의학박사 학위논문

파킨슨병 환자에서 F-18 FP-CIT PET 로 측정한 도파민 운반체 밀도의 종적 변화: PPMI cohort 와의 비교

Longitudinal change of dopamine transporter density measured with [^{18}F]FP-CIT PET in Parkinson's disease patients: A comparison with PPMI cohort study

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이 논문을 의학박사 학위 논문으로 제출함

2022 년 8 월

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Abstract

Purpose: Functional brain imaging targeting the presynaptic dopamine transporter (DAT) is an imaging biomarker for monitoring disease progression and therapeutic effects in Parkinson's disease (PD). This study investigated the characteristics of striatal [^{18}F]FP-CIT uptake changes in the first year after initial diagnostic [^{18}F]FP-CIT/CT in newly diagnosed PD and essential tremor (ET) patients through subregional quantitative analysis; the results were then compared with the [^{123}I]FP-CIT SPECT data of the PPMI (Parkinson's Progression Markers Initiative) database.

Method: Between April 2018 and April 2019, six patients with ET (one female and five males, mean age 63.5 ± 4.8 years) and 17 patients with PD (eight females and nine males, mean age 65.8 ± 7.0 years, Hoehn & Yahr stage 2.3 ± 0.7) were prospectively recruited; two [^{18}F]FP-CIT PET/CT scans were performed after clinical diagnosis and one year later. Asan medical center (AMC) test-retest cohort data were used to investigate short-term precision (n = 27, PD 12, ET 15). PET images were spatially normalized and analyzed with eight striatal (right and left ventral striatum [VS], caudate [CA], anterior putamen [AP], posterior putamen [PP]) templates and one occipital volume-of-interest (VOI) template. Longitudinal data were extracted from the PPMI database at the first visit after diagnosis and at follow-up [^{123}I]FP-CIT SPECT for one year. By calculating the specific to nonspecific binding ratio (SNBR) of the striatal subregion, the short-term precision of the SNBR and the one-year change (%) of each subregion were investigated. In addition, we analyzed clinical factors that may affect the one-year rate of change of SNBR.

Results: The short-term bias and variability of striatal mean SNBR measured by [^{18}F]FP-CIT PET/CT amounted to -2.6% and 5.4% in the PD group, and 2.8% and 8.3% in the ET group, respectively. Among the striatal subregions in the one-year follow-up AMC cohort measured by [^{18}F]FP-CIT PET/CT, the putamen showed significantly change of SNBRs in the PD group (affected anterior putamen -10.5± 8.1%, p = 0.002, affected posterior putamen -4.6 ± 8.1%, p = 0.05); however, there was no significant change in the ET group. In the one-year PPMI

cohort adjusted for age and disease duration, CA and putamen SNBR change were -9.6 ± 18.3% and -13.3 ± 20.8% ($p < 0.001$), respectively. The change of striatal SNBRs during one year did not show any significant correlation with patient age, symptom duration, and H&Y stage in either the AMC cohort or the PPMI cohort; furthermore, only the PPMI cohort showed a weak correlation with baseline SNBR ($p = 0.02$). When multiple regression analysis was performed based on clinical characteristics in the PPMI cohort, the explanatory power was very low (adjust $R^2 = 0.03$, $p = 0.007$).

Conclusion: In patients with PD, striatal dopamine transporter density measured by [^{18}F]FP-CIT PET/CT and [^{123}I]FP-CIT SPECT significantly decreased in the putamen for one-year after clinical diagnosis. The annual decline rates measured by [^{123}I]FP-CIT SPECT in PPMI cohort was higher than those by [^{18}F]FP-CIT PET/CT in AMC cohort. However, there was no significant clinical symptom and signs which affect this progression of DAT loss in both cohorts.

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Introduction

Parkinson's disease (PD) is characterized by a dopamine deficiency in the striatum on the neurotransmitter level. There is no known cure for the PD, so treatments must be adjusted throughout the course of disease [1]. Functional brain imaging that targets the presynaptic dopamine transporter (DAT) is an imaging biomarker for monitoring disease progression and therapeutic effectiveness in Parkinson's disease (PD). While there are a number of DAT tracers for PET and SPECT imaging, the most commonly used tracers are the ^{123}I-, ^{18}F- or ^{11}C-linked tropane-derivatives β-CIT (2β-carbomethoxy-3β(4-iodophenyl)tropane), and FP-CIT (N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane) [2]. Striatal DAT loss measured by PET and SPECT imaging have shown significant correlations with global severity of PD [3]; therefore, knowing the longitudinal pattern of striatal DAT loss could be an important milestone in determining the severity and patient-specific treatment of PD.

Several longitudinal studies reported that the annual decline rate of striatal DAT binding on DAT imaging was 4.2-13.1% [2]. However, in most previous studies, the image technique used for quantitative analysis was SPECT using ^{123}I. [^{18}F]FP-CIT has been approved by the

Korean Food and Drug Administration and has already been incorporated into clinical practice in several Korean and European hospitals. [^{18}F]FP-CIT PET/CT has several benefits such as high affinity (Ki = 3.5 nM) and selectivity to a DAT, relatively fast kinetics, non-radioactive nor-beta-CIT metabolite, suitability for PET neuroimaging with excellent spatial resolution, as well as sophisticated attenuation correction allowing for a rapid quantification of DAT binding [4]. Since it is a PET tracer, more accurate subregional and quantitative analysis is possible, and its metabolite is non-radioactive, facilitating a better quantification than the one afforded by DAT SPECT [5].

PD patients usually have their first visit within one to two years after symptom onset, and the first one to five years after the onset of disease are important for diagnosis and getting access to treatment [6]. Therefore, assessment of striatal DAT and its annual changes after initial diagnosis would be helpful for the diagnosis and monitoring disease progression as a more objective indicator. However, there is no prospective data on the initial annual decline in striatal DAT binding of [^{18}F]FP-CIT after diagnosis of PD.

Therefore, we evaluated the first one-year progression pattern of striatal DAT loss in patients

with newly diagnosed PD using [^{18}F]FP-CIT PET/CT. Then we compared the results with those of [^{123}I]FP-CIT SPECT data from the Parkinson's Progression Markers Initiative (PPMI) database to evaluate the difference between SPECT and PET imaging, and also between small and large cohort studies.

Materials and Methods

Subjects

The one-year prospective AMC cohort

Between April 2018 and April 2019, we enrolled prospective six patients with ET (one female and five males; mean age ± SD, 63.5 ± 4.8 years) and 17 patients with PD (eight females and nine males; mean age ± SD, 65.8 ± 7.0 years; H&Y stage 2.3 ± 0.7) at our institution. According to the purpose of the study to evaluate the changes in the first year after diagnosis, four patients with a disease duration of over five years were excluded from the analysis, so a total of 13 patients with PD (seven females and six males, mean age ± SD, 64.2 ± 6.6 years; H&Y stage 2.1 ± 0.6) were included. The diagnosis of ET was based on the proposed Consensus Statement of the Movement Disorder Society on Tremor [7]. The diagnosis of PD was based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria [8]. The following exclusion criteria were used: (a) hypersensitivity or allergy to [^{18}F]FP-CIT; (b) history of alcohol or drug abuse; (c) history of stereotactic surgery; (d) medication history of the use of amphetamine (CNS stimulant), phentermine (CNS stimulant),

mazindol (CNS stimulant), methylphenidate (CNS stimulant), benzatropine (anticholinergics), cocaine, all of which are known to act as competitors for the binding of [^{18}F]FP-CIT to DAT. All patients were assessed by neurologists in the movement clinic. Each study participant underwent two sequential [^{18}F]FP-CIT PET/CT scans at the one-year interval after clinical diagnosis. The study was approved by the Asan Medical Center (AMC) institutional review board (2018-0183), and all participants signed an informed consent form. All patients gave written informed consent before each scan.

Short term precision cohort

[^{18}F]FP-CIT PET performed at two-month intervals with 27 AMC short-term test-retest cohorts (15 ET patients (11 females and two males; mean age ± SD, 67.7 ± 6.6 years) and 12 PD patients (six females and six males; mean age ± SD, 68.1 ± 6.7 years) enrolled between April 2018 and October 2018 was analyzed.

The PPMI database

The Parkinson's Progression Markers Initiative (PPMI) is an international, multi-center, prospective cohort study designed to discover and validate biomarkers that predict the

heterogeneous progression of PD. Further detail and methodology of the study were published elsewhere (Parkinson Progression Marker Initiative, 2011) and are available on the PPMI website (http://ppmi-info.org/study-design).

Longitudinal data including [^{123}I]FP-CIT SPECT were extracted from the PPMI database (www.ppmi-info.org/data). Only 365 (127 females and 238 males) patients with baseline (year 0) and one-year [^{123}I]FP-CIT SPECT images were included. The data were downloaded from the PPMI database on August 12, 2021.

For comparison with patients undergoing the [^{18}F]FP-CIT PET/CT, we collected data from 204 (65 females and 139 males) patients with disease duration of less than five years, ages between 64 ± 7 years.

[^{18}F]FP-CIT PET/CT

[^{18}F]FP-CIT was synthesized as previously described [9]. All [^{18}F]FP-CIT PET/CT scans were performed with a Biograph Truepoint 40 PET/CT camera (Siemens) at three hours after intravenous injection of [^{18}F]FP-CIT (185 ± 18.5 MBq). PET images were acquired for 10 minutes in the 3-dimensional mode immediately after the brain computed tomographic scan

for attenuation correction and image fusion. CT scanning was performed at 120 kVp and 228 mAs and with a slice thickness of 1.5 mm. [^{18}F]FP-CIT PET images were reconstructed with a TrueX algorithm and an all-pass filter using a 336×336 matrix.

Image processing [^{18}F]FP-CIT PET/CT

Image processing was performed with SPM12 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK) within MATLAB R2013a for Windows (The MathWorks, Inc.) and MRIcro version 1.40 (Chris Rorden, Columbia, SC; http://www.mricro.com). All reconstructed PET images were spatially normalized to Talairach space using a standard [^{18}F]FP-CIT PET template, which was made in-house, as previously described [10]. One-year follow-up PET images were realigned with the mean from the baseline PET images. The other process was the same as described above.

The VOIs were applied to the PET images. To eliminate inter-operator variation, the automatically normalized VOI template was adjusted manually (allowing shift, but without changes of the VOI size) by one operator using our in-house VOI editing software called "ANTIQUE (AMC NM Toolkit for Image Quantification of Excellence)" [11].

The quantitative analyses were conducted on 8 volume-of-interest (VOI) templates of bilateral striatal subregions [ventral striatum (VS), caudate (CA), anterior putamen (AP), posterior putamen (PP)] and one of the occipital subregions. The level of concentrated activity in each VOI was calculated.

Quantitative Analyses

The specific to non-specific binding ratio (SNBR) was defined as follows: [mean standardized uptake value (SUV) of the striatal subregional VOI – mean SUV of the occipital VOI] / mean SUV of the occipital VOI], considering the occipital uptake to be non-specific binding. For each subregion, the change in percent for one year (% change) was calculated as follows: [(follow-up SNBR – initial SNBR) / initial SNBR] x100.

Statistical Analyses

We used a Wilcoxon matched pair test and paired-t test to find out whether the follow-up SNBR was different from the baseline. A Mann-Whitney U test was used for the comparison of quantitative parameters between PD and ET groups. Spearman correlation and Pearson's coefficients between the variables were calculated. Simple linear regression and multiple

linear regression analysis were performed on the PPMI data for assessing the clinical factors that may affect the change of DAT loss. The Statistical Package for the Social Sciences (SPSS) for Windows (version 21.0; SPSS Inc.) and R software (version 4.2.0; r-project.org) were used for the statistical analyses, and a *p*-value below 0.05 was considered to be statistically significant. The data for the study variables were expressed as the mean ± standard deviation (SD).

Results

Patient characteristics

Clinical data of the patients are summarized in Table 1. There was no significant difference in age between PD and ET groups of AMC cohort. When comparing the [^{18}F]FP-CIT PET and [^{123}I]FP-CIT SPECT groups, the H&Y stage was lower in the SPECT group.

Short-term and one year follow-up changes of striatal [^{18}F]FP-CIT uptake

The short-term bias and variability of striatal mean SNBRs measured by [^{18}F]FP-CIT PET/CT amounted to -2.6% and 5.4% in the PD group, and 2.8% and 8.3% in the ET group, respectively (Fig. 1). The change (%) for 2 months, the PD group showed the change of 0.4% to -4.5%, and the ET group showed the change of about 1.9% to 3.8%. However, there were no statistically significant decrease or increase trends between baseline and short-term follow-up scans in either group (Table 2).

In the one-year prospective follow-up AMC cohort, the initial SNBRs of striatum in the PD group were significantly lower than those in the ET group in all subregions. In the PD group,

the initial SNBRs of PP exhibited the lowest value of 2.6 ± 0.6, followed by AP (4.6 ± 0.9), VS (5.0 ± 0.7), and CA (5.1 ± 1.2) (Table 3). The affected side showed lower values than the contralateral side (Putamen; 3.2 ± 0.7 vs. 3.6 ± 0.7, PP; 2.4 ± 0.6 vs. 2.8 ± 0.7, AP; 4.5 ± 1.0 vs. 4.8 ± 0.9). The difference between the PD and ET groups was particularly noticeable in PP (2.6 ± 0.6 vs. 7.3 ± 0.4; $p < 0.001$), and the smallest in the CA (5.1 ± 1.3 vs. 6.3 ± 0.9; $p = 0.02$). Compared to the one-year follow-up scan, the PD group had a significant decrease in SNBR in all areas, especially in AP ($p < 0.001$). There was no significant difference between the baseline and 1-year follow-up scans in the ET group. The one-year change (%) of the PD group was significantly greater AP, PP, and CA than those in the ET group. Especially in AP, it was approximately three times greater at -9.3 ± 6.7 than at -2.9 ± 8.5 of the ET group (Table 3, Fig. 2).

Possible clinical factors that may affect the change of DAT loss such as onset age, disease duration, and baseline SNBRs of AP and PP showed weak negative correlations with one-year change (%) of striatal SNBRs; however, these correlations did not reach statistical significance ($p > 0.05$).

One-year change of striatal [^{123}I]FP-CIT uptake

Baseline SNBRs of the CA and the putamen in the one-year PPMI cohort were 2.0 ± 0.5 and 0.8 ± 0.3, respectively. SNBRs of the age and disease duration matched PPMI (one-year adjust PPMI) cohort were not significantly different from those of the one-year PPMI cohort. One-year follow-up scan showed a significant decrease in SNBR ($p < 0.001$) of CA and putamen (Table 3). The one-year change (%) of the putaminal SNBRs ($p = 0.03$) and contralateral putaminal SNBRs ($p = 0.01$) in the one-year PPMI cohort was greater than those in the AMC cohort. The change (%) of the contralateral putaminal SNBRs in the one-year PPMI cohort was about two-fold greater than that of the affected putamen in the AMC cohort. However, the one-year change (%) of the CA SNBRs and the affected putaminal SNBRs were not significantly different between both cohorts ($p > 0.05$).

When considering factors that may affect DAT loss, the change (%) of the putamen showed a weak correlation with baseline SNBR of the putamen (putamen mean r = -0.3, $p < 0.001$; affected putamen r = -0.4, p < 0.001; contralateral putamen r = 0.3, $p < 0.001$). In addition, age at the baseline scan, disease duration, and H&Y stages did not correlate with the change

(%) of the putamen in the one-year PPMI cohort.

In the one-year PPMI cohort, a simple linear regression analysis and a multiple linear regression analysis were performed using the one-year change (%) of SNBRs and the baseline clinical characteristics obtained from the PPMI cohort data (moca score, total rigidity score, UPDRS3 score, Letter Number Sequencing Score, Hopkins Verbal Learning Test, Epworth Sleepiness Scale Score, Geriatric Depression Scale Score, REM Sleep Behavior Disorder Questionnaire Score, SCOPA-AUT Total Score, QUIP Score, Symbol Digit Modalities Score, Semantic Fluency Total Score, UPSIT Score, and STAI Total Score) as independent variables to investigate the clinical factor that may affect the change of DAT loss. Multiple linear regression was a fitted model with variables with *p*-values less than 0.1 in simple linear regression. On the basis of $p < 0.05$, only two variables were selected, so $p < 0.1$ was used as the standard (Durbin-Watson = 2.0, adjust $R^2 = 0.030$, $p = 0.007$). Symptom duration, total rigidity score, UPDRS3 score, and UPSIT score were selected as suitable variables in backward elimination stepwise regression (Multiple linear regression2); however, the explanatory power of this model was 4%. (adjust $R^2 = 0.035$, $p = 0.003$) (Table 4).

Discussion

In this study, we prospectively evaluated the one-year progression pattern of striatal DAT loss in patients with newly diagnosed PD using [^{18}F]FP-CIT PET/CT. The initial [^{18}F]FP-CIT uptake of the PD group was significantly lower than that in the ET group, especially in PP. In PD patients, affected PP and AP uptake was lower than the contralateral side. This result is consistent with previous studies reporting that PP is the most severely affected subregion in the striatum, whereas the CA is a relatively spared subregion [12-14]. The one-year rate of decline for the [^{18}F]FP-CIT binding of the putamen and the caudate was approximately 7.8% and 5.3%, respectively. This result is consistent with those reported in previous studies. For instance, in a previous study of dopamine transporter imaging with [^{18}F]FP-CIT PET, the rates of annual decline in the putamen and CA were 6.7% and 5.1%, respectively [15]. Sung et al. reported the annual decline rate of the striatal subregion in the PD and non-PD groups, followed by the CA (6.0% vs.1.7%), VS (4.6% vs. 0.7%), AP (8.3% vs. 1.0%) and PP (9.6% vs. 1.2 %)[16]. In our study, the one-year decline rate of AP (9.3 ± 6.7%) was slightly higher than that of PP (6.0 ± 7.8%), and the one-year decline rate of affected AP (10.5 ± 8.1%) was slightly higher than that

of contralateral AP (8.2 ± 5.9%) although there was no statistical significance ($p > 0.61$). Since the initial SNBRs were the lowest in the PP, the decline rate of the AP with relative potential may be greater. In addition, the retrospective study used an annual-adjusted rate, so it may differ from the exact one-year follow-up study. When the ET group of this prospective study and the non-PD group of the retrospective study [16] were compared, more changes occurred in all subregions of this prospective study. This difference is not clear due to the small number of patient groups in both studies (n = 6 vs. n = 9). Although the variability of the ET group was greater than the PD group, the difference of the baseline and follow-up in the ET group did not show any statistically significant decline ($p = 0.35$). Referring to the test-retest reproducibility with **[**^{18}F**]**FP-CIT PET study, the ET group showed higher variability than the PD group [17]. We could predict that striatal DAT binding in non-PD patients would be significantly affected by individual conditions. The time activity curves for specific striatal [^{18}F]FP-CIT binding reached a plateau phase at approximately 60 minutes in the PD patients [18]. In contrast, in healthy controls, specific striatal [^{18}F]FP-CIT uptake did not reach a complete plateau over 100 minutes, and the striatum to occipital ratio linearly increased even

after a specific uptake reached a plateau [18]. In this study, striatal [^{18}F]FP-CIT binding in ET patients may not yet have reached a pseudo-equilibrium state although striatal uptake was measured 3 hour after injection of [^{18}F]FP-CIT, and the hemodynamic status is vulnerable to each individual's biological factors.

In the age- and disease duration-matched PPMI group, the one-year decline rate of DAT binding in the CA and the putamen were -9.6 ± 18.3% and -13.3 ± 20.8%, respectively. These one-year decline rates in PPMI cohort are greater than those in the AMC cohort although both groups had a higher one-year decline rate in putamen compared to CA. The major reason of the discrepancy between PPMI cohort and AMC cohort in terms of annual decline rate could have been different sensitivities and spatial resolution of SPECT and PET. The most important advantage of PET imaging over SPECT is that of exhibiting a much higher sensitivity[19]. Since the spatial resolution and sensitivity of SPECT, which is 2-3 times lower than those of PET, can result in lower baseline uptake values in small brain regions such as CA and putamen, even a small change may seem like a bigger change. In this study, baseline SNBRs of putamen in PD patients of PPMI cohort are lower than those of AMC cohort (0.7 ± 0.3 vs 3.4 ± 0.7, *p*

< 0.001). In meta-analysis, unlike in previous studies using PET which showed similar changes in the putamen, the fluctuation range of total striatum in the DAT SPECT imaging using a ^{123}I-tracer was widely distributed at about 4.2~11.2% [2].

Another cause of the discrepancy could be the characteristic difference between the PPMI and AMC cohorts. At enrollment, PPMI PD subjects were untreated with PD medications, within 2 years of diagnosis, H&Y stage <3 [20]. However, AMC subjects were not restricted to drug treatment or to the H&Y stage. While several studies of animal PD models and PD patients suggest that chronic dopaminergic stimulation with levodopa or pramipexole may not produce significant changes in striatal DAT uptake [21-23], several previous studies described DAT binding changes after Anti-PD medications [24]. A potential effect of dopaminergic drugs on the decline of DAT binding in AMC cohorts cannot be excluded. Furthermore, the difference in H&Y stage at the time of enrollment may have resulted in the recruitment of AMC subjects as patients with more severe disease severity than PPMI subjects. There was also a difference in race between the two cohorts. Although PPMI cohort is a multicenter, international study, 99% of PPMI subjects were white, and 96% of 365 subjects used in the comparative analysis were

white, and only 1% (4 subjects) of Asians. On the other hand, the AMC cohort consisted of 100% Asians (Koreans).

In the one-year PPMI cohort, change (%) of contralateral putamen was much larger than that of affected putamen. This can be explained by the bottom effect, as in the one-year AMC group, the change (%) of AP was greater than that of PP and the change (%) in the contralateral PP was greater than the change (%) in the affected PP. The reason why the change (%) of the contralateral AP was lower than that of the affected AP was probably because the contralateral AP is a region where the preservation is relatively late as compared to the PP. As such, PET enables sophisticated subregion analysis. Therefore, the [^{18}F]FP-CIT PET/CT will be useful as a more sophisticated tool for the evaluation of disease patterns and therapeutic effects.

Difference and change (%) of striatal SNBRs during one year did not show a significant correlation with age, disease duration, and H&Y stages in both the one-year AMC cohort and the PPMI cohort. Only baseline SNBR showed a weak correlation ($R = -0.21$, $p = 0.02$) in the one-year PPMI cohort. In multiple regression analysis, neither baseline characteristics, nor clinical feature scores were explanatory enough to explain putaminal change (%) ($R^2 = 0.04$).

Several cross-sectional studies showed a correlation with striatal DAT binding and disease severity. For instance, Cao et al. reported PD patients with RBD disorder had a significantly greater DAT loss compared to PD patients without RBD disorder [25]. The correlation between disease severity and dopamine loss, as assessed by the MDS-UPDRS score, was weak in a cross-sectional study. Furthermore, the correlation was stronger in the caudate than in the putamen [2, 26]. However, in a longitudinal study, there was no correlation between the rate of change of SNBR and UPDRS score [26].

Some limitations of the present study should be addressed. First, unlike for the AMC cohort, subregional analysis was not performed for the PPMI cohort using only the calculated SNBR results. As access to raw data was possible, if we analyzed from image processing with a VOI template similar to that of PET analysis, more direct result comparison would have been possible. Second, the one-year AMC cohort was not tested for UPDRS when PET/CT was undergone. If access to extensive information on clinical feature including UPDRS score had been available, it would have yielded more accurate data on the subjects' condition and disease progression as a prospective study as well as correlation with striatal DAT binding. Third, no

analysis was performed to compare ET patients in the AMC cohort to the PPMI cohort. Since ET is a concept included in scans without evidence of dopaminergic deficit (SWEDD), a comparison with SWEDD patients was considered, but SWEDD is a broader concept than ET. Since there is a possibility of having other disease such as DOPA-responsive dystonia, vascular parkinsonism, drug-induced Parkinsonism, and myoclonus-dystonia, a simple comparison was judged to be inappropriate. If longitudinal follow-up of [^{18}F]FP-CIT PET had been performed for healthy controls, age-related changes in striatal DAT in healthy control, as well as comparison with PD patients, and comparison with SPECT studies published so far would have been possible. Fourth, the patients' medication could not be controlled. Previous studies described DAT binding changes after anti-PD medications [24]. Therefore, knowing the pattern of DAT binding in PD patients would help to monitor not only disease progression. Finally, AMC cohort had a small sample size and a short follow-up period of one year. Differences in sample size may have caused discordance in the DAT decline rates between the groups. In addition, several studies have reported different long-term longitudinal patterns of DAT binding (linear decrease or a negative exponential progression pattern) [2]. In order to take

advantage of the benefits of PET/CT of [^{18}F]FP-CIT, a large-scale study with a sufficiently long follow-up period, including the patients' clinical features and medication, would be required, and additional follow-up tests for the control group would be necessary.

Conclusion

In patients with PD, striatal dopamine transporter density measured by [^{18}F]FP-CIT PET/CT and [^{123}I]FP-CIT SPECT significantly decreased in the putamen for one-year after clinical diagnosis. The annual decline rates measured by [^{123}I]FP-CIT SPECT in PPMI cohort was higher than those by [^{18}F]FP-CIT PET/CT in AMC cohort. However, there was no significant clinical symptom and signs which affect this progression of DAT loss in both cohorts.

Table 1. Clinical characteristics of the study participants

Characteristic	[^{18}F]FP-CIT PET/CT		[^{123}I]FP-CIT SPECT	
	PD (n = 13)	ET (n = 6)	one-year PPMI (n = 365)	one-year adjust PPMI (n = 204)
Age at baseline	64 ± 7	64 ± 5	62 ± 10	64 ± 7
Sex (M/F), n	6 / 7	5 / 1	238 / 127	139 / 65
Disease duration (year) at baseline	1.9 ± 1.3	NA	2.0 ± 1.9	1.6 ± 1.0
Hoehn-Yahr stage at baseline	2.1 ± 0.6	NA	1.5 ± 0.5	1.6 ± 0.5
Scan interval (months)	12 ± 1	12 ± 1	12 ± 1	13 ± 1

ET, essential tremor; PD, Parkinson's disease

Table 2. Short-term (< 2 months) change of striatal SNBRs on [^{18}F]FP-CIT PET/CT

	Baseline		**2nd**		**Change (%)**	
Region	**PD**	**ET**	**PD**	**ET**	**PD**	**ET**
	(n = 12)	**(n = 15)**	**(n = 12)**	**(n = 15)**	**(n = 12)**	**(n = 15)**
VS	4.4 ± 1.1	6.6 ± 0.5	4.2 ± 0.9	6.7 ± 0.6	**-4.5 ± 4.0**	1.9 ± 7.0
CA	4.3 ± 1.4	7.0 ± 1.2	4.2 ± 1.4	7.1 ± 1.3	**-1.0 ± 4.0**	2.8 ± 9.0
AP	3.7 ±1.2	8.3 ± 1.2	3.7 ± 1.1	8.6 ± 1.0	**0.4 ± 5.9**	3.8 ± 9.0
PP	2.5 ± 0.7	7.5 ± 1.0	2.4 ± 0.6	7.6 ± 0.9	**-0.9 ± 6.2**	2.8 ± 8.9

PD, Parkinson's disease; ET, essential tremor; VS, ventral striatum; CA, caudate; AP, anterior putamen; PP, posterior putamen

Table 3. Specific to non-specific binding ratios (SNBRs) and one-year change (%) of striatal subregions in the PD and ET groups

Region	**Cohort**	**Baseline** (SNBRs)		**1yr F/U** (SNBRs)		**Change (%)**	
		PD	**ET**	**PD**	**ET**	**PD**	**ET**
VS	AMC	5.0 ± 0.7	6.5 ± 0.2	4.7 ± 0.8	6.1 ± 0.8	- 6.4 ±10.0*	-6.9 ± 9.6
CA	AMC	5.1 ± 1.3	6.3 ± 0.9	4.8 ± 1.3	6.2 ± 1.4	-5.3 ± 11.6*	-2.9 ± 9.4
	PPMI	2.0 ± 0.5		1.8 ± 0.5		-9.5 ± 16.0**	
	Adjust PPMI	2.0 ± 0.5		1.7 ± 0.5		-9.6 ± 18.3**	
AP	AMC	4.6 ± 0.9	8.4 ± 0.4	4.2 ± 0.8	8.1 ± 0.9	-9.3 ± 6.7**	-2.9 ± 8.5
Affected AP	AMC	4.5 ± 1.0		4.0 ± 0.8		-10.5 ± 8.1*	
Contralateral AP	AMC	4.8 ± 0.9		4.34 ± 0.9		-8.2 ± 5.9**	
PP	AMC	2.6 ± 0.6	7.3 ± 0.4	2.5 ± 0.5	7.0 ± 0.9	-6.0 ± 7.8*	-3.9 ± 7.0
Affected PP	AMC	2.4 ± 0.6		2.3 ± 0.5		-4.6 ± 8.1*	
Contralateral PP	AMC	2.8 ± 0.7		2.6 ± 0.6		-6.7 ± 9.4*	

Putamen	AMC	3.4 ± 0.7	7.7 ± 0.9	3.1 ± 0.6	7.4 ± 0.9	-7.8 ± 6.7*	-3.4 ± 7.5
	PPMI	0.8 ± 0.3		0.7 ± 0.3		-13.0 ± 21.7**	
	Adjust PPMI	0.8 ± 0.3		0.7 ± 0.3		-13.3 ± 20.8**	
Affected Putamen	AMC	3.2 ± 0.7		3.0 ± 0.6		-7.9 ± 7.3*	
	PPMI	0.7 ± 0.3		0.6 ± 0.2		-6.9 ± 32.6**	
	Adjust PPMI	0.7 ± 0.3		0.6 ± 0.2		-8.0 ± 30.1**	
Contralateral putamen	AMC	3.6 ± 0.7		3.3 ± 0.6		-7.5 ± 6.9*	
	PPMI	1.0 ± 0.4		0.8 ± 0.3		-14.3 ± 25.5**	
	Adjust PPMI	0.9 ± 0.4		0.8 ± 0.3		-14.1 ± 26.3**	

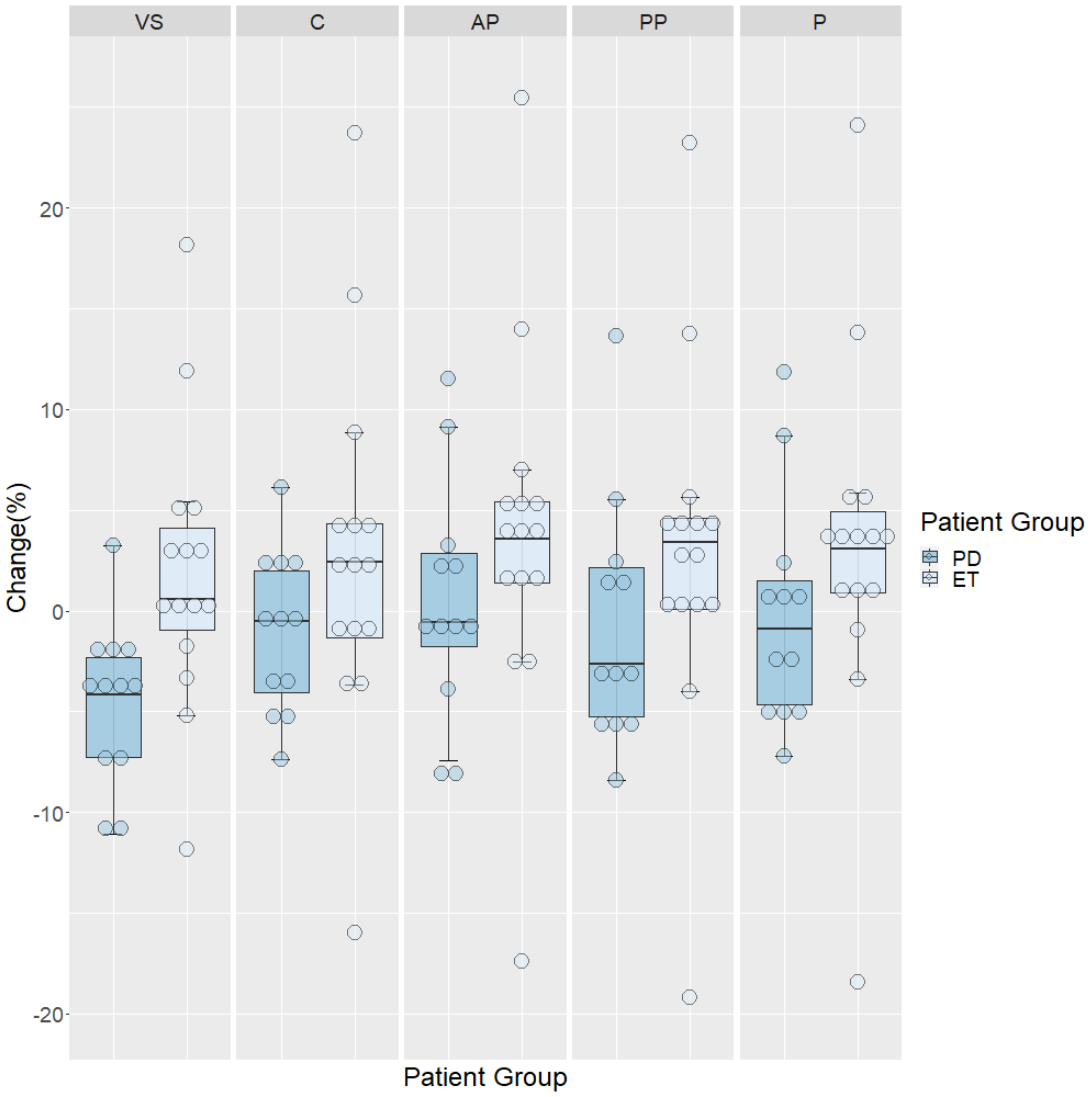
AMC, the one-year prospective AMC cohort with [^{18}F]FP-CIT PET/CT scan (n = 13); PPMI, the PPMI cohort with baseline and one-year [^{123}I]FP-CIT-SPECT scan (n = 365); Adjust PPMI, the one-year PPMI cohort with adjusted for age and disease duration (n = 204); ET, essential tremor; PD, Parkinson's disease; CA, caudate; AP, anterior putamen; PP, posterior putamen, $p < 0.05$* $p < 0.001$**

Table 4. Effect of each variable on change (%) of affected putamen in one-year F/U PPMI cohort (n = 365)

Variable	**Multiple linear regression** (n = 364)					**Multiple linear regression2** (n = 354)				
	beta	Se(beta)	t value	*p*-value	tolerance	beta	Se(beta)	t value	*p*-value	tolerance
Age onset	-0.157	0.195	-0.805	0.423	0.738					
Symptom duration	0.621	0.253	2.455	0.015	0.996	0.743	0.251	2.960	0.003	0.994
Rigidity	1.211	0.652	1.857	0.064	0.978	1.814	0.904	2.007	0.046	0.496
UPDRS3						-0.426	0.276	1.543	0.124	0.491
UPSIT	0.302	0.222	1.360	0.175	0.864	0.433	0.204	2.123	0.035	0.980
Symbol Digit Modalities	0.243	0.207	1.174	0.242	0.775					
	$R = 0.210$, $R^2 = 0.044$, Adjusted $R^2 = 0.030$ $F = 3.270$, $p = 0.007$, Durbin-Watson = 1.989					$R = 0.213$, $R^2 = 0.045$, Adjusted $R^2 = 0.035$ $F = 4.157$, $p = 0.003$, Durbin-Watson = 1.951				

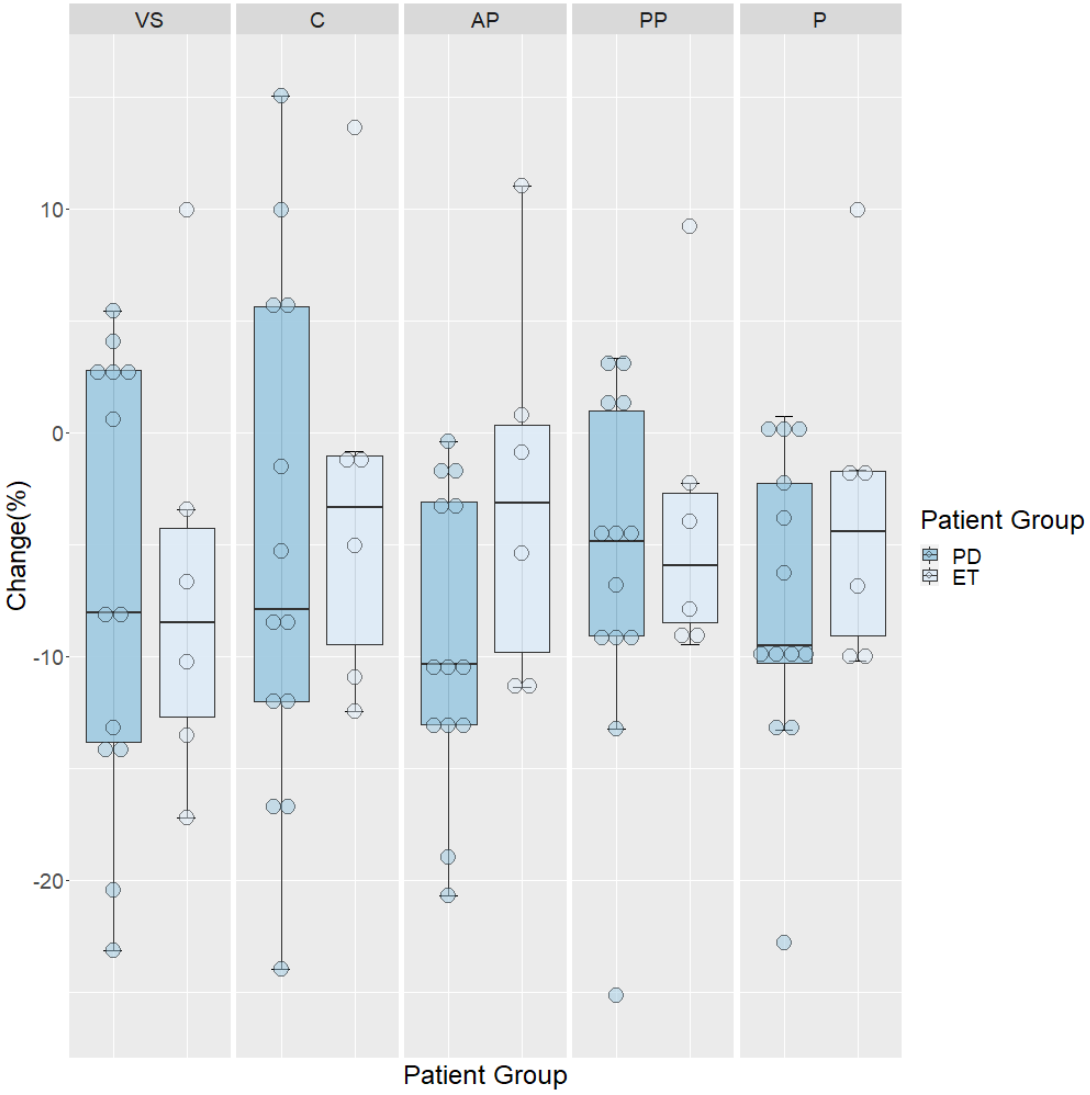
Multiple linear regression, simple linear regression filtering multiple linear regression; Multiple linear regression2, backward elimination stepwise regression. Missing values were excluded from the analysis.

Figure 1. Short-term test-retest change (%) of striatal SNBRs in PD and ET patients in the 2-month follow-up AMC cohort



PD, Parkinson's disease; ET, essential tremor; VS, ventral striatum; C, caudate; AP, anterior putamen; PP, posterior putamen; P, putamen mean

Figure 2. Change (%) of striatal SNBRs in PD and ET patients in the one-year follow-up AMC cohort



PD, Parkinson's disease; ET, essential tremor; VS, ventral striatum; C, caudate; AP, anterior putamen; PP, posterior putamen, P, putamen mean

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국문요약

목적: 시냅스전 도파민 수송체(DAT)를 표적으로 하는 기능적 뇌 영상은 파킨슨병(PD)의 질병 진행 및 치료 효과를 모니터링하기 위한 영상 바이오마커이다. 본 연구는 소구역 정량 분석을 통해 새로 진단된 PD 와 본태성 떨림(ET) 환자에서 진단 후 첫 1 년간의 선조체 [^{18}F]FP-CIT 섭취 변화의 특징을 알아보고, 이를 PPMI(Parkinson's Progression Markers Initiative) 데이터베이스의 SPECT 데이터와 비교하였다.

방법: 2018 년 4 월부터 2019 년 4 월에 처음 임상적으로 진단된 ET 환자 6 명(여자 1 명, 남자 5 명, 평균 연령 63.5 ± 4.8 세)와 PD 환자 17 명(여자 8 명, 남자 9 명, 평균 연령 65.8 ± 7.0 세, Hoehn & Yahr 병기 2.3 ± 0.7)을 전향적으로 모집하여, 첫 진단 후 1 년 간격으로 2 회의 [^{18}F]FP-CIT PET/CT 검사를 시행하였다. 단기 정밀도를 알아보기 위해 AMC test-retest cohort 데이터를 사용하였다. (n = 27, PD 12 명, ET 15 명). PET 이미지는 8 개의 선조체 하위영역(좌우의 복측선조체, 미상핵, 피각전부, 피각후부) 및 1 개의 후두 VOI 템플릿으로 공간적 정규화 후 분석하였다. PPMI 데이터베이스에서 진단 후와 1 년 추적 [^{123}I]FP-CIT-SPECT 를 시행한 종단데이터를 추출했다. 선조체 하위영역의 특이적 대 비특이적 결합비(specific to nonspecific binding ratio, SNBR)를 계산하여 SNBR 의 단기 정밀도와 각 하위영역의 1 년간 변화를 알아보았다. 또한 SNBR 의 1 년 변화율에 영향을 미칠 수 있는 임상 요소를 분석하였다.

결과: [^{18}F]FP-CIT PET/CT 로 측정한 선조체 SNBR 의 단기 정밀도(bias & variability)는 PD 군에서 각각 -2.6%와 5.4%, ET 군에서 2.8%와 8.3% 였다. [^{18}F]FP-CIT PET/CT 로 1 년간의 변화를 측정한 AMC 코호트의 선조체 하위영역 중 PD 군에서 피각의 SNBR 이 유의하게 감소하였으나 (환측 피각전부 -10.5± 8.1%, p = 0.002, 환측 피각후부 -4.6 ± 8.1%, p = 0.05), ET 군에선 유의한 변화가 없었다. 연령과 유병기간으로 보정한 1 년추적 PPMI 코호트에서 미상핵과 피각은 각각 -9.6 ± 18.3% 및 -13.3 ± 20.8%으로 피각에서 더 큰 감소를 보였다. 이러한 1 년 동안의 선조체 SNBR 의 변화는 AMC 코호트과 PPMI 코호트 모두 연령, 유병 기간 및 Hoehn & Yahr 병기

와 유의한 상관성을 보이지 않았고 PPMI 코호트에서만 baseline SNBR 과 약한 상관관계를 보였다 (p = 0.02). PPMI 코호트에서 일년간 선조체 DAT 변화에 영향을 줄 수 있는 임상정보를 다중회귀 분석을 시행했을 때 설명력이 높은 임상적 특징은 없었다 (adjust R^2 = 0.030 p = 0.007).

결론: 파킨슨병환자에서 [^{18}F]FP-CITPET/CT 와 [^{123}I]FP-CIT SPECT 로 측정한 선조체의 도파민 운반체 밀도는 첫 진단 후 1 년간 피각에서 모두 유의하게 감소하였다. 그러나 도파민운반체 밀도의 감소율에 유의한 영향을 주는 임상증상과 지표는 없었다.