td>
<td>4.5 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Putamen</td>
<td>0.00046 (0.00034)</td>
<td>0.00054 (0.00024)</td>
<td>0.00043 (0.00045)</td>
<td>6.3 (3.8)</td>
<td>4.2 (1.4)</td>
<td>7.1 (3.0)</td>
<td>6.0 (5.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>0.00036 (0.00024)</td>
<td>0.00020 (0.00012)</td>
<td>0.00035 (0.00027)</td>
<td>6.0 (3.4)</td>
<td>4.6 (1.5)</td>
<td>6.5 (3.6)</td>
<td>6.0 (3.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AR, akinetic-rigid; EQ, equivalence; K, influx constant; PD, Parkinson disease; PET, positron emission tomography; TR, tremor.

*P = .02 vs ipsilateral caudate of EQ-type patients (analysis of variance with Bonferroni correction).

Figure 2. Logarithmic estimation of preclinical period duration in 31 study subjects with Parkinson disease. Boxes indicate the mean influx constant (K) values (K[t1], K[t2]) and mean symptom duration (t1, t2) at the time of both PET scans (t1 and t2). The beginning of the disease process is determined by the reduction of K from the level in healthy control subjects. Rate constant of mean putaminal K loss (c) = -0.0026; preclinical period duration before symptom manifestation (t0) = 5.6 years; putaminal log10 ([18F]-fluorodopa) at the time of symptom onset (K[k1]) = -2.06 (31% reduction from the controls’ level). PET indicates positron emission tomography.

Table 4. Required Sample Sizes for Detecting a 30% Protective Effect of a Putative Agent by Means of Fluorodopa F 18 PET Based on Nonlinear Putaminal Progression Rates (P<.05, 80% Power)*

<table>
<thead>
<tr>
<th>Scan-to-Scan Interval, y</th>
<th>1-y Symptom Duration</th>
<th>10-y Symptom Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76</td>
<td>141</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>116</td>
</tr>
</tbody>
</table>

Abbreviation: PET, positron emission tomography.

*Data are given for 1- and 5-year scan-to-scan intervals in patients with 1- and 10-year symptom durations before study inclusion.

The neurodegenerative process in PD seems to follow a negative exponential course and slows down with increasing symptom duration. The nonlinear kinetics of degeneration provide the important rationale for research efforts that are directed at modification of disease progression. Moreover, our results suggest that neuroprotection studies with PET imaging as a surrogate marker require lower sample sizes and are more promising to achieve significant results if they are initiated as early as possible in the course of the disease.

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Author Contributions: Study concept and design: Hilker, Schweitzer, Jacobs, Rudolf, Heiss. Acquisition of data: Hilker, Schweitzer, Herholz. Analysis and interpretation of data: Hilker, Schweitzer, Coburger, Ghaemi, Weisen...

REFERENCES