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Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson's Disease

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Abstract

Dopamine (DA) transporter (DAT) imaging has been studied as a diagnostic tool for degenerative parkinsonism. Our aim was to measure the prognostic value of imaging for motor and nonmotor outcomes in Parkinson's disease (PD). We prospectively evaluated a Parkinson's cohort after enrollment in a de novo clinical trial with a battery of motor (UPDRS), cognitive (Montreal Cognitive Assessment), and behavioral measures. DAT imaging with [^{123}I][β]-CIT and single-photon emission computerized tomography (SPECT) was performed at baseline and after 22 months. In total, 491 (91%) of the 537 subjects had evidence of DA deficiency on their baseline scan, consistent with PD, and were included in the analyses. The cohort was followed for 5.5 (0.8) years, with a mean duration of diagnosis of 6.3 (1.2). Lower striatal binding at baseline was independently associated with higher risk for clinical milestones and measures of disease severity, including motor-related disability, falling and postural instability, cognitive impairment, psychosis,

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and clinically important depressive symptoms. Subjects in the bottom quartile for striatal binding, compared to the top quartile, had an odds ratio (95% confidence interval) of 3.3 (1.7, 6.7) for cognitive impairment and 12.9 (2.6, 62.4) for psychosis. Change from baseline in imaging after 22 months was also independently associated with motor, cognitive, and behavioral outcomes. DAT imaging with [^{123}I][β]-CIT and SPECT, shortly after the diagnosis of PD, was independently associated with clinically important long-term motor and nonmotor outcomes. These results should be treated as hypothesis generating and require confirmation.

Keywords

Parkinson's disease; dopamine transporter; imaging; prognosis

The clinical progression of Parkinson's disease (PD) is heterogeneous.[1] Predictors of clinical outcomes would be useful for clinical research and clinical care, but the development of prognostic tests requires long-term follow-up of large cohorts for adequate precision. Dopamine (DA) transporter (DAT) imaging has been studied extensively as a potential diagnostic tool for identifying patients with degenerative forms of parkinsonism. However, there are little long-term data on the prognostic value of DAT imaging or other DA-based imaging modalities in PD, especially for nonmotor outcomes.[2,3]

We report on the use of DAT imaging for predicting outcomes in a large PD cohort that was followed prospectively after enrollment in a *de novo* PD clinical trial.[4] Subjects were initially imaged within months of diagnosis, before they were taking any dopaminergic therapy. This cohort has now been systematically followed for over 5 years, providing an opportunity to examine the relationship between DAT imaging and the progression of motor and nonmotor signs and symptoms of PD.

Patients and Methods

The PostCEPT cohort consists of 537 subjects who have been followed since they had early, untreated PD. They were originally enrolled in a controlled clinical trial of a mixed-lineage kinase inhibitor (PreCEPT trial) and were not taking any antiparkinsonian medications at baseline.[5] They are now participating in an ongoing, longitudinal clinical assessment program for biomarker development in PD (LABS-PD) with annual visits and remote follow-up.[4] Institutional review board approval was obtained for each participating site.

Deidentified data collected in this program are publicly available through the National Institute of Neurological Disorders and Stroke. Motor function assessments include UPDRS) Parts I to IV,[6] Modified H & Y Stage,[7] and the Schwab and England Activities of Daily Living Scale (S/E ADL).[8] The cognitive and behavioral outcomes include the Mini–Mental Status Exam (MMSE),[9] Montreal Cognitive Assessment (MoCA),[10] and the 15-item Geriatric Depression Scale (GDS-15).[11] Quality of life (QoL) was measured using the Parkinson's Disease Quality of Life (PDQ39).[12] When possible, we defined clinically important cutoffs or subscores on the following scales: cognitive impairment (MoCA score <26 and MMSE<24),[13,14] psychosis (UPDRS thought disorder item score ≥2), depressive syndromes (GDS-15≥5),[11] falling (UPDRS falling item scored ≥1), postural instability

(UPDRS postural stability item scored ≥2), the PDQ39 summary score in the highest quartile, and functional decline based on a decline of ≥15 from baseline on the (S/E ADL) score.

Imaging

All subjects received a [^{123}I][β]-CIT single-photon emission computed tomography (SPECT) (β-CIT) scan at the PreCEPT baseline and a follow-up scan approximately 22 months later. β-CIT tracer binds to the DAT on presynaptic dopaminergic nerve terminals in the caudate and putamen.[15] The primary quantitative imaging outcome measure, the striatal binding ratio (SBR) comparing the target β-CIT uptake to an occipital reference region, was determined through a standardized analysis method; this method has been described previously.[16–18] Measures of interest were the SBR at baseline and the annual percent change in β-CIT SBR between the baseline and 22-month scan. Based on a separate database of 100 healthy subjects, baseline PreCEPT scans were categorized as either DAT deficient (≤80% age-expected lowest putamen β-CIT uptake) or not (Scans Without Evidence of Dopaminergic Deficit) (>80% age-expected lowest putamen β-CIT uptake).[18] Only subjects with DAT-deficient scans, consistent with PD, were included in our analyses.

Statistical Analyses

We conducted multiple logistic regression analyses for dichotomous outcome measures and multiple linear regression analyses for continuous outcome measures. We examined the association between the independent variables of striatal binding from baseline β-CIT scans and the dependent variables of motor and nonmotor measures of PD severity assessed at the most recent PostCEPT visit. Mean striatal binding was selected as the primary imaging variable and was divided into quartiles for the primary analyses. In each of the models, we controlled for age, gender, PD duration, randomized treatment assignment in the original PreCEPT clinical trial, and subsequent use of levodopa or DA agonist (DAA) at the most recent assessment. Analyses of S/E ADL decline also included baseline S/E ADL. Similar analyses were performed using annualized changes in β-CIT scans, with the corresponding initial scan variable included in each model. In additional analyses of continuous outcomes, we controlled for baseline measures of PD motor and cognitive impairment using the baseline total UPDRS and MMSE scores; the parameter estimates for β-CIT uptake remained statistically significant and these results are reported in the Supporting Materials. Only subjects who had complete data were included in the analyses. Analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC), and all *P* values were two-sided; *P* values were not adjusted for multiple comparisons.

Results

In total, 491 (91%) of the 537 subjects in the Post-CEPT cohort had evidence of DA deficiency on their baseline β-CIT scan, consistent with PD, and were included in the analyses. At the PreCEPT baseline visit, these subjects had a mean age (standard deviation; SD) of 59.6 (SD, 9.4), total UPDRS scores of 23.4 (SD, 9.5), and S/E ADL scores of 93.0 (SD, 4.9) and were not taking any antiparkinsons therapy. Sixty-six percent were male. Table 1 shows the characteristics of this cohort at the PreCEPT baseline and at the most recent

annual assessment. The cohort had an average duration of illness of 6.3 (SD, 1.2) years and was prospectively followed for 5.5 (SD, 0.8). The relatively small change in UPDRS scores is the result of the fact that, at baseline, subjects were not taking dopaminergic therapy, but were on dopaminergic therapy at follow-up. At the most recent assessment, 79 (16%) were on a DAA, 174 (35%) were on L-dopa, and 200 (41%) were on both. Table 2 shows mean (of left and right) baseline β-CIT striatal binding and annualized percentage changes from baseline to follow-up imaging, which occurred 1.9 (SD, 0.1) years after baseline.

Multiple logistic regression models show consistent relationships between baseline β-CIT binding in the striatum and clinically important motor and nonmotor dichotomous outcomes (Table 3). Lower striatal binding of β-CIT at baseline is associated with a significantly higher risk for motor-related disability, falling and postural instability, cognitive impairment, psychosis, and clinically important depressive symptoms. For example, subjects in the bottom quartile had an odds ratio (OR; 95% confidence interval; CI) of 12.9 (95% CI: 2.6, 62.4) for developing psychosis and 3.3 (95% CI: 1.7, 6.7) for having a MoCA <26, as compared to the top, reference quartile.

Linear regression analyses show the effect of presynaptic DA deficits in the striatum based on continuous measures of PD severity (Table 4). Subjects in the bottom quartile had a 1.9-unit greater decline in MoCA scores and a 7.1-unit increase in UPDRS part III (motor) scores, when compared with those in the top quartile, despite adjusting for concomitant Parkinson's medications and baseline demographics. Associations for UPDRS parts II (activities of daily living; ADL) and III (motor) were significant for both the caudate and putamen individually (see Supporting Table 1).

The association of baseline β-CIT binding with motor outcomes remained significant when adjusting for baseline total UPDRS score (Supporting Table 2). Similarly, the association of cognitive outcomes with imaging remained significant after adjusting for baseline MMSE score (Supporting Table 3). This suggests that DAT imaging offers prognostic information that may complement these clinical scales.

Follow-up scans were obtained for 461 subjects at 22 months. Annualized change in striatal β-CIT binding (Table 2) was associated with dichotomous and continuous outcomes (Table 5 and Supporting Tables 4). For example, subjects in the bottom quartile had an observed annual decline in striatal β-CIT binding of −12.02% (−23.88, −8.45). These subjects had an OR of 2.1 (95% CI: 1.1, 3.9) for having a MoCA score of <26 and 5.4 (95% CI: 1.2, 23.7) for having an MMSE score of <24, as compared to those in the top quartile of annualized change.

Discussion

These findings show that DAT imaging, within approximately 2 years of the clinical diagnosis of PD, is associated with important motor and nonmotor outcomes after 5 to 6 years of follow-up. Subjects with lower baseline striatal binding were more likely to develop motor-related disability as well as cognitive impairment, psychosis, and depression. DAT imaging with β-CIT and SPECT is independently associated with these outcomes and may

complement clinical assessments of disease severity. DAT imaging remained significantly associated with the long-term clinical outcomes when controlling for PD duration at baseline, age, gender, PD medications at the time of assessment, and baseline PD severity, as measured by total UPDRS score and MMSE. For many of the measured outcomes, there was a dose-response relationship, such that subjects in the second and third quartiles had intermediate risk for worse motor and nonmotor outcomes.

The strength of the observed associations vary with outcome of interest and imaging measure. For example, those in the bottom quartile of mean striatal binding at baseline had a 7.1-unit worsening in UPDRS part III scores, relative to the top quartile, after more than 5 years of follow-up. This finding was largely driven by putamen uptake. A 1-unit higher putamen value at baseline (nearly 1 SD) was associated with a 4.6-unit lower (less severely affected) UPDRS part III (motor) score and a 2.3 lower (less affected) UPDRS part II (ADL) score (Supporting Table 1). These are clinically meaningful outcomes[19] and are comparable in magnitude to changes observed with the initiation of low-dose L-dopa[20] or DAA.[21] This finding is notable, because most of these subjects were on PD medications and were being treated by experienced clinicians in the Parkinson Study Group. The association of imaging with motor outcomes remained statistically significant after adjusting for baseline motor UPDRS (Supporting Table 2), but accounted for only a small increase (approximately 1.3%) in overall variability in outcomes explained by the model, which also included baseline demographics and dopaminergic treatment. The clinical utility of these findings for motor and nonmotor outcomes, beyond baseline clinical measures, is not known and will require further study.

The strength of the associations was smaller for the changes based on the follow-up scans than for the baseline scans. This suggests that striatal dopaminergic deficits near the time of diagnosis may have more prognostic value than the subsequent rate of change over 22 months. The initial scan may reflect years of degeneration and/or a faster rate of DAT decline in the early stages of disease.

The mechanistic interpretation of the associations of DAT imaging with motor and nonmotor outcomes is uncertain. The imaging findings may reflect the extent of more-widespread, but otherwise unmeasured, neuronal pathology. For example, alpha-synuclein expression has been shown to reduce DAT on the cell surface in several cell lines, including cultured neurons.[22] Alternatively, these results may reflect specific deficits resulting from striatal DA deficiency. There are aspects of the data that support both hypotheses. The fact that we found DAT imaging with SPECT to be broadly associated with a range of cognitive and behavioral outcomes suggests a lack of specificity. Although we did not examine subregions of the caudate and putamen, as would be expected, overall putamen uptake was more strongly related to motor function than the caudate.[16, 23] This suggests that the observed associations may be relatively specific to dopaminergic innervations of the striatum.

Dopaminergic projections from the tegmental area and substantia nigra modulate the activity of medium spiny neurons, the main output neurons of the striatum, and thereby modulate memory, learning, motivation, and affective control.[24] Three striatal outflow circuits support nonmotor behaviors often affected in PD, including projections to the dorsolateral prefrontal

cortex (working memory and mental flexibility),[25] the anterior cingulate gyrus (response selection and motivation), and the orbital-frontal cortex (inhibition and release of instinctive, intellectual, and affective behaviors).[26,27] The relationship between striatal DA and the cognitive and behavioral manifestations of PD has been shown in cross-sectional imaging studies in PD subjects. One study using ^{99mc}Tc-TRODAT-1, a DAT tracer, with SPECT showed that anxiety and depression scores in PD subjects were correlated with decreased uptake in the left putamen among subjects with a moderate duration of PD (mean, 5.8 ± 5.4 years), similar to subjects in our study.[28] In a separate study using a different DAT tracer, ^{123}I-FP-CIT, and subjects with an average PD duration of 7.5 years (± 5.5), higher scores on the Montgomery Asberg Depression Rating Scale, indicating more depressive symptoms, were correlated with lower DAT uptake in the striatum bilaterally ($r = -0.51$). DAT uptake in the caudate was also related to executive function, as measured by the Tower of London Task.[29] Taken together with the PostCEPT longitudinal findings, these studies suggest that measurement of striatal DAT *in vivo* may help explain the heterogeneity in the cognitive and behavioral manifestations of PD.

Previous longitudinal studies have found more-limited relationships between dopaminergic imaging and motor and nonmotor outcomes.[3] However, the current study is considerably larger and longer than previous studies and used more extensive cognitive and behavioral assessments than most clinical trial cohorts.[20,21]

There are potential sources of random error and bias in the collection of the data and in the analytical approach that may have affected the observed results. This study was retrospective and these results should be treated as hypothesis generating and requiring replication. Because of the exploratory nature, we did not adjust for multiple comparisons. This is a *de novo* clinical trial cohort, not a community-based cohort. The utility of DAT imaging may depend on the timing of the evaluation or the type of subject that enrolled in the trial. However, homogenous samples, such as clinical trial cohorts, and the drop out that occurred during follow-up tend to reduce the ability to find associations and are therefore an unlikely explanation for the observed results. Although we did adjust for baseline PD motor severity with UPDRS scores, not all of the cognitive and behavioral measures were collected at baseline. We could only adjust for baseline MMSE to assess whether or not DAT is an independent predictor of cognitive outcomes (follow-up MMSE remained significantly associated with DAT imaging). This is a limitation of using a clinical trial cohort, and future studies addressing this issue should use more-extensive cognitive assessments from baseline through follow-up. DAT imaging is not a direct measure of the number or function of dopaminergic neurons, and the issue of whether or not medications could alter DAT uptake remains open to debate.[30] However, subjects were not taking dopaminergic drugs at baseline and had not for at least 6 months. Additionally, we adjusted for both baseline PD severity and PreCEPT study medication, as well as PD medication use at the time of follow-up assessment, to assure that imaging was treated as an independent predictor of outcomes beyond the response to dopaminergic therapy. Finally, in our analyses, we divided DAT uptake into quartiles for the purposes of determining if there is an association with clinical outcomes. We did not examine smaller increments of DAT uptake that may confer differences in risk for clinical outcomes, although this could be explored in future prospective studies.

These findings indicate that DAT imaging, especially shortly after diagnosis, may be useful in understanding clinical progression and support the focused use of DAT and other DA-imaging modalities in longitudinal studies. The Parkinson's Progression Marker Initiative, sponsored by the Michael J. Fox Foundation (http://www.michaeljfox.org), is an ideal cohort in which to attempt to replicate these findings. This 5-year, early PD study includes annual DAT imaging, blood and colony-stimulating factor biomarkers, along with motor- and domain-specific cognitive assessments. Continued follow-up of a large proportion of the original cohort in the LABS-PD study[5] will provide important insights into the use of DAT imaging and other clinical and biological markers for predicting parkinsonian disability. Identification of individuals at higher risk for adverse outcomes with imaging modalities may enhance clinical care and provide enriched populations for future clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Cohort characteristics at baseline and most recent assessment

	PreCEPT Baseline* N = 491 Mean (SD)	PostCEPT Most Recent Visit N = 491 Mean (SD)
Age, years	59.61 (9.43)	65.13 (9.39)
Duration of symptoms, years	2.06 (1.38)	7.58 (1.63)
Duration since diagnosis, years	0.79 (0.80)	6.31 (1.19)
MMSE exam	29.34 (0.99)	28.65 (2.48)
Total UPDRS	23.42 (9.50)	31.84 (17.37)
UPDRS motor	16.53 (7.34)	21.34 (11.71)
UPDRS ADL	6.18 (3.23)	8.93 (6.11)
S/E ADL	92.97 (4.85)	87.15 (11.85)
MoCA	NA	26.31 (3.71)
GDS	NA	2.60 (2.61)
Years of follow-up	NA	5.52 (0.81)

*Patients at baseline of PreCEPT were not receiving L-dopa or DAA. Abbreviation: NA, not available.

TABLE 2

Striatal DAT binding at baseline and follow-up imaging after 22 months

	PreCEPT Baseline Scan N = 491 Mean (SD)	**Annualized % Change N = 461 Mean (SD)**
Ipsilateral caudate	4.99 (1.11)	−2.79 (6.78)
Ipsilateral putamen	2.54 (0.71)	−7.43 (8.67)
Contralateral caudate	4.38 (1.03)	−3.40 (6.96)
Contralateral putamen	1.95 (0.47)	−5.02 (11.13)
Mean caudate	4.69 (1.04)	−3.13 (6.43)
Mean putamen	2.24 (0.55)	−6.69 (7.91)
Mean striatum	3.46 (0.76)	−4.37 (6.13)
	Mean (Range)	Mean (Range)
Quartiles mean striatum		
Q1	2.53 (1.57, 2.94)	−12.02 (−23.88, −8.45)
Q2	3.19 (2.94, 3.40)	−6.28 (−8.40, −4.53)
Q3	3.67 (3.40, 3.93)	−2.76 (−4.48, −0.73)
Q4	4.47 (3.93, 6.13)	3.58 (−0.65, 17.89)

TABLE 3

ORs for dichotomous outcomes by quartiles of baseline mean striatal binding

	Number of Subjects	Outcome Rate (%)	*P* Value for Trend	ORs (95% CI)			
				Q1	Q2	Q3	Q4
MMSE <24	491	19 (3.9)	0.0293	7.6 (0.8, 68.4)	5.8 (0.6, 51.7)	2.3 (0.2, 26.7)	1
MoCA <26	489	137 (28.0)	0.0002	3.3 (1.7, 6.7)	1.7 (0.9, 3.4)	1.4 (0.7, 2.8)	1
Psychosis	491	34 (6.9)	0.0002	12.9 (2.6, 62.4)	6.4 (1.3, 30.9)	3.0 (0.6, 16.3)	1
GDS >=5	490	97 (19.8)	0.0056	2.8 (1.3, 5.7)	1.8 (0.9, 3.6)	1.4 (0.7, 2.8)	1
Postural instability	488	37 (7.6)	0.0018	4.9 (1.6, 15.2)	2.0 (0.7, 6.4)	0.9 (0.2, 3.3)	1
Falling	490	60 (12.2)	0.0089	2.2 (0.9, 5.1)	1.7 (0.7, 3.7)	0.4 (0.1, 1.2)	1
QoL decline	489	122 (25.0)	0.0537	1.8 (0.9, 3.4)	1.3 (0.7, 2.4)	0.9 (0.5, 1.8)	1
S/E ADL decline ≥ 15	490	67 (13.7)	0.0066	2.8 (1.2, 6.3)	1.1 (0.5, 2.5)	0.7 (0.3, 1.6)	1

ORs (95% CIs) from separate logistic regressions adjusted for age, gender, duration of disease, and PreCEPT study treatment, as well as for use of DAAs and/or L-dopa at most recent visit. S/E ADL analysis was also adjusted for baseline S/E ADL. Mean values for quartiles are shown in Table 2. The highest quartile (4) is the reference category.

TABLE 4

Estimated differences in continuous outcomes by quartiles of baseline mean striatal binding

				Estimated Differences (95% CI)			
		Number of Subjects	***P* Value for Trend**	**Q1**	**Q2**	**Q3**	**Q4**
MMSE	↓	491	0.0067	−0.9 (−1.6, −0.3)	−0.3 (−0.9, 0.3)	−0.2 (−0.8, 0.4)	0
MoCA	↓	489	<0.0001	−1.9 (−2.9, −1.0)	−0.6 (−1.5, 0.3)	−0.1 (−0.9, 0.8)	0
UPDRS motor	↑	487	<0.0001	7.1 (4.1, 10.1)	2.1 (−0.8, 4.9)	1.7 (−1.1, 4.4)	0
UPDRS ADL	↑	489	<0.0001	3.3 (1.7, 4.9)	1.3 (−0.2, 2.9)	0.3 (−1.2, 1.7)	0

Parameter estimates (95% CIs) from separate multiple regressions adjusted for age, gender, duration of disease, and PreCEPT study treatment, as well as for use of DAAs and/or L-dopa at most recent visit (or assessment). Arrow indicates direction of worsening. Mean values for quartiles are shown in Table 2. The highest quartile is the reference category.

TABLE 5

ORs for dichotomous outcomes by quartiles of annual percentage change in mean striatal binding

				ORs (95% CI)			
	Number of Subjects	**Outcome Rate (%)**	***P* Value for Trend**	**Q1**	**Q2**	**Q3**	**Q4**
MMSE <24	461	19 (4.1)	0.0385	5.4 (1.2, 23.7)	0.4 (0.0, 4.6)	2.1 (0.4, 10.3)	1
MoCA <26	459	129 (28.1)	0.0278	2.1 (1.1, 3.9)	1.3 (0.7, 2.6)	1.2 (0.6, 2.3)	1
Psychosis	461	32 (6.9)	0.0018	6.4 (1.9, 21.3)	2.5 (0.7, 9.3)	2.4 (0.6, 8.7)	1
GDS >=5	460	90 (19.6)	0.1304	1.6 (0.8, 3.2)	2.0 (1.0, 4.0)	1.3 (0.7, 2.8)	1
Postural instability	459	35 (7.6)	0.5030	1.4 (0.5, 3.7)	0.8 (0.3, 2.5)	0.8 (0.3, 2.3)	1
Falling	460	57 (12.4)	0.0485	2.1 (0.9, 5.3)	3.0 (1.2, 7.1)	1.7 (0.7, 4.1)	1
QoL decline	459	113 (24.6)	0.4453	1.2 (0.7, 2.4)	1.5 (0.8, 2.9)	1.3 (0.7, 2.5)	1
S/E ADL decline ≥ 15	460	63 (13.7)	<0.0001	6.5 (2.4, 17.8)	6.1 (2.3, 16.7)	2.6 (0.9, 7.5)	1

ORs (95% CIs) from separate logistic regressions adjusted for baseline mean striatum, age, gender, duration of disease, and PreCEPT study treatment, as well as for use of DAAs and/or L-dopa at most recent visit. S/E ADL analysis was also adjusted for baseline S/E ADL. Mean values for quartiles are shown in Table 2. The highest quartile is the reference category.