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Intrasubject relationship between striatal ^{18}F-FP-CIT uptake and cardiac ^{123}I-MIBG uptake differs by motor subtype in early Parkinson disease

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Abstract

Parkinson disease (PD) is a heterogeneous neurodegenerative disorder. Dopamine transporter imaging using ^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane (FP-CIT) and noradrenergic cardiac imaging using ^{123}I-meta-iodobenzylguanidine (MIBG) have been used in combination or separately to study PD patients. Published results regarding uptake of the 2 tracers in each motor subtype are fairly abundant and mostly in agreement. However, data on the intrasubject association between dopaminergic and noradrenergic systems in PD patients are relatively scant and vary. We aimed to assess the intrasubject relationship between striatal dopamine transporter density using a PET tracer and cardiac sympathetic innervation in tremor-dominant subtype (TD) and akinetic-rigid subtype (AR) of PD.

This study has a cross-sectional design. Thirty-one patients with early PD (17 TD/14 AR) who underwent both ^{123}I-MIBG cardiac scintigraphy and ^{18}F-FP-CIT PET/CT were retrospectively selected. We assessed the relationship between heart-to-mediastinum ratio (H/M) of ^{123}I-MIBG and specific (striatal)-to-nonspecific (cerebellar) dopamine transporter binding ratio (S/N) measured from 4 separate regions-of-interest (bilateral caudate nuclei and lentiform nuclei) of ^{18}F-FP-CIT in each motor subtype.

S/N of all 4 striatal regions were significantly lower in the AR subgroup than in the TD subgroup. H/M was not significantly different. There was a significant intrasubject correlation between H/M and S/N of the lentiform nucleus in AR-PD but no correlation between H/M and any of 4 S/N in TD-PD.

Our data suggest a coupled degeneration of nigrostriatal dopaminergic and myocardial sympathetic denervation in AR subtype, but not in TD subtype, of early PD patients. These different results between the 2 motor subtypes likely reflects the heterogeneous pathophysiology of PD.

Abbreviations: AR = akinetic-rigid, FP-CIT = 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane, H&Y = Hoehn and Yahr, H/M = heart-to-mediastinum, IRB = Institutional Review Board, MIBG = meta-iodobenzylguanidine, PD = Parkinson disease, ROIs = regions-of-interest, S/N = specific-to-nonspecific binding ratio, SUV = standardized uptake value, TD = tremor-dominant, UPDRS = Unified Parkinson Disease Rating Scale.

Keywords: ^{18}F-2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane, ^{123}I-meta-iodobenzylguanidine, intrasubject relationship, motor subtype, Parkinson disease

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WJ and JYL contributed equally to the manuscript.

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1. Introduction

Parkinson disease (PD) is a progressive neurodegenerative movement disorder associated with a selective loss of the dopaminergic neurons in the substantia nigra pars compacta of the brain. Oxidative stress is thought to be the common underlying mechanism that leads to cellular dysfunction and cell death in PD.[1–3] PD is a heterogeneous disease with variable clinicopathologic phenotypes associated with a broad spectrum of motor and nonmotor symptoms.[4] Given variable natural history and prognosis, identification of distinct PD subtypes is considered important for predicting clinical progression and developing management through a personalized approach. While new proposals for subtyping PD continuously appear in the literature,[5–7] 2 distinct subtypes, that is, tremor-dominant (TD) subtype and nontremor dominant or akinetic-rigid (AR) subtype,[8] have been used to classify PD. Clinically, the 2 subtypes are associated with a different clinical course and outcome.[9,10] For example, the TD subtype is reported to be associated with younger age of onset and a slower progression of the disease,[11] and the AR subtype showed a higher burden of nonmotor symptoms.[12] Data in the literature have also indicated that TD-PD and AR-PD subtypes have different pathophysiologies.[13,14]

Symptoms of PD are associated with various neurotransmitter systems,[15,16] and imaging modalities have increasingly been used to identify the neural circuits and connectivity involved in dopaminergic and/or nondopaminergic systems in PD. For example, ^{123}I-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy has been used to assess the noradrenergic system in PD[17] and SPECT using ^{123}I-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane (FP-CIT)[18] has been used to evaluate the presynaptic dopaminergic system by measuring the density of striatal dopamine transporter. Some authors found ^{123}I-MIBG cardiac scintigraphy to be helpful in detecting PD in clinically suspected patients but with normal ^{123}I-FP-CIT SPECT.[19] Others assessed the role of ^{123}I-FP-CIT SPECT for differentiating between PD from other degenerative parkinsonian syndromes in patients with normal ^{123}I-MIBG cardiac scintigraphy,[20] or used combined ^{123}I-FP-CIT SPECT and ^{123}I-MIBG cardiac scintigraphy to differentiate PD from other degenerative parkinsonian syndromes.[21,22] On the other hand, data on the intrasubject relationship between cardiac ^{123}I-MIBG uptake and striatal ^{123}I-FP-CIT uptake (reflecting the intrasubject association between dopaminergic and noradrenergic systems) in TD and AR subtypes are relatively scant and vary.[23,24]

Owing to a significantly better spatial resolution and more sophisticated and accurate quantification capability, PET imaging generally provides more accurate qualitative and quantitative information than SPECT imaging. Indeed, ^{18}F-FP-CIT PET has even been used to differentiate atypical parkinsonism, such as progressive supranuclear palsy and multiple system atrophy from PD,[25] while such differential diagnosis is difficult with ^{123}I-FP-CIT SPECT imaging.

To that end, we set out to assess: whether or not there is any intrasubject relationship between ^{18}F-FP-CIT (instead of ^{123}I-FP-CIT) striatal uptake and ^{123}I-MIBG cardiac uptake in patients with TD-PD and in patients with AR-PD at relatively early stages (Hoehn and Yahr (H&Y)[26]; stages 1 and 2), and whether or not there are any differences in this relationship between the 2 subtypes.

2. Methods

2.1. Subject

Forty-one consecutive PD patients with H&Y stages 1 and 2 who underwent both ^{18}F-FP-CIT PET and ^{123}I-MIBG cardiac scintigraphy during a 14-month period were enrolled in this retrospective study.

Idiopathic PD was diagnosed according to the criteria of the UK Parkinson Disease Society Brain Bank.[13] Based on the Unified Parkinson Disease Rating Scale (UPDRS)-III motor examination score,[27] patients were classified into 2 clinical subtypes, TD and AR, by 2 experienced movement disorder specialists using a tremor score and nontremor score calculated for each patient in a manner similar to Lewis et al.[28] The tremor score was derived from the sum of UPDRS items 20 (tremor at rest) and 21 (action or postural tremor of hands) divided by 7 that is the number of single sub-items (for each body region if separated). The nontremor score was derived from the sum of UPDRS items 18 (speech), 19 (facial expression), 22 (rigidity), 27 (arising from chair), 28 (posture), 29 (gait), 30 (postural stability), and 31 (body bradykinesia and hypokinesia) divided by 12 that is the number of single sub-items (for each body region if separated). PD was classified as the TD subtype if the tremor score was equal to or greater than twice the nontremor score, or as the AR subtype if the nontremor score was equal to or greater than twice the tremor score.

Patients who do not belong to either category, that is, the tremor and nontremor score differed by less than factor 2, were excluded from the analysis. In addition, subjects with relevant cardiac problems, medical disorders, a history of neuropathy, or current use of medications that could influence the ^{18}F-FP-CIT PET/CT or ^{123}I-MIBG cardiac scintigraphy were excluded. Finally, there were 17 patients with TD-PD (M:F = 3:14, median age: 64 years, range: 52–78 years) and 14 patients with AR-PD (M:F = 8:6, median age: 62.5 years, range: 43–82 years). This retrospective study protocol was approved by the Institutional Review Board. The need for informed consent was waived by the Institutional Review Board.

2.2. ^{123}I-meta-iodobenzylguanidine cardiac scintigraphy

Anterior and posterior views were obtained 20 minutes and 3 hours after intravenous injection of 111 MBq (3 mCi) of ^{123}I-MIBG using a dual-head gamma camera (ECAM, Siemens Medical Systems, Chicago, IL). The cardiac and mediastinal regions-of-interest (ROIs) were drawn on the anterior view for the semiquantification of the ^{123}I-MIBG uptake. The heart-to-mediastinum uptake ratio (H/M) was calculated using the following formulas:

Early H/M = cardiac counts/pixel at 20 minutes ÷ mediastinal counts/pixel at 20 minutes;
Delayed H/M = cardiac counts/pixel at 3 hours ÷ mediastinal counts/pixel at 3 hours

2.3. ^{18}F-2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane PET/CT

PET/CT scans were performed 2 hours after intravenous injection of 185 MBq (5 mCi) of ^{18}F-FP-CIT. All PET/CT examinations were performed using a Biograph True Point 16 scanner (Siemens Medical Systems, Hoffman Estates, IL). Emission PET data were

acquired for 10 minutes, and the CT data were used for the attenuation correction.

For the purpose of data analysis, the ipsilateral or contralateral striatum was determined in relation to the more symptomatic body side. A slice best showing bilateral striatum was identified, and 6 ROIs were drawn on this slice, that is, 1 each on bilateral caudate nuclei, bilateral lentiform nuclei (since it was difficult to accurately separate putamen and globus pallidus on PET images, a single ROI encompassing both parts of a lentiform nucleus was drawn), and bilateral occipital cortices. The same 6 ROIs were overlaid on 2 adjacent slices (1 above and 1 below) so that a total of 18 individual standardized uptake values (SUVs) were measured, that is, 3 from the contralateral caudate, 3 from the ipsilateral caudate, 3 from the contralateral lentiform nucleus, 3 from the ipsilateral lentiform nucleus, and 6 from bilateral occipital cortices. By averaging SUVs obtained from 3 adjacent slices, the representative SUVs for each of the 4 striatal subregions (2 caudate nuclei and 2 lentiform nuclei) were obtained. The occipital SUV was obtained by averaging 6 SUVs (=bilateral occipital SUVs on 3 slices). The specific-to-nonspecific binding ratio (S/N) for each of caudate and lentiform nuclei was calculated using the following formula:

$$S/N = \frac{SUV\ of\ caudate\ or\ lentiform\ nucleus - SUV\ of\ the\ occipital\ cortex}{SUV\ of\ the\ occipital\ cortex}$$

2.4. Statistical analyses

Baseline characteristics were presented as the number (percentage) for sex and the mean (standard deviation) for age and disease duration. Other variables with nonnormally distributed continuous data were expressed as median (interquartile range). The Mann–Whitney *U* test was used to compare the individual striatal S/N of ^{18}F-FP-CIT and H/M of ^{123}I-MIBG between the subgroups. The Fisher exact test was also used as appropriate. The Spearman test was used to determine the correlation between striatal S/N of ^{18}F-FP-CIT and H/M of ^{123}I-MIBG (hereafter referred to as the 'FP-CIT/MIBG correlation'). All statistical analyses were performed using the SPSS software program (IBM SPSS statistics, Version 21; IBM Corp., Armonk, NY). *P* values less than .05 were considered to indicate statistical significance.

3. Results

3.1. Comparison of demographic, clinical, and imaging parameters between the 2 motor subtypes

Table 1 shows the comparison of demographic (sex and age), clinical (disease duration and UPDRS-III score), and imaging (S/N and H/M) parameters between 17 patients with TD-PD, and 14 patients with AR-PD. There was a significant difference in several parameters between the 2 subgroups. The male-to-female ratio and was significantly higher in the AR subgroup than in the TD subgroup, while age or disease duration was not significantly different between the 2 subgroups. Neither early nor delayed H/M ratio of the ^{123}I-MIBG uptake was significantly different between the 2 subgroups, whereas all 4 S/N obtained from bilateral caudate and lentiform nuclei were significantly lower in the AR-PD subgroup than in the TD-PD subgroup.

3.2. 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane/meta-iodobenzylguanidine correlation

When all patients' data were analyzed without separating subgroups, S/N of bilateral lentiform nuclei significantly correlated with early H/M (Table 2). However, when the individual subgroup data were analyzed separately, remarkable differences in these correlations were noted between the 2 subgroups as below.

3.2.1. 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane/meta-iodobenzylguanidine correlation in the TD-PD subgroup. Neither early nor delayed H/M correlated with any of the 4 striatal S/N.

3.2.2. 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane/meta-iodobenzylguanidine correlation in the AR-PD subgroup. Early H/M positively correlated with S/N of the contralateral lentiform nucleus (r=0.565, *P*=.035) and

Table 1

Baseline demographic data, clinical data, ^{123}I-MIBG cardiac uptake, and ^{18}F-FP-CIT striatal uptake in early Parkinson patients with TD or AR subtype.

	Total n=31	TD-PD n=17	AR-PD n=14	*P* TD-PD vs AR-PD
Sex (male, n, %)	11 (35%)	3 (18%)	8 (57%)	.031[†,*]
Age (yr, mean ± SD)	63.45±8.41	63.88±7.57	62.71±9.63	.984[‡]
Disease duration (mo, mean±SD)	27.48±23.83	25.65±26.32	29.71±21.18	.421[‡]
Early H/M ratio	2.10 (0.87)	2.30 (0.84)	1.71 (0.94)	.421[‡]
Delayed H/M ratio	1.85 (1.22)	1.99 (1.29)	1.60 (1.12)	.625[‡]
Contralateral CN, S/N	3.46 (1.69)	4.02 (1.10)	2.91 (1.16)	.015[‡,*]
Ipsilateral CN, S/N	3.97 (1.56)	4.36 (1.08)	3.33 (1.36)	.026[‡,*]
Contralateral LN, S/N	2.24 (0.59)	2.40 (0.59)	1.98 (0.47)	.003[‡,*]
Ipsilateral LN, S/N	2.69 (0.94)	3.06 (0.71)	2.49 (0.85)	.008[‡,*]

AR=akinetic-rigid, CN=caudate nucleus, FP-CIT = 2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane, H/M=heart-to-mediastinum, LN=lentiform nucleus, MIBG = meta-iodobenzylguanidine, PD = Parkinson disease, SD = standard deviation, S/N=specific-to-nonspecific binding ratio, TD=tremor-dominant.

Values are the median (IQR: Q1–Q3), except sex, age, and disease duration.

[*] Asterisks for statistically significant below .05.

[†] Fisher exact test.

[‡] Mann–Whitney *U* test.

Table 2

Correlations using Spearman test between striatal ^{18}F-FP-CIT uptake and clinical parameter and between striatal ^{18}F-FP-CIT uptake and cardiac ^{123}I-MIBG uptake.

		Total (n=31)			TD-PD (n=17)			AR-PD (n=14)		
S/N		Duration	Early H/M	Delayed H/M	Duration	Early H/M	Delayed H/M	Duration	Early H/M	Delayed H/M
Contralateral CN	r	0.023	0.232	0.148	0.042	–0.034	–0.140	0.097	0.481	0.591
	P	.902	.210	.426	.873	.896	.593	.742	.081	.026*
Ipsilateral CN	r	0.069	0.156	0.062	0.074	–0.204	–0.306	0.144	0.459	0.499
	P	.712	.402	.740	.778	.433	.232	.623	.098	.069
Contralateral LN	r	–0.075	0.421	0.349	0.108	0.313	0.184	–0.074	0.565	0.631
	P	.687	.018*	.054	.679	.222	.480	.801	.035*	.016*
Ipsilateral LN	r	–0.115	0.418	0.354	0.025	0.266	0.150	–0.248	0.618	0.631
	P	.536	.019*	.051	.925	.302	.567	.393	.019*	.016*

AR = akinetic-rigid, CN = caudate nucleus, FP-CIT = 2β-carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl)-nortropane, H/M = heart-to-mediastinum, LN = lentiform nucleus, PD = Parkinson disease, S/N = specific-to-nonspecific binding ratio, TD = tremor-dominant.

* Asterisks for statistically significant below .05.

also with that of the ipsilateral lentiform nucleus (r = 0.618, *P* = .019), but not with S/N of either caudate nucleus. Delayed H/M ratio positively correlated with S/N of contralateral lentiform nucleus (r = 0.631, *P* = .016), with S/N of ipsilateral lentiform nucleus (r = 0.631, *P* = .016), and S/N of contralateral caudate nucleus (r = 0.591, *P* = .026), but not with S/N of ipsilateral caudate nucleus.

4. Discussion

^{123}I-FP-CIT SPECT imaging and cardiac ^{123}I-MIBG imaging have been used in combination or separately to study PD patients for various purposes. Also, using these imaging modalities, PD subtypes have been assessed either in combination or separately. When assessed separately by subtype, most studies have consistently found striatal ^{123}I-FP-CIT uptake to be lower in the AR subtype than in the TD subtype.[29–31] Using PET imaging that has higher resolution and sensitivity than SPECT imaging, we validated the prior results based on ^{123}I-FP-CIT SPECT imaging; striatal ^{18}F-FP-CIT uptake was also lower in patients with AR-PD compared with TD-PD.

Cardiac ^{123}I-MIBG uptake has also been reported to be lower in patients with AR-PD than in patients with TD-PD at all H&Y stages as well as at early stages.[32,33] Our results were in the same direction, that is, H/M being slightly lower in the AR-PD subgroup, although the difference in H/M between the 2 subgroups was not statistically significant, possibly due to our small sample size.

As discussed above, published results regarding relative uptake of these tracers in each subtype are fairly abundant and without significant controversy. However, data on the intrasubject FP-CIT/MIBG correlation (reflecting the association between dopaminergic and noradrenergic systems) in PD patients are not only relatively scant but vary among studies in terms of the presence or absence of a significant FP-CIT/MIBG correlation or of the degree of correlation, if a significant correlation is present. In the literature, one of the common reasons for inconsistent results among studies is different sample sizes. However, inconsistent intrasubject FP-CIT/MIBG correlations among studies appear to be less likely due to different sample sizes given that Spiegel et al[23] reported a reasonably good FP-CIT/MIBG correlation in one of their studies despite a small sample size, whereas another study by the same investigators with a considerably larger sample size showed a weaker correlation.[34] Yoshii et al[21] study, which had a reasonably large sample size, also found a weak correlation. Therefore, the sample size difference does not fully explain the inconsistent results among studies. Other clinical variables, such as age, age at disease onset, disease duration, or disease severity, were not found to be significant factors affecting the FP-CIT/MIBG correlation.[34]

While no convincing reason could be found to explain the inconsistent results regarding the intrasubject FP-CIT/MIBG correlation in the literature, our data showed a quite remarkable difference in this correlation between the 2 motor subtypes. We found a modest correlation (Spearman Rho values ranging from 0.565 to 0.631, *P* = .016) in the AR-PD subgroup between H/M and S/N of contralateral lentiform nucleus, ipsilateral lentiform nucleus, and contralateral caudate nucleus. By contrast, none of the 4 striatal S/N correlated with H/M (either early or delayed) in the TD-PD subgroup. These results suggest that inconsistency in the reported data on the FP-CIT/MIBG correlation could have partly been because patients with both types of PD were combined in most studies.

Even among studies that found a significant FP-CIT/MIBG correlation, there were inconsistencies as to which side (ipsilateral vs contralateral vs both) of striatum correlates significantly with H/M and also as to which subregion's FP-CIT uptake correlates with cardiac MIBG uptake, for example, putamen vs caudate nucleus vs both. While some studies reported results from separate analysis of putamen and caudate nucleus[24,34] others did not.[21,23] Spiegel et al[23] showed a strong relationship between the contralateral striatum and H/M. However, they reported significant correlations in another publication between ^{123}I-MIBG uptake and both contralateral and ipsilateral ^{123}I-FP-CIT uptake of both caudate nucleus and putamen.[34] Chiaravalloti et al[24] reported a weak correlation between H/M and ^{123}I-FP-CIT uptake in the ipsilateral striatum in patients with the AR subtype. Yoshii et al[21] even selected either contralateral or ipsilateral striatum, whichever was associated with more impaired ^{123}I-FP-CIT uptake, and, using this region, found a weak FP-CIT/MIBG correlation.

Having experience with ^{123}I-FP-CIT SPECT imaging and knowing its limited resolution and sensitivity, we believe that it would be quite challenging to obtain accurate quantitative results separately from each of the caudate nucleus and putamen. Even with ^{18}F-FP-CIT PET/CT imaging where separation of the 2 structures could be more easily done, we did not feel that we could accurately separate the globus pallidus and the putamen

from each other with confidence. Therefore, we chose to use the word lentiform nucleus instead of putamen in the current study. As presented earlier, significant correlations that we found were primarily between S/N of lentiform nuclei and cardiac MIBG uptake. Therefore, between the putamen and caudate nucleus, our results favored the former as the subregion that is associated with a better FP-CIT/MIBG correlation. However, in a very recent study, Oh et al performed a MR-guided spatial normalization method to quantify ^{18}F-FP-CIT uptake in multiple striatal subregions including globus pallidus. They found that the globus pallidus was the subregion showing the best FP-CIT/MIBG correlation in patients with early PD. The correlation that they found was independent of age, disease duration, disease severity, and other subregional dopamine uptake patterns.[35] While this result is somewhat different than others, it seems to partly support our result, that is, the lentiform nucleus being the main subregion showing a better FP-CIT/MIBG correlation than caudate nuclei as the globus pallidus is 1 of the 2 structures forming the lentiform nucleus. On the other hand, it is unknown how Oh et al results would have been altered in each of the different motor subtypes by analyzing them separately. All in all, given our results as well as Oh et al, the use of low-resolution ^{123}I-FP-CIT imaging could have been another important reason for inconsistent results in the literature.

We chose to study only early PD patients with H&Y stages 1 and 2 for the following reasons. While imaging parameters that differ among PD subtypes may be of clinical value, they would be even more valuable if such differences were present at early stages because early identification of PD subtypes is important in prognosis prediction and determining therapeutic course in a clinical setting. In addition, we were not sure how the differences between the 2 subtypes would be blunted by mixing PD patients of all stages in a small sample as severe degeneration of nigrostriatal dopaminergic pathway in the advanced stage of PD might prevent or mislead in characterizing the pathophysiologic mechanism. In the future, comparing the differences in the relationship between ^{18}F-FP-CIT and ^{123}I-MIBG in early PD and advanced PD patients may be of interest.

The most significant limitation of our study would be the small sample size. Nonetheless, we believe that our study adds valuable information to the literature regarding a subject with limited data and significant controversies, especially because PET offers higher resolution and enables more accurate subregional quantification compared to ^{123}I-FP-CIT SPECT imaging.

5. Conclusion

Our data suggest a coupled degeneration of nigrostriatal dopaminergic and myocardial sympathetic denervation even at early stages of PD but only in patients with the AR subtype. The difference in the FP-CIT/MIBG correlation between the 2 motor subtypes likely reflects the heterogeneous pathophysiology of PD. Further researches on the relationship between nondopaminergic and dopaminergic system in PD using large samples and high-resolution, high-sensitivity PET imaging seem to be warranted to identify possible roles of these techniques in the management of PD patients.

Author contributions

Conceptualization: Ji Young Kim.
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