Progression of dopaminergic dysfunction in a *LRRK2* kindred

A multitracer PET study

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ABSTRACT

Objective: Little is known about the progression of dopaminergic dysfunction in *LRRK2*-associated Parkinson disease (PD). We sought to characterize the neurochemical progression with multitracer PET in asymptomatic members of parkinsonian kindred (family D, Western Nebraska) carrying *LRRK2* (R1441C) mutation.

Method: Thirteen family D subjects underwent PET scans of presynaptic dopaminergic integrity and five subjects were rescanned 2 to 3 years later.

Results: In subjects 8, 9 (mutation carriers), and 13 (genealogically at risk subject), there was a decline in PET markers over the course of the study that was significantly greater than the expected rate of decline in healthy controls. Reduced dopamine transporter binding was the earliest indication of subclinical dopaminergic dysfunction and progression to clinical disease was generally associated with the emergence of abnormal fluorodopa uptake.

Conclusion: PET study of presymptomatic members of our *LRRK2* kindred revealed dopaminergic dysfunction that progressed over time. This represents an ideal group to study the natural history of early disease and the potential effects of neuroprotective interventions. *Neurology*® 2008;71:1790-1795

GLOSSARY

DAT = dopamine transporter; **DTBZ** = ^{11}C -($\pm$)- α -dihydrotetrabenazine; **FD** = ^{18}F -6-fluoro-L-dopa; **MP** = ^{11}C -d-threo-methylphenidate; **PD** = Parkinson disease; **ROI** = region of interest; **sPD** = sporadic PD.

Parkinsonism due to *LRRK2* (leucine-rich repeat kinase 2) mutation accounts for 0.5–3% of sporadic and 5–7% of familial Parkinson disease (PD).¹ While the pathology of *LRRK2* PD is highly pleomorphic,^{2,3} the clinical phenotype is one of late onset, progressive, levodopa responsive parkinsonism with typical motor complications of dopaminergic therapy. The neurochemical phenotype as assessed by PET is indistinguishable from that of sporadic PD (sPD).⁴ Dopaminergic abnormalities have been described in asymptomatic mutation carriers.⁴ Serial PET assessment of at-risk family members presents an excellent opportunity to study the progression of dopaminergic dysfunction and the evolution to clinical PD. Family D (Western Nebraska) is a well-documented family with PD due to *LRRK2* (R1441C) mutation.² We used multitracer PET to explore progression of dopaminergic dysfunction in vivo in asymptomatic members of family D.

METHODS Study population. Thirteen members from family D underwent multitracer PET using ^{18}F -6-fluoro-L-dopa (FD), ^{11}C -($\pm$)- α -dihydrotetrabenazine (DTBZ; vesicular monoamine transporter 2 ligand), and ^{11}C -d-threo-methylphenidate (MP; dopamine transporter [DAT] ligand) at baseline. The scanning team and the authors were blinded as to the mutation status of the subjects during scan acquisition and analysis. Table 1 shows the clinical characteristics. Five subjects (3, 5, 8, 9, and 13) were rescanned using the same protocol 21 to 36 months later to assess progression of DA terminal dysfunction. We included for comparison PET data from 34 healthy volunteers and 75 patients with clinically definite sPD,⁵ obtained with identical imaging and data analysis protocols.

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Table 1 Characteristics of subjects and controls

Family subjects	Mutation status*	Clinical status	Age, y† (55±)	UPDRS	
				Visit 1	Visit 2
1	+	PD	>	7	
2	+	PD	>	6	
3	–	U	<	1	1
4	–	U	>	3	
5	–	U	>	0	2
6	–	U	<	2	
7	–	U	>	1	
8	+	U	<	4	10
9	+	U	>	0	9
10	+	U	>	5	
11	+	U	<	3	
12	+	U	<	0	
13	N/A	U	<	1	1
Normal controls (n = 34)			55.22 ± 14.21‡		
sPD controls (n = 75)			60.65 ± 10.04‡	23.89 ± 12.0‡	

The baseline characteristics of subjects 1–6, 8, 9, 10, and 13 have been included in an earlier report.⁴

**LRRK2* mutation.

†Age (at initial visit) and gender of at-risk subjects are not shown to protect anonymity. < = age ≤55 years; > = age >55 years.

‡Mean ± SD. Mean ± SD duration of symptoms in sPD group is 7.49 ± 5.93 years.

UPDRS = Unified Parkinson's Disease Rating Scale; PD = Parkinson disease; U = clinically unaffected; N/A = not available (this subject declined genetic analysis); sPD = sporadic Parkinson disease control group.

This study has been approved by the institutional (UBC and Mayo Clinic) Ethics boards.

PET. The scanning procedure, data processing, and reconstruction have been described in detail elsewhere.⁶ Subjects were scanned in three-dimensional mode (reconstructed resolution ~9 mm in plane and 6 mm axially, 31 slices with center-to-center separation of 3.37 mm) with an ECAT 953B/31 tomograph (CTI/Siemens, Knoxville, TN) after overnight fasting and a standard low-protein breakfast on the day of scanning. Using a Harvard infusion pump, DTBZ (185 MBq in 10 mL of saline) was injected IV over 60 s. A series of sequential emission scans was obtained (4 × 1-minute, 3 × 2-minute, 8 × 5-minute, 1 × 10-minute) starting at tracer injection, for a total acquisition time of 60 minutes. Following an interval of 2.5 hours (i.e., >7 half-lives for ¹¹C) to allow for radioactive decay, subjects were repositioned and MP (185 MBq in 10 mL of saline) was injected. Scans were acquired over 60 minutes as above. Following an additional interval of at least 2.5 hours subjects received FD (185–260 MBq in 10 mL of saline). One hour prior to FD injection subjects received 200 mg of carbidopa orally.

Data analysis and statistics. The methods of image analysis have been described in detail elsewhere.⁶ In brief, a time-integrated image was created by summing scans obtained over the last 30 minutes of acquisition time (i.e., from 60 to 90 minutes for FD, from 30 to 60 minutes for DTBZ and MP) for scan analysis. Circular regions of interest (ROIs) (8.8 mm diameter) were manually placed along the axis of the striatum, one on the head of the caudate nucleus, and three along the rostrocaudal axis of each putamen without

overlap. Larger circular ROIs (diameter 19.4 mm) were positioned three per side over the cortex of the temporo-occipital lobe as a reference region. After realigning the dynamic sequence using Automated Image Registration,⁷ all ROIs were transferred onto the same spatially summed five axial planes for each time frame, to permit the generation of time activity curves. The same ROI template was used for all tracers. ROI placement, although essentially the same for all scans, was optimized by minor adjustments to maximize counts for each tracer in an attempt to place the ROIs as consistently as possible. FD uptake rate constant (K_{occ}) was determined by multiple time graphical method for unidirectional transport with reference tissue (occipital cortex) input function.^{8,9} DTBZ and MP binding potentials (BP_{DTBZ} and BP_{MP}) were obtained by a reversible graphical approach and a reference tissue input function.¹⁰ All scans were analyzed by a single operator. Follow-up scans were realigned to the baseline scans and ROIs transferred automatically.

The overall mean putaminal Kocc and BP values were obtained by averaging the corresponding mean right and mean left putaminal measurements determined from the corresponding ROIs. Age adjustments were applied for DAT binding, based on linear regression derived from the normal controls. Each subject's results were expressed as percentage of control values, with significance derived from the corresponding percentile score. We also determined the annual rates of decline in Kocc, BP_{DTBZ} , and BP_{MP} (i.e., the slope of trajectory of tracer binding/uptake) in subjects who had undergone two scans longitudinally. The slopes of decline in PET measurements in these subjects were tested for significant difference from zero and also compared with the rate of change in healthy controls. Statistical significance was set at $p < 0.05$.

RESULTS *LRRK2* gene mutation status is shown in table 1. The mutation positive subjects all carried the R1441C mutation in the *LRRK2* gene. Subjects 1 and 2 had clinically definite PD of less than 1 year duration with UPDRS scores of 7 and 6 respectively and their baseline scans were included in an earlier report.⁴ These subjects (who became symptomatic in their sixth and eight decades, respectively) were not taking antiparkinsonian medications and the remaining subjects were asymptomatic at the time of initial evaluation. Mean age ± SD of asymptomatic mutation carriers (including genealogically at risk subject 13, who declined DNA analysis) at the time of the first scan was 57.2 ± 7.0 (range: 52–71 years) and that for non-mutation carriers was 60.2 ± 12.3 (range: 43–72 years).

PET measurements. Cross-sectional analysis of initial visit. Putaminal tracer binding/uptake values in family D subjects and controls are shown in table 2 (absolute values) and in figure 1 (expressed as percentage of normal control values). Mutation-negative subjects 3–7 had values which were statistically within the normal range (FD Kocc: 0.0088 to 0.0122 minutes^{−1} [90.8–125.5% of normal]; BP_{DTBZ} : 0.9251 to 1.0461 [97.0–109.7%]; and age adjusted BP_{MP} : 1.2169 to 1.4827 [97.9–119.3%]). Subject 6 could not complete the FD scan. In subjects 1 and 2 (symptomatic mutation carriers), PET abnormalities demonstrated asymmetry and rostrocaudal gradient typical of sporadic PD. In subjects 8–10 (asymptomatic mutation carriers), age-adjusted

Table 2 Putaminal* PET measurements in family D subjects and controls

Subjects	Mutation status	FD Kocc (min ⁻¹)		DTBZ BP		Age-adjusted MP BP	
		Initial visit	Follow-up	Initial visit	Follow-up	Initial visit	Follow-up
1	+	0.0080*		0.5255*		0.8544*	
2	+	0.0062*		0.4259*		0.5135*	
3	–	0.0088	0.0085	1.0461	0.9820	1.4827	1.2629
4	–	0.0122		0.9555		1.2546	
5	–	0.0104	0.0102	0.9251	0.8867	1.2237	1.1858
6	–			1.0036		1.2169	
7	–	0.0095		0.9325		1.2564	
8	+	0.0099	0.0088	0.9003	0.7044*	0.9056*	0.9305*
9	+	0.0083	0.0072*	0.5997*	0.4836*	0.6563*	0.7193*
10	+	0.0099		0.8034		0.911*	
11	+	0.0096		0.8894		0.9970	
12	+	0.0081		0.9178		1.0517	
13	N/A	0.0089	0.0083	0.7866	0.7191*	1.1919	0.9477*
Normal controls (n = 34), mean ± SD		0.0097 ± 0.0010		0.9536 ± 0.1162		1.2425 ± 0.2570	
sPD controls (n = 75), mean ± SD		0.0046 ± 0.0015*		0.3608 ± 0.1480*		0.4917 ± 0.2147*	

*Mean putaminal values (average of measurement of the two sides).

*Significantly abnormal values.

FD = ¹⁸F-6-fluoro-L-dopa; Kocc = uptake rate constant; DTBZ = ¹¹C-(±)-α-dihydrotetrabenazine; BP = binding potential; MP = ¹¹C-d-threo-methylphenidate; sPD = sporadic Parkinson disease.

MP values (BP_{MP} 0.9056 [72.9%], 0.6563 [52.8%], and 0.911 [73.3%]) were reduced ($p < 0.05$) relative to the normal data. Subject 8 had FD Kocc and BP_{DTBZ} within the normal range. In addition to reduced DAT binding, subject 9 had reduced DTBZ binding in the putamen (BP_{DTBZ} 0.5997 [62.9%], $p = 0.001$), while FD uptake (Kocc = 0.0081 minutes⁻¹ [81.2%]) was reduced in the left putamen only ($p = 0.047$). In subject 10, FD uptake was normal while BP_{DTBZ} was marginally reduced in the left putamen (BP 0.7567 [77.1%], $p = 0.055$). Subjects 11 and 13 demonstrated normal uptake/binding of all three tracers, while subject 12 showed a decline in right putaminal FD uptake (Kocc = 0.0078 minutes⁻¹ [81.2%], $p = 0.049$).

Cross-sectional analysis of follow-up visit. Among the subjects who were rescanned, mutation negative subjects 3 and 5 had no demonstrable reduction in tracer binding relative to healthy controls (figure 2). Of the mutation positive individuals, the motor UPDRS score (conducted at the time of PET) in subject 8, who had previous poliomyelitis, was 10. Follow-up scans in this subject now revealed reduced DTBZ (BP_{DTBZ} = 0.7044 [73.9%], $p = 0.017$) and MP binding (age-corrected BP_{MP} 0.9305 [74.9%], $p = 0.032$) relative to healthy controls, while FD uptake was 90.2% of normal (Kocc = 0.0088 minutes⁻¹, $p = 0.182$). This subject has still not been diagnosed with clinical PD by his or her treating physicians.

Subject 9 had subtle clinical parkinsonism with a motor UPDRS score of 9 at follow-up. In this subject, mean putamen FD uptake, DTBZ, and MP binding were reduced relative to healthy controls (FD Kocc 0.0072 minutes⁻¹ [74.1%], $p = 0.009$, BP_{DTBZ} 0.4836 [50.7%], $p < 0.001$; and age-adjusted BP_{MP}, 0.719 [57.9%], $p = 0.001$). In subject 13, age-adjusted putaminal MP binding was reduced to 76.3% (BP_{MP} 0.9477, $p = 0.04$); BP_{DTBZ} was 0.7191 (75.4%, $p = 0.023$) and FD uptake was reduced in the left putamen (Kocc = 0.0078 minutes⁻¹ (78.1%), $p = 0.026$). Motor examination in this subject was normal (motor UPDRS score of 1).

Longitudinal analysis of initial and follow-up visits. The two longitudinal PET measurements showed high correlations in subjects 3, 5, 8, 9, and 13, who were rescanned (Pearson's r : 0.926 for Kocc × 100; 0.948 for BP_{DTBZ}; and 0.977 for BP_{MP}, $p < 0.001$). In the mutation carrier subject 8, the annual rate of decline in BP_{DTBZ} was -0.067 ± 0.013 (mean ± SE), $p < 0.001$, in comparison to zero and healthy controls. In this subject, the repeat absolute measurements of FD uptake were within the normal range, the slope of decline (Kocc × 100) was -0.04 ± 0.014 , significantly different from zero and from healthy controls. In subject 9 (mutation carrier with phenoconversion), there was a decline in BP_{DTBZ}

N = normal controls; FD = [18 F]-fluoro-L-dopa; DTBZ = [11 C]-dihydrotetrabenazine; MP = [11 C]-d-threo-methylphenidate. *Significantly reduced tracer binding vs normal controls.

(-0.04 ± 0.014) and $K_{occ} \times 100$ (-0.036 ± 0.014) different from zero and from healthy controls ($p < 0.05$). BP_{MP} in subjects 8 and 9, which was already outside the normal range at baseline (figure 3), remained unchanged during the study period. While the slope of decline in DAT binding (-0.118 ± 0.016) was distinctly abnormal ($p < 0.001$) in subject 13 (genealogically at-risk subject with unknown genotype) (figure 3), the rate of decline in BP_{DTBZ} and K_{occ} in the mean putamen was not different from control values.

DISCUSSION The baseline PET findings in family D subjects 1–6, 8, 9, 10, and 13, including clinically affected subjects 1 and 2, were described earlier.⁴ In this communication, we present the PET findings of

three additional subjects, 7, 11, and 12, and progression of neurochemical changes in subjects 3, 5, 8, 9, and 13. The subjects in whom follow-up data are presented here are different from those previously reported.⁴ The current work documents for the first time the progression of dopaminergic dysfunction in family D kindred, at both clinical and subclinical (PET) levels. PET revealed dopaminergic abnormalities in mutation carriers even in the absence of clinically evident parkinsonism. In subjects 8, 9, and 10 even at the initial visit, and 13 at the time of second scan, significantly reduced MP binding with normal or borderline decline in FD uptake and reduced or normal DTBZ binding were in keeping with down-regulated DAT expression and upregulated dopa decarboxylase activity in early PD.⁶ However, although subject 13 was genealogically at risk, the genotype of subject 13 is not known and findings in this subject must be interpreted with caution.

In subjects 8, 9 (mutation carriers), and 13 (genealogically at risk subject), there was a decline in PET markers over the course of the study that was significantly greater than the expected rate of change in healthy controls. During the study period, VMAT 2 density in subject 8 changed from being normal at baseline scan to abnormal reduction relative to healthy controls at follow-up. Interestingly, the repeated measurements of FD uptake were within normal range, while the annual rate of decline in K_{occ} was significantly abnormal. In subject 9, we have documented the progression from subclinical neurochemical change to clinical disease. In the presymptomatic phase, this subject had abnormal VMAT 2 and DAT binding in the putamen along with borderline decline in FD uptake (in the left putamen only) cross-sectionally. FD uptake became abnormally (bilaterally and asymmetrically) low in the symptomatic stage. The previously abnormal DAT binding in subjects 8 and 9 did not reveal further decline during the study period. On the other hand, in subject 13, there was marked longitudinal reduction in DAT binding over the course of study. This subject also demonstrated abnormality in the other facets of DA processing (from normal VMAT 2 binding and FD uptake at baseline to abnormal reduction at follow-up), although the rates of decline in BP_{DTBZ} and K_{occ} were not significant. Our findings indicate that PET abnormalities can identify asymptomatic subjects early in the illness who might then go on to develop subtle disease on follow-up. In families with unknown genotype, such characterization in vivo may allow reclassification of subject thought to be normal on clinical grounds, but who have a high probability of carrying the as yet unidentified mutation. Recruitment of such subjects with

N = normal controls; FD = [18 F]-fluoro-L-dopa; DTBZ = [11 C]-dihydrotetrabenazine; MP = [11 C]-d-threo-methylphenidate. *Significantly reduced tracer binding vs normal controls.

Figure 3 Dopamine transporter (DAT) binding vs age in the healthy controls and family D subjects (the actual observed values without applying age correction) at initial (denoted by [a] in those subjects who were rescanned) and follow-up (b) PET assessment

The superimposed solid lines represent ^{11}C -d-threo-methylphenidate (MP)-age regression line (middle line) and 95% confidence bands (upper and lower lines) in the healthy controls.

subclinical dopaminergic dysfunction would be expected to improve the power of multiplex pedigrees and the value of linkage statistics in disease gene identification. PET endophenotype has also been explored and found to be useful under simulated phenoconversion in genetic linkage studies.¹¹ Our study, despite the limitation of small sample size, provides further credence to the utility of PET in this regard. Indeed, the identification of asymptomatic subjects with dopaminergic dysfunction on PET imaging provided much assistance in subsequent tracking of the genetic mutation in this kindred.

Reduced DAT binding was the earliest indication of dopaminergic dysfunction in these individuals, implying that DAT imaging is more sensitive in detecting subclinical deficits in the nigrostriatal pathway. Motor function appeared to be preserved until the capacity to synthesize and store dopamine, as assessed by FD uptake, was impaired. The possible exception to this was subject 8, who had abnormal DTBZ and MP binding, but normal FD uptake over the study course. Subject 8 had prior polio which might have affected the clinical findings. As noted above, FD uptake in this subject did decline significantly between the two visits. However, study of a much larger sample of subjects is required to ascertain the relationship between the evolution of motor dysfunction and changes in PET markers. As the subjects were not taking antiparkinsonian medication because of asymptomatic status or very early disease, there was no lingering drug effect on tracer binding/uptake. The mutation negative subjects were included and followed up with PET, as the investigators were blinded as to the mutation status of the kindred during the study period. These subjects served as internal controls with similar genetic and environmental background.

The neurochemical abnormalities as assessed with

PET and the clinical expression of PD are both age dependent. In a clinical study of *LRRK2* R1441C mutation carriers (including family D members) from three continents, more than 90% of carriers became symptomatic by the eighth decade, whereas fewer than 20% manifested with PD before age 50.¹² Asymptomatic individuals older than 80 years and heterozygous for G2019S mutation have been described.¹³⁻¹⁵ PET findings in these subjects are not known. Subject 11 (asymptomatic mutation carrier), who demonstrated normal tracer binding on PET imaging, was at least 10 years younger than the mean age at onset of motor symptoms in family D. Hence, continued follow-up of the presently asymptomatic subjects is essential to ascertain the progression to subclinical dopaminergic dysfunction and later development of clinical disease, and for the purpose of genetic counseling. Longitudinal follow-up of more of these subjects should ultimately permit a more precise estimation of the preclinical period. Further, such in vivo assessment will be useful in characterizing the progression of early disease. Familial subjects represent an ideal group in which to study potential neuroprotective strategies aimed at arresting or delaying the clinical onset of PD. Potential reasons for the failure of past neuroprotective studies include application of rescue or restorative measures late in the cellular neurodegeneration (i.e., in early symptomatic subjects) in pathogenetically heterogeneous disorders (such as sporadic PD). In contrast to the marked heterogeneity observed in sporadic PD, *LRRK2* families provide a more powerful, homogeneous population and multitracers PET imaging, by identifying subclinical dopamine dysfunction, might permit selection of individuals during the window of maximum potential benefit. Such considerations have relevance for other neurodegenerative disorders.

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