Striatal Dopamine Transporter Binding Assessed by \([I-123]\)IPT and Single Photon Emission Computed Tomography in Patients With Early Parkinson’s Disease

Implications for a Preclinical Diagnosis

Johannes Schwarz, MD; Rainer Linke, MD; Martina Kerner, MD; P. David Mozley, PhD; Claudia Trenkwalder, MD; Thomas Gasser, MD; Klaus Tatsch, MD

**Background:** Specific binding to dopamine transporters may serve as a tool to detect early loss of nigrostriatal dopaminergic neurons in patients with Parkinson’s disease.

**Objective:** To determine striatal dopamine transporter binding using the cocaine analogue \([I-123]\)IPT and single photon emission computed tomography.

**Patients and Methods:** We studied 9 control subjects (mean age, 58 years; range, 41-69 years) and 28 patients with early Parkinson’s disease (Hoehn and Yahr stages I \(n = 14\) and II \(n = 14\) [symptom duration, <5 years]; mean age, 55.5 years; range, 36-71 years). Single photon emission computed tomography was performed 90 minutes after injection of 120 to 150 MBq of radioactive \([I-123]\)IPT.

**Results:** Specific striatal \([I-123]\)IPT binding (mean ± SD) was significantly reduced in patients with early Parkinson’s disease (ipsilateral striatum: 4.09 ± 0.97; range, 2.46-6.40; contralateral striatum: 3.32 ± 0.76; range, 1.80-5.13) compared with controls (left striatum: 7.28 ± 0.94; right striatum: 7.41 ± 1.28; range, 5.78-8.81; right striatum: 2.96 ± 0.73) compared with those with Hoehn and Yahr stage I (ipsilateral striatum: 4.72 ± 0.75; contralateral striatum: 3.69 ± 0.61 \(P < .001\)). The ipsilateral striatum of patients with Hoehn and Yahr stage I showed a significant mean ± SD reduction of IPT binding (ipsilateral striatum: 4.72 ± 0.75) compared with either right or left striatum of controls \(P < .001\). Only in 1 patient was IPT binding to the ipsilateral striatum (ratio, 6.40) higher than the lowest value observed in the striatum of a control subject (ratio, 5.58).

**Conclusions:** Use of \([I-123]\)IPT and single photon emission computed tomography demonstrates a reduction of dopamine transporter binding in patients with early Parkinson’s disease. Significantly reduced IPT binding already observed in the ipsilateral striatum of patients with Hoehn and Yahr stage I demonstrates the potential of this method to detect preclinical disease.

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PATIENTS, MATERIALS, AND METHODS

PATIENTS

The study protocol was approved by the local ethics committee and government authorities. Informed consent was obtained from every patient and documented in writing. Nine controls and 28 patients with PD were included in this study.

All patients fulfilled the clinical criteria steps 1 and 2 established by the Parkinson’s Disease Society Brain Bank,8 indicating that all patients had bradykinesia and at least 1 of the other cardinal features of PD—resting tremor, rigidity, or impairment of postural reflexes. None of the patients showed any of the exclusion criteria as defined by the Parkinson’s Disease Society Brain Bank.8 Considering the prospective supportive criteria, all patients had a progressive disorder, resting tremor, unilateral onset, or persisting asymmetry. To be included, patients had to be rated as Hoehn and Yahr stage 1 or II, and the duration from onset of parkinsonian symptoms had to be less than 5 years. Disease duration (mean ± SD) was 20 ± 11 months (range, 12-48 months) in patients with Hoehn and Yahr stage 1 and 36 ± 20 months (range, 6-60 months) in patients with stage II.

Fifteen patients had not received dopaminergic drugs before the study. All of these patients subsequently underwent testing with either apomorphine or levodopa and had to show an improvement on the Unified Parkinson’s Disease Rating Scale (UPDRS), part III, of at least 20%. Apomorphine (2-3 mg subcutaneously) was administered after pretreatment with domperidone (20 mg 3 times a day for 2 days); UPDRS rating was performed before and 30 minutes after injection of apomorphine. Levodopa, 200 to 250 mg, plus peripheral dopa-decarboxylase inhibitor were administered without pretreatment; UPDRS rating was performed before and 45 to 60 minutes after administration.

For control, we used data from 9 age-matched healthy subjects older than 40 years (mean age, 58 years; range, 41-69 years) without any known neuropsychiatric disorder. The control data were partly reported previously.9 None of the controls had a lifetime history of a disease that could have affected the distribution or elimination of the tracer.

[I-123]IPT SPECT

An analogue of cocaine, IPT has a high binding affinity for the dopamine transporter of 0.2 nmoL/L.10 The IPT precursor was radiolabeled as described in detail previously.10,11 The [I-123] sodium iodide was purchased from a commercial vendor (Cygne BV, Eindhoven, the Netherlands). The radionuclide purity was greater than 99.9%, and the specific activity was calculated as $2 \times 10^{12}$ Bq/mol. The final product was analyzed for purity before injection. Patients were injected with 120 to 150 MBq of radioactive [I-123]IPT in an antecubital vein. For acquisition, we used a triple-headed gamma camera equipped with high-resolution fan beam collimators (Prism 3000; Picker International, Cleveland, Ohio). The acquisition variables consisted of a rotational radius of 13 cm or less, a 20% energy window centered on 159 keV, 120 projection angles over 360°, and a 128 × 128 matrix with a pixel width of 2.11 mm in the projection domain. Data collection started 90 minutes after injection and lasted for approximately 30 minutes (45 seconds per projection). The method of reconstruction and semiquantitative assessment has been described in detail previously.12 Mean specific activity in basal ganglia regions was calculated with the region of interest (ROI) technique by subtracting the mean counts per pixel in the background (BG) from the mean counts per pixel in the basal ganglia and dividing the result by the mean counts per pixel in the BG (ROI – BG)/BG. Templates were used for defining the striatum, caudate, and putamen ROIs. The size and shape of the templates (striatum, 91 pixels; caudate, 32 pixels; putamen, 38 pixels) were established and optimized using data from the control group. The nonspecific BG activity was estimated by drawing a large ROI (range, 1600-1800 pixels) around the entire supratentorial brain on the slices containing the basal ganglia, which excluded the basal ganglia and thalamus. In each patient data were evaluated in the 6 consecutive transverse slices (slice thickness, 2.27 mm) showing the highest tracer accumulation in the basal ganglia. Results are given as arithmetic mean of the 6 slices. Data are given as mean ± SD.

For statistical analyses, the Wilcoxon signed rank test and simple regression analysis were used.

RESULTS

In controls, we measured specific [I-123]IPT uptake ratios of 7.28 ± 0.94 in the left striatum and 7.41 ± 1.28 in the right striatum. Ratios ranged from 5.78 to 8.81 in the right striatum and from 5.58 to 9.44 in the left striatum. There were only minor differences between the binding ratios of the right and left striatum. Left-to-right differences ranged from 1.2% to 7.9% (4.7% ± 2.3%).

Patients with early PD showed markedly reduced binding in the striatum bilaterally (ipsilateral striatum: 4.09 ± 0.97; range, 2.46-6.40; contralateral striatum: 3.32 ± 0.76; range, 1.80-5.13), representing a 44% reduction in the ipsilateral striatum and a 55% reduction in the contralateral striatum compared with the mean total striatal binding of controls. Specific striatal tracer uptake was significantly lower in patients with Hoehn and Yahr stage II (ipsilateral striatum: 3.47 ± 0.75; contralateral striatum: 2.96 ± 0.73) compared with those with Hoehn and Yahr stage I (ipsilateral striatum: 4.72 ± 0.75; contralateral striatum: 3.69 ± 0.61) (P < .001). In both patient groups there was a significant difference between tracer uptake in the ipsilateral and contralateral stria-
tum (Hoehn and Yahr stage I: P < .001; Hoehn and Yahr stage II: P < .005).

Comparing data from the ipsilateral striatum in patients with Hoehn and Yahr stage I only with the values obtained in controls, we detected a significant difference between the ipsilateral striatum in patients with unilateral disease (ipsilateral striatum: 4.72 ± 0.75; range, 3.66-6.40) compared with the right or left striatum of controls (P < .001). Only in 1 patient was IPT binding to the ipsilateral striatum (ratio, 6.40) higher than the lowest value observed in the striatum of a control (ratio, 5.58).

We studied 15 untreated and 13 treated patients. Although the ratio in the Hoehn and Yahr stage I group was 9 to 5 in favor of the untreated patients, IPT uptake ratios in total striatum did not show a significant difference (untreated patients: 3.82 ± 0.93; treated patients: 3.59 ± 0.68; P = .4).

Individual binding data for patients and controls are given in the Figure. We did not detect a significant correlation of specific striatal [I-123]IPT uptake and age by simple regression analysis in patients and controls.

We used dopamine transporter imaging with [I-123]IPT and SPECT to assess dopamine transporter function in patients with early PD and controls. Our data indicate that dopamine transporter imaging can differentiate patients with PD from controls with minimal overlap of measurements for specific striatal tracer uptake. In addition, the dopamine transporter binding was already significantly reduced in the ipsilateral striatum of patients with unilateral disease. Only 1 patient with PD showed a specific [I-123]IPT binding ratio in the ipsilateral striatum that exceeded the respective value of the control with the lowest striatal tracer uptake.

At present, imaging of dopaminergic nerve terminals in the striatum represents the most sensitive tool for detecting a lesion of the substantia nigra. Using fluorodopa F 18 and PET, it is possible to detect a reduction of presynaptic function in patients at risk of developing PD. These patients had reduced striatal fluorodopa F 18 uptake but were neurologically asymptomatic. It is not known whether dopamine transporter imaging with SPECT or PET using various cocaine analogues is as sensitive and might enable diagnosis of such a preclinical lesion. One might speculate that the expression of the dopamine transporter is down-regulated, whereas dopamine metabolism as measured by fluorodopa F 18 uptake might be up-regulated in the remaining dopaminergic neurons to compensate for the dopamine deficit in the striatum. Experimental evidence supports both of these speculations. Therefore, imaging of the dopamine transporter should provide a sensitive method to detect reduced dopaminergic innervation in the striatum.

In patients with early PD and unilateral disease, Hoehn and Yahr stage I, the ipsilateral striatum compared with the affected side of the body might serve as a model of a preclinical striatal dopaminergic deficit. Using a related cocaine analogue and SPECT, Marek et al measured in those patients a reduction of specific dopamine transporter binding in the ipsilateral striatum compared with age-matched controls. Based on this observation, the authors concluded that imaging of dopamine transporter binding might serve as a tool to identify individuals with developing dopaminergic pathological conditions before the onset of motor symptoms. Our data agree with those findings. In the study by Marek et al, all 8 patients with unilateral disease had specific binding in the ipsilateral striatum lower than the striatal binding observed in the respective individual age-matched control used for comparison. A technique that would allow detection of preclinical disease should separate such persons at risk from healthy individuals with minimal overlap. Although Marek et al never detected ipsilateral striatal binding exceeding the respective binding in the left or right striatum of the individual age-matched control, they did not comment on the total overlap between patient and control data. Four of 8 patients had specific ipsilateral binding that was in the range of ratios obtained in controls.

Several reasons might account for the more accentuated overlap in their study (4 of 8 patients) compared with ours (1 of 14 patients). First, the number of patients they studied was low. In particular, a single control exhibited relatively low binding ratios. Second, differences in tracer kinetics might result in a different discrimination capacity. Because age of the study population and duration of disease were similar in both studies, these factors less likely serve as explanation.

Guttman and coworkers, using 2 different cocaine analogues and PET, did not detect a significant difference between controls and ipsilateral striatal dopamine transporter binding in patients with early PD. Only when calculating specific uptake in subregions of the putamen did these investigators detect a
**CONCLUSIONS**

Our findings indicate that [I-123]IPT and SPECT are sensitive methods to identify patients with early PD. Significantly reduced IPT binding already observed in the ipsilateral striatum of patients with unilateral disease demonstrates the potential of this method to identify preclinical loss of dopamine transporter function.

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Corresponding author: Johannes Schwarz, MD, Division of Biology 156-29, California Institute of Technology, 1201 E California Blvd, Pasadena, CA 91125 (e-mail: johannes@cco.caltech.edu).

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