Young-Onset Parkinson Disease With and Without Parkin Gene Mutations

A Fluorodopa F 18 Positron Emission Tomography Study

Stéphane Thobois, MD; Maria-Joao Ribeiro, MD, PhD; Ebba Lohmann, MD; Alexandra Dürr, MD, PhD; Pierre Pollak, MD; Olivier Rascol, MD, PhD; Stéphane Guillouet, PharmD; Elizabeth Chapoy, MD; Nicolas Costes, PhD; Yves Agid, MD, PhD; Philippe Remy, MD, PhD; Alexis Brice, MD; Emmanuel Broussolle, MD, PhD; for the French Parkinson’s Disease Genetics Study Group

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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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) motor score observed after a short-term levodopa challenge (mean ± SD 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 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

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>
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**Patients Without Parkin Mutations**

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<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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<tr>
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<td>800</td>
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<td>3/F/64</td>
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<td>B</td>
<td>-</td>
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*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.
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 68Ge–68Ga (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, anterior putamen vs posterior putamen, and posterior putamen vs controls). The fluorodopa F 18 Ki 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 Ki value, which represents the rate of striatal fluorodopa F 18 uptake and storage.
The fluorodopa F 18 influx rate constants (K) for the caudate nucleus, anterior putamen, and posterior putamen. Error bars indicate SD. Parkin patients indicate 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 mutations 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.13,14,20 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.13,14,20 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 exon 7 to 12, and patients with 2 truncating mutations with those with at least 1 missense mutation.

A marked reduction of fluorodopa F 18 K, was observed in all striatal ROIs (P<.001). This reduction was of 23.0%, 43.6%, and 73.0% for the caudate nucleus, anterior putamen, and posterior putamen, respectively. Mean±SD fluorodopa F 18 K values (×10⁻³ min⁻¹) were 8.7±0.22, 6.6±0.18, and 2.9±0.09 for the caudate nucleus, anterior putamen, and posterior putamen, respectively. These values were statistically different (caudate vs anterior putamen, caudate vs posterior putamen, anterior vs posterior putamen; P<.001) (Table 2 and Figure). The mean fluorodopa F 18 K values for the more and less affected caudate nucleus and the more and less affected anterior putamen were not statistically different. The mean fluorodopa F 18 K values for the more and less affected posterior putamen were statistically different (P=.02) (Table 2). A correlation was noted between the anterior and posterior putamen fluorodopa F 18 K values 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 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.8 However, this notion of imaging and genetic correlations remains debated, since recent studies24,25 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.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 al18 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 studies14,24 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 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 a recent PET study.26 Interestingly, although in idiopathic PD and in nonparkin patients from other studies, the fluorodopa F 18 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-naive 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 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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Author contributions: Study concept and design (Drs Thobois, Ribeiro, Lohmann, Durr, Pollak, Rascol, Costes, Agid, Remy, Brice, and Broussolle); acquisition of data (Drs Thobois, Ribeiro, Lohmann, Durr, Pollak, Guillonet, Chapoy, Costes, Remy, and Broussolle); analysis and interpretation of data (Drs Thobois, Ribeiro, Lohmann, Durr, Pollak, Rascol, Chapoy, Costes, Agid, Remy, Brice, and Broussolle); drafting of the manuscript (Drs Thobois, Ribeiro, Lohmann, Durr, Pollak, Chapoy, Remy, Brice, and Broussolle); critical revision of the manuscript for important intellectual content (Drs Thobois, Ribeiro, Lohmann, Durr, Pollak, Rascol, Guillonet, Chapoy, Costes, Agid, Remy, Brice, and Broussolle); statistical expertise (Drs Thobois, Durr, Costes, and Remy); obtained funding (Drs Thobois, Remy, Brice, and Broussolle); administrative, technical, and material support (Drs Thobois, Lohmann, Durr, Pollak, Guillonet, Chapoy, Costes, Brice, and Broussolle); study supervision (Drs Thobois, Pollak, Rascol, Costes, Agid, Remy, Brice, and Broussolle).

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Members of the French Parkinson’s Disease Genetics Study Group are as follows: Y. Agid, A. M. Bonnet, A. Brice, A. Durr, J. Feingold, M. Martinez, C. Penet (INSERM Unité 289, Hôpital Pitié-Salpêtrière, Paris), M. Borg (Hôpital Pasteur, Nice), E. Broussolle (Hôpital Pierre Wertheimer, Lyon), P. Damier (CHU, Nantes), T. De Broucker (CH, Saint-Denis), A. Desèe (CHRU [Centre Hospitalier Regional et Universitaire], Lille), F. Durif (CHU, Clermont-Ferrand), F. Dubas (CHU, Angers), G. Fenelon (Hôpital Henri Mondor, Créteil), P. Pollak (CHU, Grenoble), O. Rascol (Hôpital Purpan, Toulouse), F. Tison (CHU, Bordeaux), C. Tranchant, J. M. Warter (Hôpitaux Civils, Strasbourg), M. Vénin (CHU, Rennes), F. Viallet (Hôpital d’Aix-en-Provence), and M. Vidalhét (Hôpital Saint-Antoine).

Corresponding author and reprints: Stéphane Thobois, MD, Service de Neurologie D, Hôpital Neurologique Pierre Wertheimer, 59 Bd Pinel, 69003 Lyon, France (e-mail: stephane.thobois@chu-lyon.fr).
REFERENCES


