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.

Arch Neurol. 2003;60:713-718

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, hypertrelexia, 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 predominated 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 F18 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 F18 uptake compared with YOPD patients without parkin mutation (nonparkin patients).

### 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 lists the patients' characteristics.

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

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Age at Onset, y</th>
<th>First Symptoms</th>
<th>Hyperreflexia</th>
<th>Family History</th>
<th>Parkin Mutations</th>
<th>Levodopa Equivalent Dose, mg/d</th>
</tr>
</thead>
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<tr>
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<td>37</td>
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<td>+</td>
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<td>–</td>
<td>+</td>
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<td>+</td>
<td>del.ex2/del.ex3</td>
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**Patients Without Parkin Mutations**

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Age at Onset, y</th>
<th>First Symptoms</th>
<th>Hyperreflexia</th>
<th>Family History</th>
<th>Parkin Mutations</th>
<th>Levodopa Equivalent Dose, mg/d</th>
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<td>5/36</td>
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<td>B</td>
<td>–</td>
<td>+</td>
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<td>800</td>
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</tbody>
</table>

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.

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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.

**PET SCANNING**

**Acquisition**

We performed PET on a tomograph (CTI-Siemens Ecat Exact HR+; Siemens, Knoxville, Tenn) in the 3-dimensional mode, yielding 63 consecutive slices (transaxial resolution, 4.3 mm). The PET scans were performed either at the CERMEP, Lyon, France, or at the Service Hospitalier Frédéric Joliot, Orsay, France. For the scan, patients had not been taking dopaminergic medication for at least 12 hours. They lay on a bed with their heads fixed by a thermoformed mask. Control of the head position throughout the examination was made by laser alignment along with reference points on the Reid line. A transmission scan was performed for attenuation correction using a $^{68}$Ge-$^{68}$Ga (germanium 68–gallium 68) external rotating source. Fluorodopa F 18 was infused intravenously for 15 seconds. The mean±SD injected activity was 3.19±0.44 mCi (118.2±16.3 MBq), 3.10±0.33 mCi (114.6±12.1 MBq), and 3.14±0.41 mCi (116.1±15.3 MBq) for healthy controls, parkin patients, and nonparkin patients, respectively. All patients received orally either 50 mg of benserazide or 100 mg of carbidopa 1 hour before the radiotracer injection to inhibit peripheral levodopa decarboxylation. Scanning was initiated at the time of tracer injection and frames were acquired for 90 minutes. The 3-dimensional emission data were reconstructed by 3-dimensional filtered back projection (Shep Logan or Hanning filter; cutoff frequency, 0.5 cycles per pixel), giving a transaxial resolution of 6.5-mm full-width at half-maximum and displayed in a 128×128 pixel format with 63 planes, creating approximately 2-mm cubic voxels. For each patient, an integrated image with 63 planes was made from the emission data obtained from 30 to 90 minutes.

**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_i) 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.

The fluorodopa F 18 uptake depended on the clinical disability in nonparkin but not in parkin patients.

**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 and patients with heterozygous mutations, patients with mutations on exon 1 to 6 and patients with mutations on exons 7 to 12, and patients with 2 truncating mutations with those with at least 1 missense mutation.

**Fluorodopa F 18 Uptake in Parkin and Nonparkin Patients**

In both groups of YOPD patients, there was a marked 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 of striatal fluorodopa F 18 uptake in both parkin groups. A correlation was noted between the anterior and posterior putamen fluorodopa F 18 uptake and the lateralized UPDRS motor score (Spearman rank correlation, 0.63 and 0.70 for the anterior and posterior putamen, respectively; P = .03) but not with disease duration. A significant difference of fluorodopa F 18 uptake between both parkinsonian groups was only noted for the more affected posterior putamen in which fluorodopa F 18 uptake was less in the nonparkin than in the parkin patients (P = .05).
parkin patients were in accordance with the degeneration of presynaptic dopaminergic neurons as has been found at autopsy.18 Interestingly, in our study, despite the wide spectrum of mutations found, no relationship was seen between the type of mutation and the fluorodopa F18 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.8 However, this notion of imaging and genetic correlations remains debated, since recent studies24,25 have shown that the reduction of striatal fluorodopa F18 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.34 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 al19 found an asymmetrical striatal decrease of fluorodopa F18 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,14,24 which demonstrated no asymmetry of fluorodopa F18 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 a recent PET study.20 Interestingly, although in idiopathic PD and in nonparkin patients from other studies27,28 the fluorodopa F18 PET alterations correlated with the severity of the symptoms, no clinical PET correlation could be demonstrated in parkin patients, which may indicate the existence of postsynaptic adaptive mechanisms. However, the results of preliminary PET studies with raclopride labeled with carbon 11, a dopaminergic postsynaptic radiotracer, performed in parkin patients are, to date, still conflicting.14,23,24 A recent PET [11C]raclopride study showed an up-regulation of D2 receptors in drug-naïve parkin patients but a down-regulation in treated patients.35

In conclusion, this study, performed in a large population of YOPD patients with and without parkin mutations, showed minor differences of striatal fluorodopa F18 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.

Accepted for publication January 27, 2003.

From the Service de Neurologie D and CERMEP (Centre d’Exploration et de Recherche Médicales par Emission de Positions) (Cyclotron Unit), Hôpital Neurologique Pierre Wertheimer, Lyon (Drs Thobois, Guilhonet, Chapoy, Costes, and Broussolle); URA CEA-CNRS (Unité de Recherche Commissariat à l’Energie Atomique–Centre National de la Recherche Scientifique) 2210, Service Hospitalier Frédéric Joliot, Orsay (Drs Ribeiro and Remy); Département de Génétique, Cytogénétique et Embryologie, Fédération de Neurologie, INSERM (Institut National de la Santé et de la Recherche Médicale) Unité 289, and Centre d’Investigation Clinique (Dr Agid), Hôpital de la Salpêtrière, AP-HP (Assistance Publique–Hôpitaux de Paris), Paris (Drs Lohmann, Durr, and Brice); Service de Neurologie and INSERM Unité 318, CHU (Centre Hospitalier Universitaire), Grenoble (Dr Pol-lak); Service de Neurologie, Hôpital Purpan, Toulouse (Dr Rascol); and Département de Neurosciences, CHU Henri Mondor, Faculté de Médecine, Créteil (Dr Remy), France.

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This study was supported by grant BQR 2001 from the Université Claude Bernard Lyon I, Lyon, and by the Association France Parkinson, the AP-HP, Paris, and the Commissariat à l’Energie Atomique, Orsay.

We thank the patients for participating in this study. We also thank the nurses and all the technical staff of the PET centers for technical support and Magali Periquet, PhD, for molecular analyses.

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