Young-Onset Parkinson Disease With and Without Parkin Gene Mutations

A Fluorodopa F 18 Positron Emission Tomography Study

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Background: Mutations of the parkin gene are frequently encountered in patients with young-onset Parkinson disease (YOPD), but the effects of this mutation on the nigrostriatal dopaminergic degeneration are not well established.

Objective: To analyze, using positron emission tomography and fluorodopa F 18, the severity and profile of striatal dopaminergic metabolism in YOPD patients with and without parkin gene mutations.

Methods: We performed positron emission tomography with fluorodopa F 18 in 19 YOPD patients with parkin gene mutations (parkin patients), 6 YOPD patients without parkin gene mutations (nonparkin patients), and 9 healthy controls. Putamen and caudate nucleus fluorodopa F 18 uptake was assessed using regions of interest analysis.

Results: In parkin patients, the striatal fluorodopa F 18 uptake reduction was 36.3%, 51.3%, and 66.7%, respectively, for the caudate nucleus, anterior putamen, and posterior putamen compared with controls. In nonparkin patients, this reduction was 23.0%, 43.6%, and 73.0%, respectively. This reduction was asymmetrical according to the most affected hemibody for the anterior and posterior putamen in parkin patients and for the posterior putamen in nonparkin patients. A rostrocaudal gradient was observed with a severe decrease in fluorodopa F 18 uptake in the putamen and relative sparing of the caudate nucleus. There was no significant difference of striatal fluorodopa F 18 uptake between our 2 YOPD populations. In parkin patients, no significant correlation was found among fluorodopa F 18 uptake, motor disability, and the type of mutations. In nonparkin patients, there was a significant correlation between fluorodopa F 18 uptake and clinical severity.

Conclusions: The pattern of fluorodopa F 18 uptake in the striatum of YOPD patients is similar to that of patients with idiopathic Parkinson disease and does not depend on the presence or absence of mutations of the parkin gene.

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The molecular basis of several inherited forms of Parkinsonism with autosomal dominant transmission has been elucidated. However, autosomal dominant Parkinson disease (PD) remains rare. Recessive inheritance is more common in patients with young-onset PD (YOPD). Two new loci (PARK 6 and PARK 7) are also responsible for YOPD, but mutations in the parkin gene (PARK 2) located on chromosome 6q are the most frequent. Parkin functions as an E3 ubiquitin protein ligase, and its loss of function due to mutations may lead to accumulation of several of its protein substrates in nigral dopaminergic neurons with subsequent cell death. The classic clinical hallmarks of PD with parkin gene mutations combine diurnal fluctuations, sleep benefit, foot dystonia, and levodopa responsiveness with early-onset dyskinesias, hyperreflexia, and young age at onset. However, the phenotypic spectrum is broad and may be indistinguishable from idiopathic PD. Various mutations in the parkin gene may cause YOPD. Autopsy cases of PD patients with parkin gene mutations show a nerve cell loss in the substantia nigra pars compacta and locus ceruleus but the absence of Lewy bodies. Positron emission tomography (PET) studies performed in carriers of parkin mutations have shown a marked reduction of striatal uptake, which predominantly in the posterior putamen, whereas the caudate nucleus was relatively spared, a pattern similar to the one in idiopathic PD. In these studies, the relation between fluorodopa F 18 uptake and the clinical characteristics of these patients was not precisely evaluated and the number of patients was small. There

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are also a few PET studies performed in patients with YOPD but without genetically proven parkin gene mutations. The aims of this PET study were to analyze the pattern of fluorodopa F 18 uptake reduction in the striatum of a large population of YOPD patients and to correlate this pattern with the clinical characteristics of the patients and to determine if YOPD patients who carry parkin gene mutations (parkin patients) share specific abnormalities of fluorodopa F 18 uptake compared with YOPD patients without parkin mutation (nonparkin patients).

**Table 1. Clinical Characteristics of the Parkinsonian Patients**

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Onset, y</th>
<th>First Symptoms</th>
<th>Hyperreflexia</th>
<th>Family History</th>
<th>Parkin Mutations</th>
<th>Dose, mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATIENTS WITH PARKIN MUTATIONS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/5/59</td>
<td>37</td>
<td>T, B, D</td>
<td>+</td>
<td>+</td>
<td>del.ex5/c.255delA</td>
<td>900</td>
</tr>
<tr>
<td>2/5/51</td>
<td>30</td>
<td>T</td>
<td>–</td>
<td>+</td>
<td>c202-203delAG/c202-203delAG</td>
<td>1400</td>
</tr>
<tr>
<td>3/M/53</td>
<td>42</td>
<td>B, D, O</td>
<td>–</td>
<td>–</td>
<td>Gly32Bglu</td>
<td>2100</td>
</tr>
<tr>
<td>4/F/46</td>
<td>27</td>
<td>B, D, M</td>
<td>–</td>
<td>+</td>
<td>Cys441Arg/del.ex5</td>
<td>700</td>
</tr>
<tr>
<td>5/M/41</td>
<td>33</td>
<td>B, D</td>
<td>+</td>
<td>+</td>
<td>del.ex6-9/del.ex9-9</td>
<td>500</td>
</tr>
<tr>
<td>6/F/44</td>
<td>32</td>
<td>T, D</td>
<td>+</td>
<td>–</td>
<td>Cys289Gly/Cys289Gly</td>
<td>700</td>
</tr>
<tr>
<td>7/M/29</td>
<td>17</td>
<td>T</td>
<td>–</td>
<td>–</td>
<td>Arg277Trp/del.ex3</td>
<td>300</td>
</tr>
<tr>
<td>8/M/17</td>
<td>12</td>
<td>B, D</td>
<td>–</td>
<td>+</td>
<td>del.ex3-4/c255delA</td>
<td>200</td>
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<tr>
<td>9/F/20</td>
<td>14</td>
<td>B</td>
<td>+</td>
<td>–</td>
<td>del.ex3/del.ex3</td>
<td>250</td>
</tr>
<tr>
<td>10/F/40</td>
<td>21</td>
<td>T, M</td>
<td>–</td>
<td>+</td>
<td>del.ex3/del.ex3</td>
<td>300</td>
</tr>
<tr>
<td>11/F/43</td>
<td>35</td>
<td>B, M</td>
<td>–</td>
<td>+</td>
<td>del.ex3/del.ex3</td>
<td>300</td>
</tr>
<tr>
<td>12/F/51</td>
<td>30</td>
<td>T</td>
<td>–</td>
<td>–</td>
<td>dupl.ex2-4</td>
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<tr>
<td>13/M/66</td>
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<td>T</td>
<td>–</td>
<td>+</td>
<td>c255delA/C255delA</td>
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<tr>
<td>14/M/33</td>
<td>18</td>
<td>T, D</td>
<td>+</td>
<td>+</td>
<td>c255delA/c255delA</td>
<td>1200</td>
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<tr>
<td>15/M/46</td>
<td>27</td>
<td>B</td>
<td>–</td>
<td>+</td>
<td>c321-322insGT/c321-322insGT</td>
<td>600</td>
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<tr>
<td>16/F/50</td>
<td>29</td>
<td>T</td>
<td>–</td>
<td>+</td>
<td>del.ex4/c.102A − T</td>
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<tr>
<td>17/F/47</td>
<td>35</td>
<td>T, B</td>
<td>–</td>
<td>+</td>
<td>del.ex4/c.102A − T</td>
<td>750</td>
</tr>
<tr>
<td>18/F/46</td>
<td>40</td>
<td>T, B, D</td>
<td>+</td>
<td>+</td>
<td>del.ex2/del.ex3</td>
<td>100</td>
</tr>
<tr>
<td>19/M/49</td>
<td>13</td>
<td>T, B</td>
<td>–</td>
<td>+</td>
<td>del.ex2/del.ex3</td>
<td>1300</td>
</tr>
</tbody>
</table>

| PATIENTS WITHOUT PARKIN MUTATIONS |          |                |              |               |                 |             |
| 1/M/36                  | 32       | T              | –            | –             | –               | 575         |
| 2/F/42                  | 28       | T, B           | –            | +             | –               | 800         |
| 3/F/64                  | 32       | B              | –            | +             | –               | 1050        |
| 4/F/31                  | 24       | B              | –            | –             | –               | 600         |
| 5/M/39                  | 29       | T              | –            | –             | –               | 0           |
| 6/M/38                  | 27       | B              | –            | +             | –               | 800         |

Abbreviations: B, bradykinesia; D, dystonia; M, myoclonus; O, ophthalmoplegia; T, tremor; −, negative; +, positive.

*The mean ± SD age was 44 ± 12 years for patients with parkin mutations and 42 ± 12 years for patients without parkin mutations. The mean ± SD age at disease onset was 25 ± 9 years for patients with parkin mutations and 29 ± 3 years for patients without parkin mutations. The mean ± SD dose levodopa equivalent was 675 ± 520 mg/d for patients with parkin mutations and 765 ± 192 mg/d for patients without parkin mutations.

**METHODS**

PATIENTS

Twenty-five patients with YOPD were recruited according to the following criteria: (1) the presence of at least 2 or 3 cardinal signs of parkinsonism (tremor, akinesia, rigidity); (2) normal brain magnetic resonance imaging (MRI) or computed tomographic (CT) scan; (3) positive and sustained response to levodopa; (4) age younger than 45 years at disease onset; (5) no other neurologic symptoms; (6) no history of neuroleptic treatment or encephalitis; and (7) no deep brain stimulation, thalamotomy, or pallidotomy. Nineteen parkin patients (11 women and 8 men) were enrolled (Table 1). The first manifestations of the disease were unilateral in 13 and bilateral in 6 patients and consisted of the combined association of tremor and bradykinesia. Focal dystonia was present at onset in 8 (42%) of the patients. At least another sibling was affected in 12 families and a grandmother in another. A family history of tremor was noted in 4 (21%) of the patients. Myoclonus and hyperreflexia were observed in 3 patients each and supranuclear ophthalmoplegia in 1 patient. Brain MRI or CT scan findings were normal. The levodopa responsiveness was confirmed by the 50% reduction of the Unified Parkinson’s Disease Rating Scale (UPDRS) III score while not taking the drug, 30.9 ± 21.9; mean ± SD UPDRS III score while taking the drug, 15.7 ± 13.5; P = .04.31

Six nonparkin patients (3 men and 3 women) participated in this study (Table 1). The first symptoms consisted of unilateral tremor or bradykinesia, with the notable absence of dystonia or myoclonus. A family history of parkinsonism was present in 67% of the cases (3 second-degree relatives and 1 sibling). The good levodopa responsiveness was demonstrated by a short-term levodopa challenge (mean ± SD UPDRS motor score while not taking the drug, 31.8 ± 16.3; mean ± SD UPDRS motor score while taking the drug, 12.0 ± 9.6; P = .03). There was no significant difference in age, age at onset, and motor scores between parkin and nonparkin patients. However, the mean ± SD disease duration was slightly longer in parkin patients (17.0 ± 8.1 years) compared with nonparkin patients (12.7 ± 10.3 years; P = .04). In both patient groups, we calculated a levodopa equivalent dose using correspondences published previously (100 mg of levodopa = 10 mg of bromocriptine = 4 mg of ropinirole hydrochloride = 1 mg of pergolide mesylate = 1 mg of lisuride).32

Nine healthy controls were also enrolled in the PET study (mean ± SD age, 47.5 ± 8.4 years; 2 women and 7 men). After informed consent was obtained from PD patients, genomic DNA
was extracted from peripheral blood samples for screening for mutations in the parkin gene. A semiquantitative polymerase chain reaction assay was used for the detection of rearrangements of parkin exons, and all coding exons and intron-exon boundaries were directly sequenced as previously described. Among these patients, 19 had parkin gene mutations and 6 had no mutations. Exon rearrangements, point mutations, and the association of exon arrangement plus point mutations were found in 6 (32%), 5 (26%), and 7 (37%) parkin patients, respectively. All patients but 1 (patient 3) had 2 mutations. Exon rearrangements consisted mostly of deletions on exons 2, 3, 4, 3 to 4, 5, or 8 to 9 and only once to a duplication of exons 2 to 4. Eight different types of point mutations were observed, 4 truncating and 4 missense (Table 1). The study was approved by the local ethics committee, and all patients gave informed consent.

**Table 2. Fluorodopa F 18 K, Values in Different Study Groups**

<table>
<thead>
<tr>
<th>ROI</th>
<th>Caudate Nucleus</th>
<th>Putamen</th>
<th>Anterior</th>
<th>Posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>More Affected</td>
<td>Less Affected</td>
<td>More Affected</td>
<td>Less Affected</td>
</tr>
<tr>
<td>Parkin patients (n = 19)†</td>
<td>7.2 ± 1.9</td>
<td>5.7 ± 0.9</td>
<td>3.6 ± 0.6</td>
<td>7.2 ± 0.22</td>
</tr>
<tr>
<td>Nonparkin patients (n = 6)‡</td>
<td>8.7 ± 0.22</td>
<td>6.6 ± 0.18</td>
<td>2.9 ± 0.09</td>
<td>8.3 ± 0.23</td>
</tr>
<tr>
<td>Controls (n = 9)</td>
<td>11.3 ± 1.7</td>
<td>11.7 ± 1.6</td>
<td>10.8 ± 1.7</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: K, influx rate constant; NA, not applicable; ROI, region of interest.
*Values are given as mean ± SD.
†Young-onset Parkinson disease patients with parkin gene mutations.
‡Young-onset Parkinson disease patients without parkin gene mutations.

**Region of Interest Analysis**

Six regions of interest (ROIs) were defined bilaterally by inspection of the integrated axial image on the head of the caudate nucleus (circular diameter, 10 mm), the anterior part of the putamen (elliptic, 15 × 10 mm), and the posterior part of the putamen (elliptic, 15 × 10 mm). These ROIs were placed on 3 consecutive planes directly on the PET images. The nonspecific background activity was averaged from a single elliptic ROI of 5 ± 0.4 cm³ drawn over the occipital cortex on 2 consecutive planes. The fluorodopa F 18 influx rate constant (K) values were calculated from the 30- to 90-minute period after injection for tissue count activity using nonspecific occipital tissue counts as the input function. This analysis calculates the striatal fluorodopa F 18 K, value, which represents the rate of striatal fluorodopa F 18 uptake and storage.

**STATISTICAL ANALYSIS**

The mean fluorodopa F 18 K, values for each ROI in the parkin patients were compared with the mean fluorodopa F 18 K, values of the nonparkin patients and the healthy controls using a 1-way analysis of variance with Bonferroni correction for multiple comparisons. In addition, in both parkinsonian patient groups, differences of the fluorodopa F 18 K, values between each ROI and interhemispheric asymmetries were searched using the paired 2-tailed t test with a significance level of P < .05. Correlations among clinical features, mutations, lateralized UPDRS motor score, and mean fluorodopa F 18 K, values were analyzed using nonparametric Spearman rank order correlation at P < .05.

**RESULTS**

**STRIATAL FLUORODOPA F 18 UPTAKE IN PARKIN PATIENTS**

A marked reduction of fluorodopa F 18 K, was observed in all striatal ROIs (P < .001). This reduction was 36.3%, 51.3%, and 66.7% for the caudate nucleus, anterior putamen, and posterior putamen, respectively. Mean ± SD fluorodopa F 18 K, values (×10⁻³ min⁻¹) were 7.2 ± 1.9, 5.7 ± 0.9, and 3.6 ± 0.6 for the caudate nucleus, anterior putamen, and posterior putamen, respectively. These differences were highly statistically significant (caudate vs anterior putamen, caudate vs posterior putamen, ante-
The fluorodopa F 18 influx rate constants (K) for the caudate nucleus, anterior putamen, and posterior putamen. Error bars indicate SD. Parkin patients indicates patients with young-onset Parkinson disease with parkin gene mutations; nonparkin patients, patients with young-onset Parkinson disease without parkin gene mutations.

**CLINICAL FEATURES OF PARKIN PATIENTS**

Most of the classic hallmarks of autosomal recessive juvenile parkinsonism associated with parkin gene mutation were present in the patients studied: young age at onset, slow disease progression, good levodopa responsiveness, brisk tendon reflexes, absence of dementia, and focal dystonia at onset. However, observations of parkin patients with hemiparkinson-hemiatrophy, late-onset tremor dominant parkinsonism, or mild cerebellar syndrome have been reported, indicating that the phenotype of patients carrying the parkin gene mutation might be wider. In the present study, 3 patients had myoclonus and 1 a supranuclear ophthalmoplegia that, to our knowledge, has never been reported in parkin patients.

**CLINICAL FEATURES OF NONPARKIN PATIENTS**

In the nonparkin patients, dystonia, myoclonus, and hyperreflexia were not observed. Thus, the clinical presentation resembled idiopathic PD except for the long disease duration and the young age at onset. The fact that a family history of parkinsonism was found in two thirds of the cases suggests the occurrence of other mutations in this population of patients. This notably stands for mutations on the PARK 6 locus on chromosome 1p35-p36, since the clinical presentation is usually indistinguishable from idiopathic PD. However, since the PARK 6 gene is still unknown, no genetic testing was possible in our 6 patients.

**FURODOPA F 18 UPTAKE IN PARKIN AND NONPARKIN PATIENTS**

In both groups of YOPD patients, there was a bilateral reduction of striatal fluorodopa F 18 uptake and a rostrocaudal gradient. This reduction was asymmetrical in the putamen of parkin patients. The magnitude of the reduction of fluorodopa F 18 uptake correlated with the clinical features only in nonparkin patients. No correlation between the type of parkin mutation and fluorodopa F 18 values could be drawn.

In parkin patients, our data clearly showed a marked reduction in fluorodopa F 18 uptake, which predominated in the posterior putamen and then in the anterior putamen, respectively, whereas the caudate nucleus was less affected. Such anteroposterior gradient is characteristic of idiopathic PD but has also been described in a few parkin gene carriers. Our data in...
parkin patients were in accordance with the degeneration of postsynaptic dopaminergic neurons as has been found at autopsy. Interestingly, in our study, despite the wide spectrum of mutations found, no relationship was seen between the type of mutation and the fluorodopa F 18 K values. This is in line with the absence of a relationship between clinical characteristics and mutations found in patients with missense mutations and patients with truncating mutations. However, this notion of imaging and genetic correlations remains debated, since recent studies have shown that the reduction of striatal fluorodopa F 18 uptake depends on the number of mutant alleles and is also observed, although less severely, in unaffected parkin gene carriers.

In nonparkin patients, the same rostrocaudal gradient was noted, indicating a similar pattern of degeneration that predominantly affects the ventral tier of the substantia nigra. The K reduction was asymmetrical in parkin patients, except for the caudate nucleus, whereas no interhemispheric asymmetry was noticed in nonparkin patients except in the posterior putamen. In a study of a single nonparkin patient, Pal et al found an asymmetrical striatal decrease of fluorodopa F 18 uptake similar to that noted in idiopathic PD. However, this notion of asymmetry in our nonparkin group has to be considered cautiously because of the small number of patients. In addition, our nonparkin population may have a different genetic basis, indicating that a genotypically homogeneous population will be needed in future studies to differentiate parkin mutation carriers from others with autosomal recessive YOPD. Moreover, our results in parkin patients differed from previous PET studies, which demonstrated no asymmetry of fluorodopa F 18 uptake in contrast to what is classically observed in idiopathic PD. Our study thus demonstrates that the degenerative process may be similar to the one of idiopathic PD, although disease progression is slower as demonstrated in idiopathic PD. Our study thus demonstrates that the degenerative process may be similar to the one of idiopathic PD, although less severely, in unaffected parkin gene carriers.

In conclusion, this study, performed in a large population of YOPD patients with and without parkin mutations, showed minor differences of striatal fluorodopa F 18 uptake between both groups, indicating no specific PET pattern related to the presence of parkin gene mutations. In addition, this study underlined the absence of direct relationships among genotype, phenotype, and imaging pattern in YOPD.

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