IV. 8. Brain Dopamine Metabolism in Young Onset Parkinson's Disease Studied by Positron Emission Tomography


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Introduction

Onset of idiopathic Parkinson's disease is unusual in patients below the age of 40. Quinn et al. studied 60 cases of parkinsonism with onset under the age of 40 and they proposed that cases of idiopathic Parkinson's disease beginning between 21-40 years should be called "young onset Parkinson's disease", which differentiated from cases of parkinsonism beginning before age 21 years defined as juvenile parkinsonism because of clinical features with familial cases1). There were several studies indicating some clinical features observed in young onset Parkinson's disease such as more prominent dystonia, earlier manifestation of levodopa-related dyskinesia and higher frequency of levodopa-dose-related motor fluctuations than seen in idiopathic Parkinson's disease of later onset2).

Positron emission tomographic (PET) scanning using 6-[18F]fluorodopa (FDOPA) is an efficient method of studying the nigrostriatal dopaminergic system in living subjects3). Intravenously injected FDOPA crosses the blood-brain barrier, is decarboxylated to fluorodopamine by L-aromatic amino acid decarboxylase, and remain in the nerve terminals during the scanning. Recent PET studies revealed striatal uptake of FDOPA was reduced in parkinsonism caused by loss of nigrostriatal neurons4).

In the present study, we measured dopamine metabolism in patients with young onset Parkinson's disease using PET with FDOPA and analyzed the correlations between dopamine metabolism in the caudate nucleus and the putamen and clinical symptoms of the patients.

Subjects and methods

SUBJECTS

We studied 10 patients, 4 men and 6 women, who were diagnosed young onset Parkinson's disease by neurologists before age 40 years (Table 1). The age of onset of their initial Parkinson's symptoms was ranged from 24 to 39 years (mean±SD, 30.6±6.0). The mean duration of the disease was 7.5 years. All patients had effective responses to levodopa
therapy. Magnetic resonance imaging (MRI) and/or computed tomography (CT) scans of brain, obtained in all patients, were normal. No dementia was detected on formal neuropsychological testing. Patients were rated on overall disease severity rated from I to IV according to Hoehn and Yahr. The degree of main symptoms, bradykinesia, limb rigidity and tremor, was scored from 0 to 3 (0, absent; 1, mild; 2, moderate; 3, severe). Clinical assessment did not reveal any pyramidal, cerebellar, or oculomotor disturbances. The drug treatment was stopped at least 24 h before the PET study.

The control group consisted of 5 normal male volunteers with an age range of 27-40 years (mean±SD, 32.4±4.9), without a history of recent medical illness, neurological diseases, developmental disorder, or substance abuse. MRI and/or CT scans of the brain, obtained in the control group, were normal. Control subjects underwent a complete neurological examination and neuropsychological evaluation before PET scanning. The project was approved by the Research Ethics Committee of the Tohoku University School of Medicine. All subjects gave their written informed consent.

**Positron Emission Tomography**

$[{^{18}}\text{F}]$FDOPA scans were performed on a scanner, PT-931 (CT1 Inc., USA), at the Cyclotron and Radioisotope Center, Tohoku University, Sendai, Japan. Patients and subjects were positioned in the scanner, with the orbitomeatal (OM) line parallel to the detector rings according to the brain slices by MRI. A cross of light was projected onto marks on the subjects' heads from three dimensions and the heads were positioned at 40 mm above and parallel to the OM line. All studies were conducted in a quiet, semi-darkened room with minimal background noise. The subjects' eyes were open and their ears were unplugged.

A 15-min transmission scan was collected using a $^{68}\text{Ge}$-$^{68}\text{Ga}$ external ring source. $[{^{18}}\text{F}]$FDOPA was synthesized by the method described by Adam et al. with a radiochemical purity of more than 99%. After an intravenous bolus injection of FDOPA (2.5-8.3mCi or 14.9-49.5 nmol) into the subjects, positron tomography was carried out using PT-931 with an 8 mm axial and transaxial resolution. A series of 5 min emission scans was performed over 60 min and emission data were simultaneously collected from seven contiguous axial sections, each about 6 mm in thickness from OM+66 to OM+22 mm.

**Data analysis**

After data collection, the latter six contiguous images of the same brain slice scanned between 30 and 60 min after administration of FDOPA were added and composite images were obtained in order to improve the contrast between dopaminergic and non-dopaminergic brain regions to aid the definition of anatomical regions of interest (ROIs). In each case, two different pairs of images, the PET images and the images obtained by MR, were registered and matched with each other using image scaling to bring the disparate pairs of image data
into congruence at the same brain slices. To ascertain the anatomical position of each brain structure, the positions of ROIs were manually defined using the overlapped images, i.e., PET images and MR images of the same brain slices according to the previous study. Influx constants (Ki values min⁻¹) were calculated for the caudate nucleus and the putamen separately using a multiple graphical analysis method with cerebellar tissue input function. The Ki value is a rate constant that reflects uptake and decarboxylation of FDOPA into [¹⁸F]dopamine and its metabolites by the nigrostriatal nerve terminals. The average values of influx constants within each structure are presented as means±SD. The Mann-Whitney U-test was used to compare the Ki values in each structure of the brain between patients and controls with p<0.01 considered to be statistically significant.

Results

Representative appearances of brain images at the level of the caudate nucleus and the putamen, obtained by MR or CT scan, FDOPA uptake, FDOPA influx rate and FDOPA distribution volume from a normal control and from the patients with young onset Parkinson's disease, are shown in Figure 1. FDOPA and its labeled metabolites were highly concentrated in the caudate nucleus and the putamen of both hemispheres of the normal control. On the contrary, in the patients with young onset Parkinson's disease, FDOPA uptake was markedly reduced both in the caudate nucleus and the putamen. The FDOPA uptake rate constant in the patients was significantly reduced (p<0.01) compared with normal controls as shown in Table 2.

There were not significant correlation between FDOPA influx rate and duration of illness (Figure 2A). However, FDOPA influx rate was well correlated with clinical stages according to Hoehn and Yahr (Figure 2B). The correlations between FDOPA influx rate in the caudate nucleus and the putamen and the degrees of the main clinical symptoms were analyzed. The FDOPA influx rate was more prominently correlated with the degree of rigidity than the degrees of bradykinesia and tremor (Figure 3).

Discussion

We selected apparent cases who had suffered from idiopathic Parkinson's disease beginning between age 21-40 years. The present study indicated that dopamine uptake was significantly reduced in both the caudate nucleus and the putamen of the patients with young onset Parkinson's disease as well as those seen in idiopathic Parkinson's disease of later onset from the previous study. Moreover, dopamine metabolism was more prominently affected in the putamen than in the caudate nucleus.

The relationships between dopamine uptake and degree of clinical stages of the patients were quite variable. In some cases with young onset Parkinson's disease, dopamine uptake was markedly reduced in both caudate nucleus and the putamen, although their clinical
symptoms were mild and scored in 1 stage degree according to Hoehn and Yahr. In such cases, we speculate that dopamine receptor function might be highly sensitive and compensatory up-regulation of dopamine receptor binding sites might be modified levodopa responses and their clinical pictures of main symptoms.

Based on the present study, in the patients with young onset Parkinson's disease, FDOPA uptake rate constant was significantly reduced compared with normal controls. However, FDOPA influx rate in the presynaptic sites might not be always well correlated with individual clinical measures. We speculate that compensatory up-regulation in the postsynaptic receptor sites may be modified the degree of main clinical features and disease severity of young onset Parkinson's disease9).

References

1) Quinn N., Critchley P. and Marsden D., Mov. Disord. 2 (1987) 73.

Table 1. Summary of patients with young onset Parkinson's disease.

<table>
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<tr>
<th>Patient No.</th>
<th>Age at Scan (yr)</th>
<th>Sex</th>
<th>Age of Onset (yr)</th>
<th>Duration (years)</th>
<th>Stage (H&amp;Y)</th>
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<th>T</th>
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H & Y, Hoehn and Yahr; BK, Bradykinesia; T, Tremor; R, Rigidity.
Clinical scores: 0, absent; 1, mild; 2, moderate; 3, severe.
Medications are signified numerically: 1, levodopa; 2, D2 agonist (bromocriptine); 3, anticholinergic drugs (trihexyphenidyl).
Table 2. $[^{18}\text{F}]$ Dopa influx rate measured by positron emission tomography in normal control and patients with young onset Parkinson's disease.

<table>
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<th>Caudate Nucleus (K_i)</th>
<th>Putamen (K_i)</th>
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<tr>
<td>Normal control (N=5)</td>
<td>0.0175 ± 0.0039</td>
<td>0.0164 ± 0.0044</td>
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<td>Young onset PD (N=10)</td>
<td>0.0132 ± 0.0031**</td>
<td>0.0093 ± 0.0024***</td>
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Values are given in mean ± SD. K_i=$[^{18}\text{F}]$dopa influx constant (min$^{-1}$).

N: number of subjects. **: p<0.01 significant compared with control using the Mann-Whitney U-test.

Fig. 1. Representative appearances of brain images at the level of the striatum obtained by magnetic resonance or computed tomographic scan, FDOPA uptake, FDOPA influx rate and distribution volume from a normal control (A) and from the patients with young onset Parkinson's disease (B: case 3, C: case 7, and D: case 9).
Fig. 2. Correlations between FDOPA influx rates in the caudate nucleus (●) and the putamen (□) and the duration of disease (A) and clinical stages (B) formulated by Hoehn and Yahr.
Fig. 3. Correlations between FDOPA influx rates in the caudate nucleus (●) and the putamen (□) and individual clinical symptoms (A: Brakikinesia; B: Tremor; C: Rigidity) of 10 patients with young onset Parkinson's disease.