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 dopamine 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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PARKINSON DISEASE (PD) IS A slowly progressive movement disorder based on the degeneration of nigrostriatal dopaminergic neurons. Highly variable progression rates between individual patients with PD were demonstrated repeatedly in clinical and postmortem pathological studies, leading to uncertainty about the dynamics of cell death before symptom onset.1,2 The long-latency hypothesis of dopamine cell degeneration in PD implies nigral damage early in life and a subsequent decline of intact dopaminergic neurons with normal aging.3 In contrast, later onset of dopamine cell loss closer to the manifestation of the disease with an initially high and afterward decreasing rate of nigral cell death over time favors early neuroprotective therapy strategies, which aim to decelerate or stop disease progression.

To provide further insight into this controversy, we present data on the long-term progression of striatal dopaminergic impairment in PD by means of serial fluorodopa F 18 ([18F]fluorodopa) positron emission tomography (PET) as an objective marker for dopaminergic function in 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-
cases 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±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 coaligned with standard software (MPI-Tool; Advanced Tomovision, Erftstadt, 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 scans. 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. Intravital 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 .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).

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**Table 1. Clinical and Demographic Characteristics of 31 Study Subjects 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>Age, y</td>
<td>56.0 ± 11.7 (29-75)</td>
<td>59.0 ± 12.7 (36-75)</td>
</tr>
<tr>
<td>Sex. No. M/F</td>
<td>21/10</td>
<td>20/11</td>
</tr>
<tr>
<td>Age at symptom onset, y</td>
<td>53.6 ± 11.3 (28-69)</td>
<td>53.6 ± 11.3 (28-69)</td>
</tr>
<tr>
<td>Symptom duration before PET scans, y</td>
<td>2.9 ± 2.8 (0.5-9.0)</td>
<td>8.3 ± 2.5 (5.5-11.0)</td>
</tr>
<tr>
<td>UPDRS III motor score</td>
<td>14.4 ± 8.9 (5-37)</td>
<td>27.0 ± 9.5 (13-49)†</td>
</tr>
<tr>
<td>UPDRS total score</td>
<td>23.7 ± 13.6 (9-63)</td>
<td>46.9 ± 16.9 (24-89)†</td>
</tr>
<tr>
<td>Hoehn and Yahr stage, No. of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: PD, Parkinson disease; PET, positron emission tomography; UPDRS, Unified Parkinson Disease Rating Scale.

*Values are mean±SD (range) unless otherwise specified.
†Significant increase vs UPDRS scores obtained at baseline PET scan (P<.001, paired t test).

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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.5,14,15 It is also in line with a previous anatomic study demonstrating a lower nigral neuronal density in akinetic-rigid compared with tremor-dominant patients.16

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,1 biochemical,17 and functional imaging studies using single-photon emission computed tomography with iodine 123–labeled β-carboxymethoxy-3-β-(4-iodophenyl) tropane (B-CIT).18 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.19,20 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.1,21,22 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.

### Table 2. Fluorodopa F 18 Ki 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).
of nearly 30% of putaminal $[^{18}F]$fluorodopa uptake at the time of symptom onset, which is in good agreement with previously published imaging and postmortem data.\textsuperscript{1,13} Therefore, our data contradict the long-latency hypothesis of PD proposed by Calne and Langston,\textsuperscript{3} which assumes damage to nigral dopaminergic neurons early in life and symptom manifestation after a preclinical period lasting longer than 10 years. In contrast, our PET data showing a constant exponential decline of $[^{18}F]$fluorodopa uptake suggest an active devastating disease process different from age-related dopaminergic degeneration, which steadily afflicts the present dopaminergic capacity and leads to a relatively short preclinical disease period.

Finally, our findings suggest that agents with presumed neuroprotective properties should be capable of exerting their maximum clinical efficacy in early disease stages. Recent single-photon emission computed tomographic and PET imaging studies proved a significantly slower disease progression in patients with PD treated with the new nonergot dopamine agonists pramipexole and ropinirole hydrochloride, compared with levodopa monotherapy.\textsuperscript{23-25} With respect to the future planning and design of such studies, the power analysis of our data clearly shows that clinical protection trials using $[^{18}F]$fluorodopa PET as a progression 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.

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 should be performed preferably at an early stage of PD.

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REFERENCES