Imaging of dopaminergic dysfunction with [¹²³I]FP-CIT SPECT in early-onset *parkin* disease

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Abstract—*Objective:* To investigate whether the presence of *parkin* gene mutations is associated with different nigrostriatal impairment than other early-onset parkinsonism. *Methods:* Eighteen consecutive early-onset Parkinson disease (PD) patients (nine parkin and nine nonparkin patients) and six controls were studied with [¹²³I]FP-CIT SPECT. *Results:* Parkin patients had longer disease duration (15 ± 9 vs 6 ± 2 years, $p = 0.008$) and higher Unified Parkinson's Disease Rating Scale (UPDRS) motor score (35.8 ± 13.7 vs 22.8 ± 7.9, $p = 0.025$) than nonparkin patients. Caudate and putamen DAT density were reduced by 60% and 79% in parkin and by 43% and 70% in nonparkin patients. Multiple regression analysis showed that the UPDRS and the presence of parkin gene mutations, but not the disease duration, were significantly correlated with the striatal DAT density. Parkin patients showed a more symmetric DAT loss in both caudate and putamen as compared with nonparkin patients. *Conclusions:* Parkin-related disease may be associated with a higher degree of nigrostriatal impairment, independently of the clinical severity of the disease, and a more symmetric involvement as compared with non-*parkin* early-onset disease.

Early-onset (before age 45 years) Parkinson disease (PD) is referred to as early-onset PD and is generally associated with a higher rate of treatment-related dyskinesias and greater impairment of quality of life and psychosocial functioning than the late-onset disease.[1] Early-onset PD can be associated with autosomal recessive inheritance and with mutations in the *parkin* gene. *Parkin* gene mutations were initially identified in Japanese families with autosomal recessive juvenile parkinsonism[2,3] and subsequently described also in European patients.[4,5] Their frequency is approximately 50% in familial and 15% in isolated cases with early-onset parkinsonism.[5,6] Patients with *parkin* mutations generally have earlier onset, higher frequency of dystonia, hyperreflexia, and symmetric signs at onset, a better response to levodopa at a lower dosage, a higher rate of treatment-related dyskinesias, and a slower progression than patients without mutations.[5,7] Pathologically, *parkin*-related disease is characterized by neuronal cell loss in the substantia nigra and the locus coeruleus and, except for one case with a specific mutation,[8] by the absence of Lewy bodies,[9,10] the hallmark of idiopathic PD.

In vivo studies of nigrostriatal cell function with [¹⁸F]fluorodopa PET have been reported in families with *parkin*-related disease and in early-onset PD patients with and without *parkin* mutations.[11-16] In familial *parkin*-related disease a reduction of [¹⁸F]fluorodopa uptake similar to idiopathic PD patients has been reported in affected patients[11-13] and an impaired nigrostriatal cell function has been found in heterozygous *parkin* carriers.[13] Moreover, a longitudinal PET study in a *parkin* kindred has also shown a slower decline of [¹⁸F]fluorodopa uptake in parkin patients as compared with idiopathic PD patients, suggesting a slower progression of nigrostriatal cell loss in *parkin*-related disease.[14] To date, two PET studies have compared the pattern of [¹⁸F]fluorodopa uptake reduction in early-onset PD with and without *parkin* mutations.[15,16] The first study[15] did not find any difference of striatal [¹⁸F]fluorodopa uptake between parkin and nonparkin patients, while the second study[16] reported a more severe and widespread presynaptic dopaminergic deficit in parkin patients. These studies have examined the status of the presynaptic dopaminergic system with [¹⁸F]flu-

Table 1 *Clinical, genetic, and imaging data of parkinsonian patients*

Patient no./sex/age, y	Age at onset, y	Hoehn and Yahr stage	UPDRS-motor	Disease asymmetry*/ fluctuations/ dyskinesia	Family history	Parkin mutations	Therapy (mg/d)
Patients with *parkin* mutations							
1/M/55	23	3	25	S/−/−	+	del.ex3 (homo)	LD (400), perg. (3)
2/M/58	47	2	21	S/−/−	+	del.ex3-4 (homo)	LD (400), perg. (4)
3/M/30	18	3	46	S/+/+	−	del.ex3/del.ex2-3	Apo. s.c. (114), LD (200)
4/M/29	15	3	36	S/+/+	ND	C820T/del.ex2	Apo. s.c. (60), cab. (2)
5/F/42	38	2.5	27	S/+/+	−	G96C/C1305T	LD (500), cab. (3)
6/F/56	36	3	58	S/+/+	−	G535A (hetero)	Apo. s.c. (20)
7/M/35	27	2.5	22	R/−/−	−	dupl.ex6 (hetero)	Sel. (5)
8/M/57	33	2	34	L/−/−	+	del.ex 2/del.ex 2-4	Brom. (40)
9/M/49	38	3	53	S/+/+	−	C411T (hetero)	LD (1,200)
Patients without *parkin* mutations							
10/M/43	40	1.5	10	R/−/−	−	−	Rop. (15)
11/F/47	41	2	16	R/−/−	−	−	Pram. (3), LD (450)
12/M/41	38	2	22	R/−/−	−	−	Cab. (8), LD (200)
13/F/43	34	3	35	L/+/+	−	−	Perg. (6)
14/F/47	38	3	18	S/+/+	−	−	LD (450), pram. (4.5), bip. (4)
15/F/42	38	2	26	L/−/−	+	Polymorphism C346A	−
16/M/48	43	2	20	L/+/−	−	−	LD (150), rop. (15)
17/F/49	41	2.5	32	L/+/+	−	−	Apo. s.c. (36)
18/M/40	35	2	26	L/−/−	−	−	Bip. (4), orph. (100)

* The asymmetry of the disease is reported: S = more symmetric disease based on ≤30% difference in the right-to-left scores of the UPDRS-motor; R = right side more impaired; L = left side more impaired.

UPDRS = Unified Parkinson's Disease Rating Scale; LD = L-dopa; perg. = pergolide; apo. s.c. = apomorphine subcutaneous infusion; ND = not determined: the family history in this patient could not be determined since he was adopted; cab. = cabergoline; sel. = selegiline; brom. = bromocriptine; rop. = ropinirole; pram. = pramipexole; bip. = biperidene; orph. = orphenadrine.

orodopa PET, a marker of nigrostriatal function. Other putative markers of nigrostriatal integrity such as dopamine transporter (DAT) ligands could be applied to the study of *parkin*-related disease.

We investigated the dopaminergic system in patients with early-onset parkinsonism using the DAT ligand [123I]FP-CIT and evaluated the differences in the DAT density between parkin and nonparkin patients with SPECT.

Subjects and methods. *Subjects.* Eighteen consecutive patients with early-onset parkinsonism referred to the Movement Disorder Center of the University Federico II of Napoli were evaluated. Demographic, clinical, genetic data, and therapy are reported in table 1. The age at disease onset ranged between 15 and 47 years (35 ± 9 years, with these and subsequent data reported as mean ± SD) and with the exception of one patient was less than 45 years in all patients. Patients fulfilled the UK PD Society Brain Bank diagnostic criteria for idiopathic PD[17] with the exception of positive family history in four of them. Patients were evaluated clinically with the Hoehn and Yahr staging and the motor

examination of the Unified PD rating scale (UPDRS). Patients were considered to have more symmetric or asymmetric disease on the basis of clinical evaluation and ≤30% or >30% difference in the right to left scores of the UPDRS motor score. Genetic screening for the presence of *parkin* gene mutations was performed either before or after enrollment in the imaging study. The early-onset PD patients included 9 patients found to carry mutations in at least one allele of the *parkin* gene (age 46 ± 12 years) and 9 patients without mutations (age 44 ± 3 years). The patients were compared to a group of 6 healthy controls (5 men, 1 woman, age 51 ± 13 years). Controls were either spouses of affected patients or volunteers without any neurologic or psychiatric disorders. Subjects gave their informed consent for participation in the study, which was approved by the local institutional review board.

Genetic analysis. After written informed consent was given, genomic DNA of the patients was extracted from peripheral leukocytes using standard techniques. For rapid detection of point mutations and small deletions or insertions, single-stranded conformation polymorphism (SSCP) analysis of the 12 exons of *Parkin* was performed using published intronic primers.[2] In cases of observed band shifts, direct sequence analysis of the mutated fragments was performed by an automated sequencing system (3100 Genetic Analyzer ABI Prism), using the Thermo Sequenase

dye terminator cycle sequencing pre-mix kit, v2.0 (Amersham Pharmacia Biotech). To detect heterozygous exonic deletions or duplications, gene dosage analysis was performed using the Real-Time (RT) quantitative PCR technique with the ABI PRISM 7000 Sequence Detection System (Perkin-Elmer Applied Biosystem, Applera Italia). Primers, probes, and details of the method are available on request (garavaglia@istituto-besta.it). Four patients (Patients 2, 3, 4, and 8) were tested for *Parkin* mutations as previously described.[6]

SPECT studies. SPECT studies were performed 4.2 ± 0.7 hours after IV administration of [^{123}I]FP-CIT (185 MBq) using a dual-headed camera (E.CAM, Siemens Medical Systems, Hoffman Estates, IL) equipped with low-energy high-resolution collimators. Scans were acquired with a photopeak window centered around 159 keV ± 10% with a 128 × 128 matrix (zoom: 1.23; pixel size: 3.90 × 3.90 mm). Controls underwent also an early SPECT scan 5 minutes after tracer injection to obtain a uniform tracer distribution throughout the brain and aid the spatial normalization of the delayed scans. The time after tracer injection for SPECT imaging was selected based on previous reports demonstrating that the time window between 3 and 6 hours allows stable measurement of specific-to-nondisplaceable ratio of [^{123}I]FP-CIT.[18,19] Imaging studies were performed by investigators blind to the clinical and genetic data.

Images were reconstructed using a Butterworth filter (cut-off, 0.5 cycles/pixel; order, 10) and corrected for attenuation using Chang's algorithm (μ = 0.06 cm^{-1}). No scatter correction was applied to the imaging dataset. Early scans of controls were coregistered to delayed scans and then spatially normalized in the Montreal Neurologic Institute (MNI) space to a voxel size of 4 × 4 × 4 mm using the SPECT template available in the 1999 version of SPM (SPM'99, Wellcome Department of Cognitive Neurology, London, UK). A mean image of the delayed scans of the first five controls was created to generate a [^{123}I]FP-CIT template. SPECT scans of each subject were normalized to the [^{123}I]FP-CIT template using an affine transformation without nonlinear components. Normalized images were processed for region of interest (ROI) analysis with the software ImageJ (rsb.info.nih.gov/ij/, NIH, Bethesda, MD). A template including four circular ROIs of 32 mm^2 for right and left caudate and putamen and a polygonal ROI of 3,504 mm^2 for the occipital cortex, similar to the one previously reported,[20] was applied on each normalized delayed scan on six consecutive transaxial slices (range of Z level in MNI space: −12 − 8 for striatum and 0 − 20 for occipital cortex). Outcome measures were the specific-to-nondisplaceable binding ratio, V_3'' (ROI$_{striatum}$−ROI$_{occipital}$/ROI$_{occipital}$), and the putamen-to-caudate ratio. Ipsi- and contralateral striata were assigned relative to the clinically more affected side.

Statistical analysis. Differences of age, caudate V_3'', putamen V_3'', and putamen-*to*-caudate ratio among controls and PD groups were assessed with one-way analysis of variance (ANOVA) and *t*-test with Bonferroni correction for post hoc analysis with multiple comparisons. Differences between parkin and nonparkin groups of clinical (disease duration, Hoehn and Yahr stage, and UPDRS), pharmacologic (levodopa equivalent dose[21]), and SPECT variables (V_3'' of ipsilateral caudate, ipsilateral putamen, contralateral caudate, and contralateral putamen) were assessed with two-tailed unpaired *t*-test. Differences between parkin and nonparkin groups in the asymmetry of disease, the presence of fluctuations, and dyskinesia were assessed with χ^2 test. Differences between ipsilateral and contralateral caudate and putamen V_3'' measures within each PD group were assessed with two-tailed paired *t*-test. Correlations between striatal V_3'' and disease duration, Hoehn and Yahr stage, and UPDRS in parkin and nonparkin groups were assessed with the Pearson correlation coefficient, r. Multiple regression analysis was performed to test the effect of disease duration (<10 or ≥10 years, based on the average disease duration in the whole group of PD patients), motor UPDRS (≤30 or >30, i.e., mild-to-moderate or severe clinical impairment), and genetics (presence or absence of *parkin* gene mutations) on the striatal DAT density. Significance was set at the *p* value less than 0.05 level. All tests were performed on a PC Windows XP using the software SPSS 15.1 (SPSS Inc., Chicago, IL).

Results. Details of *parkin* gene mutations are reported in table 1. Two patients were homozygotes for exon deletions (Patients 1 and 2), four patients were compound heterozygotes (Patients 3, 4, 5, 8); three patients carried a
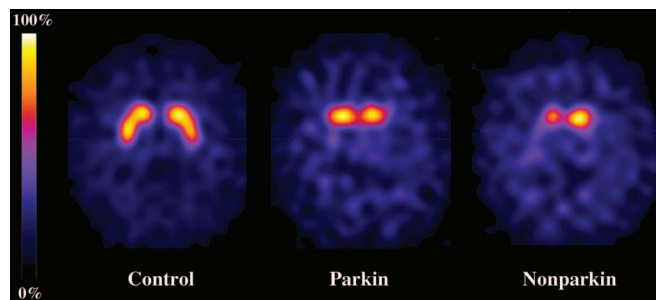

Figure 1. Transaxial slices of [^{123}I]FP-CIT scan at the level of the basal ganglia in a control (left) and two early-onset Parkinson disease patients with (middle) and without (right) parkin *gene mutations. In both patients the binding or the radiopharmaceutical was markedly reduced. In the parkin patient a more symmetric reduction of [^{123}I]FP-CIT was observed as compared with the nonparkin patient.*

mutation in only one allele (Patients 6, 7, 9). The previously reported polymorphism C346A[22] was detected in heterozygous form in one patient (Patient 15) assigned to the nonparkin group. Controls, parkin, and nonparkin patients did not differ for age. Parkin patients had earlier age at disease onset (31 ± 11 vs 39 ± 3; unpaired *t*-test, *p* = 0.043), longer disease duration (15 ± 9 vs 6 ± 2; unpaired *t*-test, *p* = 0.008), higher Hoehn and Yahr stage (2.7 ± 0.4 vs 2.2 ± 0.5; unpaired *t*-test, *p* = 0.06), and higher UPDRS motor score (35.8 ± 13.7 vs 22.8 ± 7.9; unpaired *t*-test, *p* = 0.025) than nonparkin patients. In seven parkin patients (78%) and in only one nonparkin patient (11%) the disease was more symmetric (parkin vs nonparkin χ^2 = 8.1, *p* = 0.004). There were no differences in the proportion of patients with motor fluctuations or dyskinesias. Mean levodopa equivalent dose was higher in parkin than nonparkin patients (1527.8 ± 1856.3 mg/d vs 600 ± 546 mg/d, *p* = 0.170). The corresponding data in the patients not treated with apomorphine infusion were 625 ± 402.2 mg/d in parkin and 450 ± 330.6 mg/d in nonparkin patients (*p* = 0.388).

Striatal uptake of [^{123}I]FP-CIT was markedly reduced in both parkin and nonparkin patients compared with controls (figure 1). Caudate V_3'' was reduced by 60% in parkin and by 43% in nonparkin patients compared with controls (ANOVA; F = 52.69, *p* < 0.001, table 2). Putamen V_3'' was reduced by 79% in parkin and by 70% in nonparkin patients compared with controls (ANOVA; F = 197.62, *p* < 0.001, see table 2). With post hoc analysis the difference in DAT density between parkin and nonparkin patients was significant in the caudate (*t*-test, *p* = 0.017) but not in the putamen (*t*-test, *p* = 0.089). Putamen-to-caudate ratio was reduced in both groups of early-onset PD patients compared with controls (ANOVA; F = 39.56, *p* < 0.001), but no differences between parkin and nonparkin patients were found (see table 2). In parkin patients no differences were found between ipsilateral and contralateral caudate and putamen V_3''. In nonparkin patients V_3'' in the contralateral caudate and putamen was lower than V_3'' in the corresponding ipsilateral regions (paired *t*-test, *p* < 0.05, figure 2). In parkin patients V_3'' in the ipsilateral caudate (unpaired *t*-test, *p* = 0.013), contralateral caudate (unpaired *t*-test, *p* = 0.023), and ipsilateral putamen (unpaired *t*-test,

Table 2 *Individual values and mean ± SD of caudate V_3'', putamen V_3'', and putamen-to-caudate ratio in controls and early-onset Parkinson disease (PD) patients with and without* parkin *mutations*

Subject no.	Caudate V_3''	Putamen V_3''	Putamen-to-caudate ratio
Controls			
1	3.14	3.13	1.00
2	2.84	2.32	0.82
3	2.79	2.64	0.95
4	3.00	2.52	0.84
5	3.02	2.38	0.79
6	2.67	2.53	0.95
Mean ± SD	2.91 ± 0.17	2.58 ± 0.29	0.89 ± 0.09
PD patients with *parkin* mutations			
1	1.27	0.56	0.44
2	1.22	0.74	0.61
3	1.03	0.43	0.42
4	0.98	0.69	0.71
5	1.46	0.60	0.41
6	0.70	0.29	0.41
7	1.77	0.71	0.40
8	0.89	0.47	0.53
9	1.25	0.46	0.37
Mean ± SD	1.17 ± 0.32[a,b]	0.55 ± 0.15[a,c]	0.48 ± 0.12[a]
PD patients without *parkin* mutations			
10	1.75	0.87	0.50
11	1.50	0.72	0.48
12	2.15	1.08	0.50
13	1.20	0.54	0.45
14	1.84	0.93	0.51
15	1.66	0.90	0.54
16	2.12	0.82	0.39
17	0.93	0.58	0.62
18	1.67	0.55	0.33
Mean ± SD	1.65 ± 0.39[a]	0.78 ± 0.19[a]	0.48 ± 0.09[a]

[a] Reduced compared with controls by one-way analysis of variance, $p < 0.001$.
[b] Lower than nonparkin PD patients by *t*-test with Bonferroni correction, $p = 0.017$.
[c] $p = 0.089$ by *t*-test with Bonferroni correction, parkin vs nonparkin PD patients.

$p = 0.002$) was lower than in nonparkin patients (see figure 2). No differences between the two groups were found in the contralateral putamen. Striatal V_3'' was correlated with UPDRS motor score in parkin (r = −0.774, $p = 0.014$) and showed a trend in nonparkin patients (r = −0.622, $p = 0.073$). No significant correlation was found between striatal V_3'' and disease duration or Hoehn and Yahr scale.

Independently of *parkin* mutations, there were no differences in caudate and putamen V_3'' between patients with or without motor fluctuations or with and without dyskinesias.

To investigate whether the observed differences of striatal V_3'' were related to the longer disease duration or higher UPDRS score in the parkin group, multiple regression analysis was performed to evaluate the individual con-

tribution of disease duration, UPDRS, and presence of *parkin* gene mutations (genetics) on the V_3'' data. UPDRS and genetics were the only independent predictors in the model (model corrected $R^2 = 0.717$, F = 22.56, $p < 0.001$; beta for UPDRS = −0.667, $p < 0.001$; beta for genetics = −0.37, $p = 0.017$).

Discussion. This SPECT study investigated the status of the dopaminergic system in early-onset PD comparing patients with and without *parkin* gene mutations. The two main findings of our study were a more severe reduction and a more symmetric loss of striatal DAT density in parkin as compared with nonparkin patients.

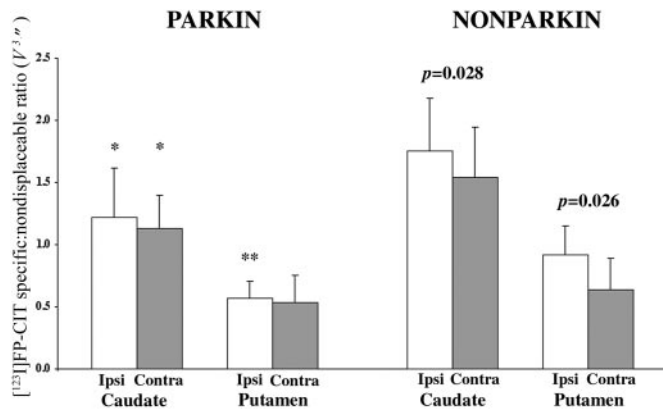The finding of a more severe DAT loss in parkin

Figure 2. Bar graph showing mean + SD of [^{123}I]FP-CIT V$_3''$ in ipsilateral (ipsi, white) and contralateral (contra, gray) caudate and putamen in parkin and nonparkin patients. p Values refer to the analysis of ipsilateral vs contralateral sides by paired t-test. *p < 0.05 and **p < 0.005: parkin vs nonparkin patients by unpaired t-test.

patients is in line with the results of a recent [^{18}F]dopa PET study in which a more widespread and severe disruption of striatal dopaminergic pathway has been reported in parkin as compared to nonparkin patients[16] and suggests a specific role of *parkin* gene mutations on the degree of nigrostriatal impairment. Parkin protein is abundant in the human substantia nigra where it probably plays an important role in the functioning and survival of dopaminergic neurons.[23] Parkin has E3 ubiquitin ligase activity,[24] targeting specific substrates (one of them is the glycosylated form of α-synuclein) for degradation through the ubiquitin-proteasome pathway.[25] Mutations of the *parkin* gene interfere with the protein's ubiquitin ligase activity, leading to the accumulation of nonubiquitinated proteins,[25] which may accelerate dopaminergic cell loss and lead to the development of the disease at a younger age. Since the age at disease onset in parkin patients is younger than nonparkin patients it could be conceivable that the physiologic age-related decline of the DAT density,[26,27] which seems to be larger in the third decade of life,[28] could further contribute to the higher loss of transporters and dopaminergic terminals when patients reach the symptomatic threshold. Additional studies in early-onset patients at the time of diagnosis could contribute to the understanding of the early changes of dopaminergic function in *parkin*-related PD.

The more marked reduction of striatal DAT in parkin as compared to nonparkin patients has to be discussed taking into account differences in duration and clinical severity of disease between the two groups. Our parkin patients had longer disease duration with an earlier age at onset than nonparkin patients. These findings are in agreement with the results of two previous studies that compared the clinical characteristics of PD patients with and without *parkin* mutations.[5,7] Along with longer disease

duration, parkin patients had also a more severe clinical impairment as compared with nonparkin patients. Both variables are related to the density of DAT as measured with [^{123}I]FP-CIT SPECT.[18] We assessed the potential influence of disease duration, UPDRS, and genetics on the DAT density by performing multiple regression analysis. Our results showed that the UPDRS and the genetics did explain the reduction on the DAT density, whereas disease duration did not have major contribution in the model.

One of the two recent PET studies in early-onset PD showed no major difference of striatal [^{18}F]fluorodopa uptake between parkin and nonparkin patients, except for a negative correlation of putamen influx constant and UPDRS in nonparkin patients.[15] These findings are different from ours and could potentially be explained by differences in radiopharmaceuticals ([^{18}F]fluorodopa vs [^{123}I]FP-CIT), techniques (PET vs SPECT), or patient populations (presence of additional undetected mutations in other genes?).

In our study the more symmetric loss of striatal DAT found in parkin patients suggests that in early-onset PD the presence of *parkin* gene mutations is associated with more symmetric nigrostriatal impairment. This finding is corroborated by the previous observation that parkin patients have a higher frequency of symmetric symptoms at onset.[5] Moreover, also in our study parkin patients showed a more symmetric disease as compared with the nonparkin patients and this could suggest that in *parkin*-related PD a more symmetric dysfunction is maintained throughout the whole disease course.

Finally, some clinical and methodologic factors that could have potentially interfered with the imaging findings have to be discussed. Among these are the different pharmacologic treatment, the choice of the imaging time window, and potential differences of individual radiopharmaceutical clearance. In our study patients were treated with various drugs at different dosage. However, differences of treatment drugs should not have affected the DAT measures in our patients since previous studies have shown no significant effects of dopaminergic or other antiparkinsonian drugs on the DAT density measured with different SPECT or PET ligands. This was demonstrated in animals treated with different dopaminergic drugs,[29] including apomorphine,[30-32] and in humans treated with pergolide,[33] L-dopa,[33-37] selegiline,[34] and pramipexole.[36,37] Concerning the differences in the amount of dopaminergic drugs, when a patient's treatment was expressed as the levodopa equivalent dose, which is an estimate of the magnitude of dopaminergic treatment, the parkin group showed a higher mean dose than the nonparkin group although the difference was not significant. This difference was mainly due to the treatment with apomorphine. We can reasonably consider that in patients treated with drugs other than apomorphine the effect of dopaminergic medication on DAT expression, if any, could either be similar in the two

groups or could be slightly higher in the parkin group, but likely still negligible as compared with the actual differences in nigrostriatal degeneration. In patients treated with apomorphine, the magnitude of dopaminergic treatment was higher than the other patients, but still in the dose range shown not to produce significant effects on striatal DAT binding sites in animals.[32] Thus, overall, we might reasonably exclude major effects of pharmacologic treatment on the imaging findings.

With regard to the imaging time window, the time postinjection of approximately 4 hours was selected based on previous reports showing stable measurement of the [^{123}I]FP-CIT specific-to-nondisplaceable ratio between 3 and 6 hours.[18,19] However, since at that time significant washout of [^{123}I]FP-CIT is still present, we used a similar time window in parkin (4.3 ± 1.1 hour), nonparkin patients (4.1 ± 0.1 hour), and controls (4.2 ± 0.5 hours) to reduce possible interference on the outcome measures due to differences in postinjection scan interval. Other sources of variability that could potentially affect the imaging outcome measures are differences in tracer pharmacokinetics among different subjects. However, no subject had kidney, lung, or liver disease that could potentially affect the metabolism or the clearance of the tracer[38] and subjects had no restriction of fluid intake during the interval between injection and scanning to avoid major differences of hydration that could potentially affect the clearance of the radiopharmaceutical. Of course, individual differences of clearance among the patients could have introduced noise in the data, but we expected this to be negligible compared with actual differences of DAT density.

The presence of *parkin* gene mutations seems to be related to a higher degree of nigrostriatal impairment. Whether a more severe dopaminergic dysfunction in *parkin*-related disease is confined prevalently to the presynaptic site or also involves the postsynaptic D$_2$ receptor site as recently suggested[16] is an interesting research question that should be further investigated to better clarify the pathophysiology of this disorder.

Acknowledgment

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