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Research Article

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Parkinson's Disease Dyskinesias Possibly Relate to Greater Dopamine Transporter Losses in the Putamen Over Time

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Abstract

The pathophysiology of levodopa-induced dyskinesias in Parkinson's disease is incompletely understood. This study was designed to investigate in Parkinson's patients, whether time-related changes in striatal dopamine transporter availability are associated to the appearance of dyskinesias. 15 Parkinson's patients had dopamine transporter-specific SPECT imaging with ^{123}I-FP-CIT twice: at baseline (when they were drug naïve) and at follow-up (6.31 ± 2.29 years from baseline), and were followed up clinically every six months. At the end of the study, patients were divided in two groups according to whether they had developed dyskinesias or not. Semi-quantification of ^{123}I-FP-CIT data was performed using the occipital cortex as the reference region. Specific binding ratios were calculated for the putamen and the caudate. During the clinical follow-up, all Parkinson's patients were treated pharmaceutically. 8 patients developed dyskinesias, while 7 remained nondyskinetic. At baseline, the two groups had similar ^{123}I-FP-CIT specific binding ratio values for the putamen and the caudate ($p > 0.05$). Also, between-group differences in age, disease duration, and Hoehn & Yahr scores were not statistically significant. Over-time, the putaminal ^{123}I-FP-CIT specific binding ratio values in the dyskinetic group decreased significantly ($p < 0.01$). The nondyskinetic patients had smaller reductions ($p < 0.05$) during the same period of time. At follow-up, the dyskinetic patients had significantly higher Hoehn & Yahr scores ($p < 0.01$) and were taking higher levodopa equivalent doses ($p < 0.001$), as compared to the nondyskinetic patients. The development of Parkinson's dyskinesias is related to a faster progression rate, as reflected by marked putaminal dopamine transporter decreases.

Keywords

Parkinson's disease, Dyskinesias, Putamen, Striatum, Single photon emission computed tomography, Imaging

Abbreviations

^{123}I-FP-CIT: [123I]N-w-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane; AIMS: Abnormal involuntary movements; DAT: Dopamine transporter; DD_{diagn}: Disease duration from diagnosis; H&Y: Hoehn and Yahr; LED: Levodopa equivalent dose; LED_{Dag}: Dopamine agonist equivalent dose; LED_{Ldopa}: Levodopa equivalent dose; LED_{Total}: Total dopaminergic-levodopa equivalent dose; LIDs: Levodopa-induced dyskinesias; PD: Parkinson's disease; SBR: Specific binding ratio; VOI: Volume of interest

Introduction

As Parkinson's disease (PD) progresses, the response to levodopa typically

decreases [1] and patients become at risk [1-3] for experiencing levodopa-induced dyskinesias (LIDs). Presynaptic mechanisms have been of great interest [4] and several studies suggest that peak dose LIDs are related to mishandling of exogenous levodopa within the striatum [3, 5-9]. However, the underlying mechanisms that lead to LIDs are still not completely understood. The dopamine transporter (DAT) is a presynaptic protein with a key role in dopamine neurotransmission and is a sensitive marker of the dopaminergic neuronal integrity [10]. Available striatal DAT sites diminish in the course of PD [11], and age is proposed to have a slight and uneven effect on it, as compared to the physiological decline that occurs with aging [12, 13]. *In vivo* imaging of the DAT with SPECT [14] has become available in an increasing number of movement disorders clinics. Notwithstanding its impact on the diagnosis of PD, DAT-specific SPECT has not been very conclusive as to whether it can predict the appearance of LIDs [15, 16] nor has it been extensively used to study PD progression in this context. In the present longitudinal SPECT study, we intended to explore whether time-related changes in striatal DAT availability are related to the appearance of future LIDs. We hypothesize that PD patients who develop LIDs relatively soon have marked decreases of striatal DAT availability over time.

Methods

Regulatory approvals

The study was approved by the West London Research Ethics Committee, the Imperial College Joint Research Compliance Office and the Administration of Radioactive Substances Advisory Committee, UK. All participants provided their written consent.

Participants, clinical data and scanning procedures

15 participants with PD were included in this study. The diagnosis of PD was confirmed following the Queen Square Brain Bank diagnostic criteria for idiopathic PD [17]. Patients were retrospectively selected from the movement disorders clinics of the Imperial College Healthcare NHS Trust, London, UK. All PD patients were diagnosed by the same clinical team, were reviewed clinically at least every six months and were prescribed levodopa and/or other dopaminergic medicines as part of their clinical care based upon their individual needs. PD patients with a clinical history of depression, cognitive impairment and/or any other neurological or psychiatric disorder were excluded from this study. None of the patients was treated with any drugs with direct action on the serotonergic system. None of the female patients of the study was pregnant or was breast-feeding during their participation in the study.

Each PD patient had two [123I]N-w-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (^{123}I-FP-CIT) brain SPECT scans; at baseline (1.19 ± 1.99 years after clinical diagnosis) and at follow-up (6.31 ± 2.29 years from baseline). At baseline, all PD patients were drug-naïve. During the clinical follow-up, all PD patients were being treated with levodopa and/or other dopaminergic medicines for a minimum of two years. At follow-up, all PD patients were scanned in "off" dopaminergic medication state i.e. PD patients were asked to withdraw from their usual medication (withdrawal time was 20 hours for standard release preparations and 48 hours for the prolonged release preparations). Retrospective clinical data were collected from medical notes and letters to general practitioners. Queries and missing data, whereas applicable, were cross checked with individual PD patients. The following clinical data were collected: disease duration from diagnosis (DD_{diagn}), personal medical and medication history and history of LIDs [including individual abnormal involuntary movement (AIMS) scale scores], and daily levodopa equivalent doses (LEDs) including LED_{Ldopa}, LED_{Dag} and LED_{Total}. LEDs were calculated as described previously [3]. The AIMS scale was administered individually while each participant was in an "on" dopaminergic medication state aiming to confirm the presence or absence of LIDs. During this rating, PD patients were in an outpatient setting and were asked to take their usual medication dose. AIMS scores were recorded over 90 minutes and averaged for each individual (Table 1 contains the mean value of these averaged individual values). Clinical assessment of PD progression was performed using the Hoehn and Yahr (H&Y) staging scale [18] in an "off" medication state. At follow-up, the 15 PD patients were divided in two groups depending on whether they had LIDs (PD LIDs group) or whether they had remained nondyskinetic (PD non-LIDs). Differences were sought between the two groups for clinical characteristics and striatal DAT specific to nonspecific binding at baseline and at follow-up.

The same SPECT imaging procedures were followed for both baseline and follow-up scans. Imaging was performed in accordance to the clinical protocol of the Nuclear Medicine department of Imperial College Healthcare NHS Trust as described previously [3]. All PD patients also had a 1.5 Tesla T1-weighted MRI scan. All MRI scans were visually reviewed by the MRI Radiology Clinic of Imperial College Healthcare NHS Trust, to exclude ischemic disease in the basal ganglia.

^{123}I-FP-CIT SPECT imaging data analysis

A semi-quantification analysis approach for each individual scan was used for the ^{123}I-FP-CIT SPECT imaging data. Acquired SPECT data were transferred to a HERMES-workstation and reconstructed with attenuation, scatter and resolution corrections. The reconstructed tomographic data were analyzed using the commercially available BRASS™ software (HERMES medical solutions, Sweden) [19, 20]. The software uses automatic image registration to align the examinee's SPECT images to their in-house template (HERMES medical solutions, Sweden). This template is made of the scans of twenty healthy controls that have been spatially registered using Hybrid Recon™ software (HERMES medical solutions, Sweden). SPECT images were reconstructed using the default software ordered subset expectation maximization algorithm that incorporates corrections for attenuation, scatter and camera and collimator resolution recovery using Hybrid Recon™ software (HERMES medical solutions, Sweden). SPECT data were corrected for camera-specific image properties as defined by respective phantom measurements. During automatic fitting with BRASS™, the

function used to determine the similarity of the realigned image to the template is the normalised mutual information [21]. The normalised mutual information algorithm is the default setting in BRASS™ for ^{123}I-FP-CIT SPECT studies [22, 23]. Following automatic fitting, a series of predefined volumes of interest (VOIs) were defined based on the in-house template. The VOIs were then applied to the image being analyzed. All scans were inspected visually and, where necessary, manually realigned to fit to the predefined template. SPECT studies with excessive motion were discarded. A volume centered on the occipital cortex was identified and used as an estimate of nonspecific binding in counts/voxel. This volume was then used to scale the counts in each voxel so that to calculate the specific to nonspecific binding ratio (SBR) for that voxel. SBR values for each region were automatically calculated as: SBR = (Target - Background) / Background. The Target value is the counts/voxel for one of the defined regions (eg. the left caudate) and the Background value is the counts/voxel from the occipital cortex, the latter being defined as the reference region. DAT specific to nonspecific binding, as reflected by the ^{123}I-FP-CIT SBR values, was calculated for each caudate and putamen for both hemispheres for each individual. Average SBR values for each VOI were calculated per individual as the mean SBR values for both hemispheres [i.e. (left SBR_{VOI} + right SBR_{VOI})/2].

Statistical analyses

Details of each statistical test are documented in the legends of the tables and figures. Briefly, homogeneity and normality in distribution were tested with Bartlett's and Kolmogorov-Smirnov tests. Comparisons of means (age, DD_{diagn}, daily LEDs, and ^{123}I-FP- SBR values) between groups for either baseline only or follow-up only data were performed with t-test for independent samples. Comparisons of means (daily LEDs, and ^{123}I-FP-CIT SBR values) separately for each group (between baseline and follow-up) were performed with paired t-test for related samples. Comparisons of H&Y scores between PD LIDs and PD non-LIDs groups were performed with Mann-Whitney U test for independent samples (for the baseline only / follow-up only data) and with Wilcoxon signed-rank test for related samples (between baseline and follow-up). Between group comparison of the intervals between the two scans was performed with Mann-Whitney U test for independent samples. For sex, being a categorical variable, chi-squared (χ^2) test was performed. The significance (alpha level) was set at α=0.05; p values below 0.05 were suggestive of statistical significance. Statistical analyses were performed using the IBM SPSS® Statistics software, Version 22 for Microsoft windows. Graph illustrations were performed using the GraphPad Prism software, Version 6 for Microsoft windows.

Results

At follow-up, 8 PD patients had developed LIDs, while 7 remained stable. At baseline, there was no statistically significant difference between the two groups in age, DD_{diagn}, and H&Y staging scores. Over time, the H&Y scores increased significantly in both groups ($p < 0.001$). However, at follow-up, between-group comparison showed that H&Y scores were higher in the dyskinetic group (N = 8) as compared to those in the PD non-LIDs group (N = 7; $p < 0.01$). In addition, LED_{Total} and LED_{Ldopa} doses were significantly higher in the dyskinetic group as compared to the PD non-LIDs group ($p < 0.01$ and $p < 0.001$, respectively) (Table 1).

Table 1: Clinical characteristics of †PD patients at baseline and at follow-up.

No. PD patients	PD non-LIDs		PD LIDs	
	7		8	
[a]Sex	5M:2F		3M:5F [ns]	
	Baseline	Follow-up	Baseline	Follow-up
[b]Age	60.75 ± 8.24	65.64 ± 7.57	52.39 ± 9.80 [ns]	59.95 ± 10.56 [ns]
[b]DDdiagn	1.52 ± 2.53	6.41 ± 2.52	0.94 ± 1.30 [ns]	8.47 ± 3.99 [ns]
[c]H&Y stage	1.50 ± 0.46	2.00 ± 0.46	1.75 ± 0.50 [ns]	2.63 ± 0.33**
AIMS scale score	-	-	-	9.75 ± 3.15
[b]Daily LED_{Total}	-	450.14 ± 138.36	-	943.69 ± 263.83**
[b]Daily LED_{Ldopa}	-	347.29 ± 107.14	-	729.19 ± 203.71***
[b]Daily LED_{Dag}	-	102.86 ± 31.27	-	214.50 ± 60.22 [ns]

† PD patients were categorized to either PD non-LIDs or PD LIDs groups at follow-up.

Data represent mean values ± 1SD; PD: Parkinson's disease; H&Y: Hoehn & Yahr staging scale in "off" medication state; AIMS: abnormal involuntary movements; Age and DDdiagn are calculated in years; Daily LED_{Total}, LED_{Ldopa}, and LED_{Dag} are calculated in mg; [a]Comparison for differences in sex was performed with chi–squared (χ^2) test; [b]Comparison of means was made with t-test for independent samples; [c]Comparison of Hoehn & Yahr scores between LIDs and non-LIDs groups was performed with Mann-Whitney U test; ns–no statistically significant difference between PD non-LIDs and PD LIDs groups for baseline or follow-up time points; **denotes statistical significance $p < 0.01$ between PD non-LIDs and PD LIDs groups for follow-up time point; ***denotes statistical significance $p < 0.001$ between PD non-LIDs and PD LIDs groups for follow-up time point.

The intervals between baseline and follow-up scans were not significantly different in the two groups. At baseline, putaminal ^{123}I-FP-CIT SBR values in the PD LIDs group (1.87 ± 0.41) were not significantly different to the ones in the PD non-LIDs group (2.01 ± 0.73). At baseline, there was also no statistically significant difference between the two groups for the caudate. Over time, all 15 PD patients had significant reductions in their ^{123}I-FP-CIT SBR values in the putamen (1.31 ± 0.45 versus 1.94 ± 0.59; $p < 0.001$) and in the caudate (2.01 ± 0.43 versus 3.06 ± 0.67; $p < 0.001$). At follow-up, putaminal ^{123}I-FP-CIT SBR values were significantly lower (1.12 ± 0.32) in the PD LIDs group as compared to the PD non-LIDs group (1.54 ± 0.46; $p < 0.05$). In the caudate, between-group comparison did not reach a statistically significant difference for ^{123}I-FP-CIT SBR values at baseline neither at follow-up (Figure 1, 2 and Table 2).

Discussion

In this longitudinal SPECT study, we investigated

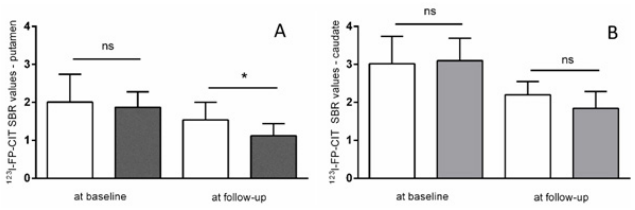

Figure 1: ^{123}I-FP-CIT specific to non-specific binding in the putamen (A) and caudate (B) shown in 7 Parkinson's disease (PD) patients without LIDs (PD non-LIDs: white bars) and 8 PD patients with LIDs (gray bars): at baseline (left), and at follow-up (right). Bars represent mean values +1SD. Mean values are calculated as an average for both hemispheres. Comparison of means was made with t-test for independent samples; ns–no statistically significant difference; *denotes $p < 0.05$ statistical significance.

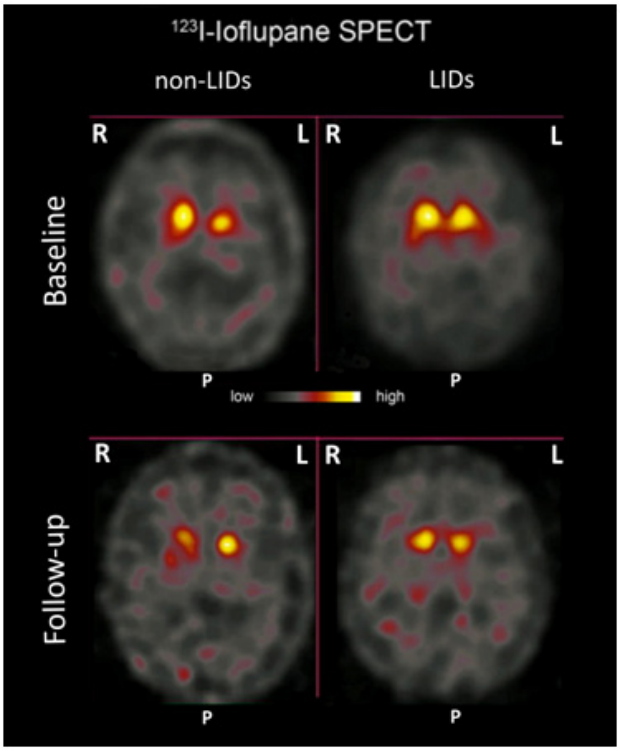

Figure 2: Representative images (on the axial plane) of ^{123}I-FP-CIT specific to non-specific binding in the striatum of two Parkinson's disease (PD) patients at baseline (upper row) and at follow-up (lower row). At baseline, both patients were drug-naïve. At follow-up, both patients had been treated with levodopa for at least two years. At follow-up the patient on the left had not developed LIDs, while the patient on the right had become dyskinetic; L: left; post: posterior; colour scale represents ^{123}I-FP-CIT specific to non-specific binding (from high to low).

whether striatal DAT availability changes in PD are related to the appearance of future LIDs. We found that PD patients who developed LIDs relatively early, had greater losses in striatal DAT availability than those who remained nondyskinetic over the same period of time. The prevalence of LIDs is higher in advanced disease and linked to higher H&Y stages [1]. Our longitudinal study confirms the above finding and supports that PD patients who progress faster (as reflected by the significant changes in their ^{123}I-FP-CIT SBR values and H&Y scores) are susceptible to developing LIDs earlier.

In a similar context, a previous larger study showed that striatal ^{123}I-FP-CIT SPECT SBR values can predict the development of dyskinesias in *de novo* PD [24]. The authors documented the clinical characteristics obtained at the end of the follow-up time point (48 months), however, they did not report the clinical data recorded at enrolment. Considering the significantly lower baseline SBR values for both the caudate and the putamen in the LIDs group [24], we speculate that those patients had more severe motor symptoms at enrolment and consequently were those who developed LIDs sooner. To avoid the above bias, we selected a homogenous group of *de novo* patients which was confirmed by the absence of a statistical difference in the characteristics of the two groups at baseline.

Table 2: Mean ^{123}I-FP-CIT SBR values.

No. of PD patients	Baseline	Follow-Up	Baseline	Follow-Up
	PD non-LIDs		PD LIDs	
	7	7	8	8
^{123}I-FP-CIT SBR values				
Putamen	2.01 ± 0.73	1.54 ± 0.46*	1.87 ± 0.41	1.12 ± 0.32**
Caudate	3.02 ± 0.72	2.20 ± 0.35*	3.10 ± 0.59	1.84 ± 0.45***

Data represent mean ± 1SD. PD: Parkinson's disease. Individual ^{123}I-FP-CIT specific to non-specific binding ratio (SBR) values were calculated as an average for both hemispheres.

Comparison of means was made with paired t-test for related samples; *denotes statistical significance $p < 0.05$ between baseline and follow-up; **denotes statistical significance $p < 0.01$ between baseline and follow-up; ***denotes statistical significance $p < 0.001$ between baseline and follow-up.

A previous report used β-CIT SPECT (DAT-specific) to estimate the rate of striatal DAT decline (relative annual rate) between PD patients who develop LIDs and PD patients who remain free of motor complications over a period of 5 years [25]. Nonetheless, the above study [25] did not directly compare the clinical characteristics of the two PD groups. In our study, the entire PD group (N=15) had variable reductions in their striatal ^{123}I-FP-CIT SBR values over time; however, between-group comparison showed that the two groups were not different for H&Y staging, age and DD_{diagn} at baseline. In addition, in our cohort, the patients who developed LIDs over time showed greater reductions (indicative of a faster decline) in the putamen in comparison to the nondyskinetic patients, and they had also progressed more from a clinical perspective (the dyskinetic PD patients had significantly higher H&Y scores and higher LED_{Total} and LED_{Ldopa} doses).

Imaging studies in controls propose that there is a physiological decline of the striatal DAT expression that is age-related [26] and that this decline is even for the caudate and the putamen [13]. In PD, studies suggest that striatal DAT availabilities decline to a greater extent than in controls

and that DAT losses in the putamen in particular are highly variable [27]. Though there was no statistically significant difference in age and DD_{diagn} between the two groups at baseline, our data for the PD LIDs group show a trend towards a younger age of onset and longer disease duration. These variables have been associated with faster progression and higher risk for developing dyskinesias [1-3]. We believe that the absence of statistical significance for these variables is due to the small sample size.

Based on these two points, and previous work [28-30], we believe that the between-group differences that we observe are not due to a pharmacological effect on striatal DAT expression as medicinal information was obtained in detail by the same clinical team at every visit. In fact, the previous studies in those larger cohorts have commented on this specific topic [28-30], however, due to inconsistency across study designs, findings are not straightforwardly applicable here [31]. We therefore believe that in this cohort, significant increases in the LED doses should be viewed alongside the increases in the H&Y scores and the significant decreases in the ^{123}I-FP-CIT SBR values, all together, as signs of faster progression.

Striatal DAT density in early *de novo* PD (as reflected by the baseline ^{123}I-FP-CIT SBR values) can be highly variable among individuals [16]. In our cohort (comprised of two groups of future PD LIDs, PD non-LIDs), there were no differences in the baseline data, similarly to our previous report [16]; this point may suggest that striatal DAT values at baseline may not be able to predict the development of LIDs later on [15,16]. In our study, *de novo* PD patients had various striatal ^{123}I-FP-CIT SBR values at diagnosis but at the same time they were matched for disease progression. Though matched for DD_{diagn}, the differences in striatal DAT availability observed in the aforementioned PET study [15] may reflect different levels of severity, as supported by their between-group statistically significant difference in the unified PD rating scale scores (motor component). Thus, while DAT-specific SPECT is indeed of great significant value at the diagnostic period, however, it may not be particularly instructive in predicting the development of LIDs on its own. We believe that with current knowledge, prediction of LIDs should be based on other factors including age at onset and disease duration.

Nevertheless, the data presented here contribute to better understanding the complex mechanisms underlying PD dyskinesias. Previous work in the field [3, 9], has shown that advanced PD patients with LIDs had higher serotonin transporter-over-DAT binding ratios in the putamen in comparison to nondyskinetic patients supporting previous work in the animal model of LIDs [32]. We argue that the 'serotonergic hypothesis' [3, 9, 32] alongside the significant work conducted in pathological signaling [33] could be a possible explanation for the differences we show in striatal DAT decline between dyskinetic and nondyskinetic patients.

In our study, the patients of the PD LIDs group were taking significantly higher amounts of levodopa as compared to the nondyskinetic group ($p < 0.001$); however, we did not find it appropriate to analyze individual LED doses and recorded AIMS scores with ^{123}I-FP-CIT SBR values under the present study design. It should also be noted that our longitudinal SPECT study was designed to assess striatal DAT availabilities at only two time points. Notwithstanding the clinical management of these patients was consistent and the two groups were rescanned at comparable intervals, the timing of SPECT scanning could not have been matched greatly to the times the clinical assessments were performed. Hence, it is difficult to estimate the rate(s) of striatal DAT decline in this cohort under the present study design.

The difference in putaminal DAT binding values between dyskinetic and nondyskinetic patients at follow-up was marginally significant. This could be attributed to the number of subjects but also to the sensitivity of ^{123}I-FP-CIT SPECT imaging in detecting small changes over time. On this matter, an interesting study, using autoradiography [34] showed that putaminal DAT was almost entirely depleted post-mortem in the primate model of PD. However, in the same study striatal DAT deficits were only partial when assessed ante-mortem with DAT-specific SPECT imaging [34]. This notion indicates that a small percentage change in DAT-specific binding is likely to reflect a larger scale change of striatal DAT expression *in vivo*. In this regard, semi-quantification of ^{123}I-FP-CIT SPECT data, though robust in differentiating PD cases from healthy controls, may be limited to capture subtle changes among individuals over a short period of time. For the purposes of this study, it would be very interesting to evaluate the features of dopaminergic degeneration within the substantia nigra. However, through the same prism, the current methodological approach with DAT-specific SPECT would not allow extraction of meaningful nigral SBRs.

Conclusion

In conclusion, our study supports the notion that the development of LIDs is possibly related to a faster progression rate, and that multiple DAT-specific SPECT imaging should be considered for monitoring PD progression.

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Conflict of Interest

All authors report no financial disclosures relevant to this manuscript.

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