Parkinsonism and Related Disorders 63 (2019) 156–161

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Striatal dopamine activity and myocardial ^{123}I-metaiodobenzylguanidine uptake in early Parkinson's disease

Yoon-Sang Oh[a], Joong-Seok Kim[a,*], Sang-Won Yoo[a], Eo-Jin Hwang[a,b], Chul Hyoung Lyoo[c], Kwang-Soo Lee[a]

[a] Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[b] Department of Radiology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[c] Department of Neurology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Parkinson's disease
Dopamine transporter scan
^{123}I-metaiodobenzylguanidine scintigraphy

ABSTRACT

Introduction: Dopamine transporter imaging and myocardial ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy have been widely used to diagnose and discriminate degenerative parkinsonism. Many studies have reported that both imaging findings are associated with a variety of motor and non-motor phenomena in Parkinson's disease (PD). However, the association between striatal dopamine activity and myocardial ^{123}I-MIBG uptake has not been well investigated. The objective of this study is to identify the dopamine transporter activity of the corpus striatum and thalamus according to myocardial ^{123}I-MIBG uptake in PD.

Methods: Ninety-six newly diagnosed, non-medicated PD patients were enrolled. All patients underwent ^{123}I-MIBG myocardial scintigraphy, positron emission tomography (PET) using ^{18}F−N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane and T1-weighted magnetic resonance imaging (MRI). Patients were stratified into normal and decreased ^{123}I-MIBG groups according to their delayed heart-to-mediastinum ratio (cutoff value = 1.78). After normalizing the PET images with spatially normalized MRI, the regional standardized uptake value ratios (SUVRs) were analyzed with a volume-of-interest template between the two groups.

Results: Thirty-one patients showed normal myocardial ^{123}I-MIBG uptake, and 65 patients showed reduced uptake. The SUVR of the globus pallidus in the group with reduced ^{123}I-MIBG uptake was significantly lower than the SUVR in the normal ^{123}I-MIBG uptake group. The heart-to-mediastinum ratio was correlated well with the SUVR of the globus pallidus, independent of age, disease duration, and the severity of motor symptoms.

Conclusion: Early PD patients with normal ^{123}I-MIBG uptake showed a relatively preserved dopamine reserve in the globus pallidus than patients with reduced ^{123}I-MIBG uptake.

1. Introduction

Dopamine transporter imaging has been widely used to diagnose and discriminate Parkinson's disease (PD) from secondary parkinsonism. Decreased striatal dopamine transporter uptake correlates with disease duration and motor symptom severity in PD [1]. Striatal dopamine depletion has also been considered as a predictor of motor complications, such as freezing of gait and wearing off [2,3]. However, dopamine transporter imaging has limitations for differentially diagnosing PD from other forms of degenerative parkinsonism [4].

^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy is a useful imaging tool for differentiating PD from atypical parkinsonism such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). Myocardial ^{123}I-MIBG uptake in the early phase reflects the density of presynaptic cardiac sympathetic nerve endings, and in the delayed phase it reflects the presynaptic functional tone of the cardiac sympathetic nerves [5,6]. ^{123}I-MIBG myocardial uptake was reduced in Lewy body diseases, represented as PD and dementia with Lewy bodies [5,7]. Some studies have revealed that myocardial ^{123}I-MIBG uptake correlated with the disease duration, severity of motor symptoms, and specific phenotype in PD, whereas other studies did not find these associations [8–10]. A number of studies have reported that PD patients with normal myocardial ^{123}I-MIBG uptake eventually developed impaired cardiac sympathetic innervations [10–12]. Moreover, the PD patients with normal ^{123}I-MIBG uptake had a lower prevalence of non-motor symptoms, and a lower incidence of

* Corresponding author.Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, 222, Banpo-daero, Seocho-gu, Seoul, 06591, Republic of Korea
E-mail address: neuronet@catholic.ac.kr (J.-S. Kim).

https://doi.org/10.1016/j.parkreldis.2019.02.012
Received 17 October 2018; Received in revised form 8 February 2019; Accepted 12 February 2019

the wearing-off phenomenon compared to those with low ^{123}I-MIBG uptake [13,14].

The association between myocardial ^{123}I-MIBG uptake and striatal dopamine transporter uptake in PD patients has not yet been well investigated. In this study, we assessed whether myocardial ^{123}I-MIBG uptake is associated with striatal dopamine uptake. We hypothesized that patients with normal ^{123}I-MIBG uptake would have different striatal dopamine uptake patterns than patients with reduced ^{123}I-MIBG uptake. The associations between myocardial ^{123}I-MIBG uptake and dopamine uptake in the striatal subregions were also investigated.

2. Methods

2.1. Subjects

De novo patients with PD who visited the movement disorder clinic of a university-affiliated hospital between January 2015 and June 2016 were included. PD was diagnosed based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [15]. Basic demographics, including age, sex, disease duration, and medical history of hypertension and diabetes mellitus, were obtained. Complete physical and neurological examinations were also performed. Parkinsonian motor symptoms were measured using the Unified Parkinson's Disease Rating Scale (UPDRS) Part III and the modified Hoehn and Yahr (H&Y) stage score. Magnetic resonance (MR) imaging of the brain, ^{18}F−N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane positron emission tomography (^{18}F-FP-CIT PET), and ^{123}I-MIBG myocardial scintigraphy were performed on all patients. All enrolled patients had decreased dopamine transporter uptake in the striatum, mainly in the posterior putamen.

Excluded subjects had: (1) normal dopamine transporter scan based on the Movement Disorder Society Clinical Diagnostic Criteria for PD [16]; (2) neurological abnormalities related to atypical or secondary parkinsonism [17,18]; (3) structural or space-occupying lesions on the basal ganglia; (4) a history of diabetic neuropathy or other peripheral/autonomic neuropathy; (5) a history of relevant cardiac disease (such as ischemic heart disease, heart failure, or cardiomyopathy) or any abnormalities on routine chest radiography or electrocardiography; or (6) medication regimens known to influence myocardial ^{123}I-MIBG uptake or striatal dopamine uptake.

The institutional review board at Seoul St. Mary's Hospital approved this study protocol. Each subject including healthy controls provided informed consent for participation. All experiments were performed in accordance with relevant guidelines and regulations.

2.2. ^{123}I-metaiodobenzylguanidine myocardial scintigraphy

^{123}I-MIBG scintigraphy was performed with a dual-head camera equipped with a low-energy, high-resolution collimator (Siemens, Munich, Germany/Infinia, GE Healthcare, Chicago, IL, USA). Data were collected 30 min (early) and 2 h (delayed) after injecting 111 MBq of ^{123}I-MIBG. A static image with a 128 × 128 matrix was obtained. Regions of interest were drawn manually around the whole heart and mediastinum. The heart-to-mediastinum (H/M) ratio was calculated from the average counts per pixel in the heart and mediastinum. Myocardial ^{123}I-MIBG washout rate was calculated as follows: [(early H/M − delayed H/M)/early H/M] x 100 [19]. The normal control values for early H/M, delayed H/M and washout rate were obtained from 25 participants who had no history of neurological disorders and no abnormalities on routine cardiac examinations such as electrocardiography and 24-hr Holter monitoring (6 men and 19 women, mean age 67.4 ± 4.8 years) and were 2.20 ± 0.25, 2.26 ± 0.23, and – 4.18 ± 15.8, respectively. In this study, we used the delayed H/M ratio, because the delayed phase measurement reflected the active neuronal uptake of myocardial ^{123}I-MIBG without passive transfer and was recommended for assessment of postganglionic presynaptic sympathetic failure in PD [20]. The delayed H/M ratio of age-matched controls was normally distributed ($p > 0.05$ by one-sample Kolmogorov-Smirnov test). Values within the reference limit of the normal delayed H/M ratio were calculated as lower limits = $mean - (t_{0.975,11}$ x $\sqrt{(n+1)/n}$ x *standard deviation)* (cutoff value = 1.78).

2.3. ^{18}F-FP-CIT PET imaging acquisition and processing

Computed tomography (CT) and ^{18}F-FP-CIT PET images were acquired using a Discovery STE PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). At 3 h after the intravenous injection of an average of 3.7 MBq/kg of ^{18}F-FP-CIT, brain CT scans were acquired for attenuation correction, followed by a 10 min ^{18}F-FP-CIT emission PET scan. PET images were reconstructed into a 512 × 512 × 110 matrix using an ordered-subsets expectation maximization algorithm. The voxel size was 0.668 × 0.668 × 2 mm. Axial T1-weighted brain MR images with 3D-spoiled gradient-recalled sequences (512 × 512 matrix, voxel spacing 0.469 × 0.469 × 1 mm) were also acquired with a 3.0-T scanner (Magnetom Verio, Siemens, Erlangen, Germany).

We used Statistical Parametric Mapping 8 software (SPM8; Wellcome Trust Centre for Neuroimaging, London, UK) implemented in MATLAB 2015a (MathWorks, Natick, MA) for co-registration and spatial normalization of the images and voxel-based comparisons. For the spatial normalization of ^{18}F-FP-CIT PET images, a MR-guided spatial normalization method was performed [21]. PET images were co-registered to individual MR images and spatially normalized to the Montreal Neurological Institute space with parameter normalizing skull-stripped MR images [21]. Subject-specific striatal volume of interest (VOI) templates derived from FreeSurfer 5.1 (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu), which is regarded as a gold standard for comparing striatal ^{18}F-FP-CIT PET binding values, were used. T1-weighted MR images were resliced to 1 mm isovoxel space, corrected for inhomogeneity, skull-stripped, and segmented into gray and white matter [21]. To measure striatal subregional and cerebellar binding values in spatially normalized PET images, we created VOI templates for the caudate, putamen, and cerebellum. Then the striatal and cerebellar segments were spatially normalized to the skull-stripped MR template within 1 mm sized isovoxel space. Using the VOI template, we measured the regional standardized uptake value (SUV) of the cerebellum and each side of the caudate, putamen, globus pallidus, thalamus, and ventral striatum in the PET images [21]. We also used an in-house MATLAB program for simple arithmetic operations on images and measuring the regional uptake values. Mean SUV ratios (SUVRs) were calculated as the target SUV divided by the cerebellum SUV.

2.4. Statistical analysis

All patients were stratified to the normal or decreased ^{123}I-MIBG group using the delayed H/M ratio (cut-off value = 1.78). Pearson's $\chi 2$ tests were used to compare frequencies for categorical variables, and independent sample t-tests or one-way analysis of variance (ANOVA) tests were used to compare mean differences among the groups. The regional and subregional SUVRs between the normal and decreased ^{123}I-MIBG groups were analyzed using an analysis of covariance (ANCOVA) while controlling for age, disease duration, and UPDRS part III score. The patients were also divided into four quartile groups by the delayed H/M ratio. Correlations between the early and delayed H/M ratios, washout rate, and SUVRs in the striatal subregions were determined using partial correlation coefficients adjusted for age, disease duration, and UPDRS part III score. A multiple linear regression analysis was performed with the delayed H/M ratio as a dependent variable, and age, disease duration, UPDRS part III score, and SUVR values of each striatal subregion as covariates.

All statistical analyses were performed in SPSS version 24.0 for Mac (IBM Corporation, New York, NY, USA). Statistical significance was set

Table 1
Clinical characteristics and ^{123}I-metaiodobenzylguanidine scintigraphy findings of patients.

	Normal H/M group (n = 31)	Decrease H/M group (n = 65)	P value
Age, years, mean ± SD	68.7 ± 11.4	68.9 ± 8.2	0.923
Sex, male (%)*	16 (51.6%)	30 (46.2%)	0.617
Hypertension (%)*	12 (38.7%)	28 (43.1%)	0.685
Diabetes mellitus (%)*	4 (12.9%)	14 (21.5%)	0.311
Disease duration, years	1.2 ± 0.8	1.2 ± 1.2	0.877
UPDRS part III score	16.6 ± 7.7	16.6 ± 8.3	0.998
Hoehn and Yahr stage	1.8 ± 0.6	1.7 ± 0.6	0.286
Early H/M ratio	1.96 ± 0.16	1.45 ± 0.20	< 0.001
Delayed H/M ratio	2.07 ± 0.18	1.36 ± 0.21	< 0.001
Washout rate	- 6.11 ± 6.47	6.30 ± 5.76	< 0.001

Abbreviations: H/M, heart-to-mediastinum; UPDRS, Unified Parkinson's Disease Rating Scale.
Values represent mean with standard deviation or numbers of patients (percentage).
Analyses were performed by independent sample t-tests and *the $\chi 2$ test.

at $p < 0.05$.

3. Results

A total of 96 patients with PD were enrolled in this study; 65 patients (67.7%) had decreased ^{123}I-MIBG uptake, and 31 patients (32.3%) had normal ^{123}I-MIBG uptake according to their delayed H/M ratio. The mean age, sex distribution, disease duration, and frequency of hypertension and diabetes mellitus in the two groups did not differ statistically. The two groups had similar motor symptoms as assessed by their UPDRS part III scores and modified H&Y stage scores (Table 1). In addition, there was no significant differences between the early and delayed H/M ratios, and washout rate according to the disease stages (Supplementary Table 1).

We analyzed the SUVRs of the PET imaging between the two groups. The decreased ^{123}I-MIBG group had a lower SUVR in the globus pallidus than the normal ^{123}I-MIBG group (normal vs. decreased: 3.78 ± 1.24 vs. 3.33 ± 0.86; p = 0.026). In the subregion analysis, the SUVRs in the right (p = 0.049) and left globus pallidus (p = 0.022) were significantly lower in the decreased ^{123}I-MIBG group. However, we found no significant differences between the two groups in the SUVRs of the caudate nucleus, putamen, thalamus, or ventral striatum (Table 2 and Fig. 1). In the subgroup analysis by quartile, the statistical significances were similar: patients in the lower two quartiles (delayed H/M ratio ≤ 1.51) showed lower SUVRs in the whole globus pallidus (1st quartile, 3.22 ± 0.54; 2nd quartile, 3.07 ± 0.71), right globus pallidus (1st quartile, 3.26 ± 0.56; 2nd quartile, 3.09 ± 0.69), and left globus pallidus (1st quartile, 3.18 ± 0.55; 2nd quartile, 3.06 ± 0.77) than those in the higher two quartiles (whole globus pallidus: 3rd quartile, 3.72 ± 1.01; 4th quartile, 3.88 ± 1.40, p = 0.007; right globus pallidus: 3rd quartile, 3.81 ± 1.13; 4th quartile, 3.93 ± 1.38, p = 0.007; left globus pallidus: 3rd quartile, 3.84 ± 1.51; 4th quartile, 3.43 ± 1.05, p = 0.016) (Fig. 2). The early H/M ratio, delayed H/M ratio, and washout rate also correlated well with the SUVRs of the globus pallidus (early: $r = 0.343$, p = 0.001; delayed: $r = 0.377$, $p < 0.001$; washout rate: $r = -0.304$, p = 0.003) and the H/M ratios were marginally related to putamen (early: $r = 0.209$, p = 0.045; delayed: $r = 0.227$, p = 0.028) irrespective of age, disease duration, and UPDRS part III score (Fig. 3).

The linear regression analysis showed that the dopamine transporter uptake of globus pallidus was also independently associated with myocardial ^{123}I-MIBG uptake in patients with early PD, regardless of age, disease duration, UPDRS part III score and other subregional dopamine uptake patterns (Table 3).

Table 2
Comparison of standardized uptake value ratios between two groups.

	Normal H/M group (n = 31)	Decrease H/M group (n = 65)	P value
Caudate	3.76 (1.69)	3.85 (1.40)	0.693
Right	3.97 (1.71)	3.89 (1.41)	0.818
Left	3.56 (1.73)	3.82 (1.45)	0.331
Anterior	3.95 (1.97)	4.09 (1.61)	0.620
Right	4.11 (1.97)	4.05 (1.60)	0.893
Left	3.80 (2.05)	4.13 (1.70)	0.296
Posterior	2.95 (1.40)	3.18 (1.20)	0.299
Right	3.27 (1.51)	3.43 (1.31)	0.518
Left	2.69 (1.36)	2.98 (1.16)	0.179
Putamen	4.35 (1.56)	3.93 (1.06)	0.120
Right	4.49 (1.74)	3.90 (1.17)	0.050
Left	4.21 (1.57)	3.95 (1.13)	0.345
Anterior	4.46 (1.84)	4.04 (1.29)	0.186
Right	4.66 (1.97)	4.03 (1.38)	0.068
Left	4.25 (1.95)	4.05 (1.41)	0.570
Posterior	3.44 (1.56)	3.06 (0.91)	0.118
Right	3.74 (2.01)	3.16 (1.14)	0.063
Left	3.21 (1.42)	2.98 (0.99)	0.343
Ventral	3.97 (1.18)	3.78 (0.73)	0.350
Right	4.00 (1.21)	3.81 (0.83)	0.385
Left	3.93 (1.23)	3.75 (0.77)	0.375
Globus pallidus	3.78 (1.24)	3.33 (0.86)	0.026*
Right	3.80 (1.24)	3.39 (0.92)	0.049*
Left	3.76 (1.34)	3.27 (0.84)	0.022*
Thalamus	1.43 (0.12)	1.43 (0.15)	0.893
Right	1.44 (0.11)	1.45 (0.16)	0.710
Left	1.41 (0.14)	1.40 (0.16)	0.922
Ventral striatum	3.97 (1.18)	3.78 (0.73)	0.139
Right	4.00 (1.21)	3.81 (0.83)	0.062
Left	3.93 (1.23)	3.75 (0.94)	0.304

Abbreviations: H/M, heart-to-mediastinum.
Values represent mean with standard deviation.
Analyses were performed by analysis of covariance (ANCOVA) test controlling for age, disease duration, and UPDRS part III score. * < 0.05.

4. Discussion

In this study, we demonstrated that patients with normal ^{123}I-MIBG uptake showed higher dopamine transporter uptake in the globus pallidus than patients with decreased ^{123}I-MIBG uptake. The analysis by quartile groups and correlation exhibited similar results. The myocardial ^{123}I-MIBG washout rate was also related to dopamine transporter activities in the globus pallidus.

Normal cardiac sympathetic innervation in PD has been considered a “good” marker in terms of several clinical manifestations; patients with normal ^{123}I-MIBG uptake have shown fewer motor deficits, fewer akinetic-rigid symptoms, and slow progression of motor dysfunctions [8–10]. Normal ^{123}I-MIBG uptake is also associated with a reduced risk of wearing-off in PD [14]. Therefore, we hypothesized that myocardial ^{123}I-MIBG uptake would be associated with striatal dopamine uptake in PD, and we found that patients with normal ^{123}I-MIBG uptake showed relatively preserved dopamine transporter activity in the globus pallidus compared with those with decreased ^{123}I-MIBG uptake.

In general, washout rate was correlated negatively with a H/M ratio, because increased washout rate is a common feature of damaged or failing myocardium [22]. The washout rate was significantly higher in patients with decreased ^{123}I-MIBG group than those with normal ^{123}I-MIBG and controls. These findings provide more direct evidence that the pathological changes in the myocardium were also related to decrement of dopamine transporter uptake in the globus pallidus.

There were few studies reporting the association between myocardial ^{123}I-MIBG uptake and striatal dopamine transporter activity in PD. One study showed that the decreased H/M ratio was associated with reduced dopamine transporter specific binding ratio in the whole striatum [23], similar to our result. However, another study demonstrated a contradictory result; in 37 patients with PD, ^{123}I-MIBG uptake

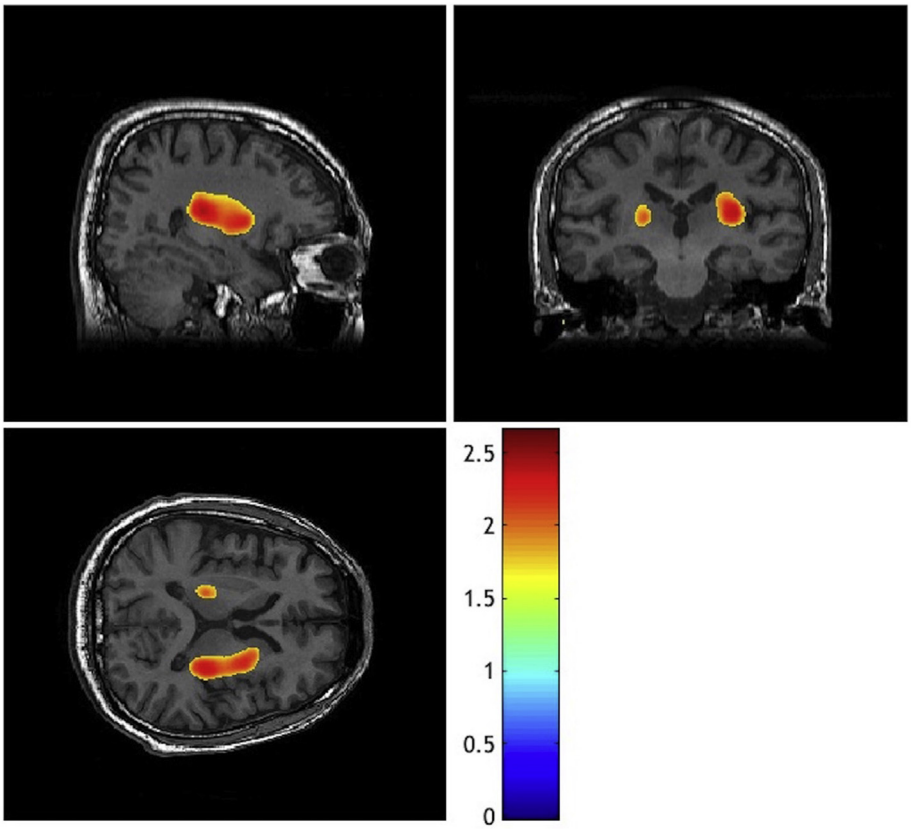

Fig. 1. Voxel-based comparison of ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane positron emission tomography (^{18}F-FP-CIT PET) controlling for age, disease duration, and UPDRS part III scores between Parkinson's disease patients with normal and decreased ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) uptake. The differences of the standardized uptake value ratios (SUVRs) between the two groups were demonstrated in the colored region. The SUVR values in the globus pallidus of patients with decreased ^{123}I-MIBG uptake decreased more than those of patients with normal ^{123}I-MIBG uptake. T values are indicated by the color bar.

was unrelated to nigrostriatal dopamine degeneration [24]. These inconsistencies could be attributed to different imaging techniques used in each study. Importantly, those researchers used single-photon emission computed tomography (SPECT) and N-(3-fluoropropyl)-2b-carbomethoxy-3b-(4-[^{123}I]iodophenyl) nortropane (^{123}I FP-CIT). In addition, that study used a small number of patients and analyzed the data using regressions or correlation coefficients. Manually drawing the regions of interest and using a semi-quantitative analysis can create bias in the form of image noise and sampling errors. Furthermore, the exclusive use of a SPECT template can lead to errors in PD patients because markedly reduced uptake in the posterior putamen results in overestimation biases. In this study, we used MR templates, not ligand-specific PET templates, by applying transformation parameters normalizing MR images to co-registered PET images for spatial normalization. This MR-guided spatial normalization method is more accurate and works independently from receptor density, and it can also assess and analyze important covariates such as age, disease duration, and motor symptom severity that create differences in striatal dopamine uptake in PD. Furthermore, we enrolled a relatively large number of de novo patients who had never taken anti-parkinsonian medications. Therefore, our ^{123}I-MIBG uptake and dopamine transporter activity results were not biased by dopaminergic medications.

Previous reports on dopamine transporter activity in the globus pallidus offer limited information about parkinsonian motor symptoms. One study revealed that the tremor-predominant PD subgroup had higher dopamine transporter uptake in the less affected hemisphere than the non-tremor group [25]. A postmortem study revealed that dopamine loss in the globus pallidus was less severe in tremor-

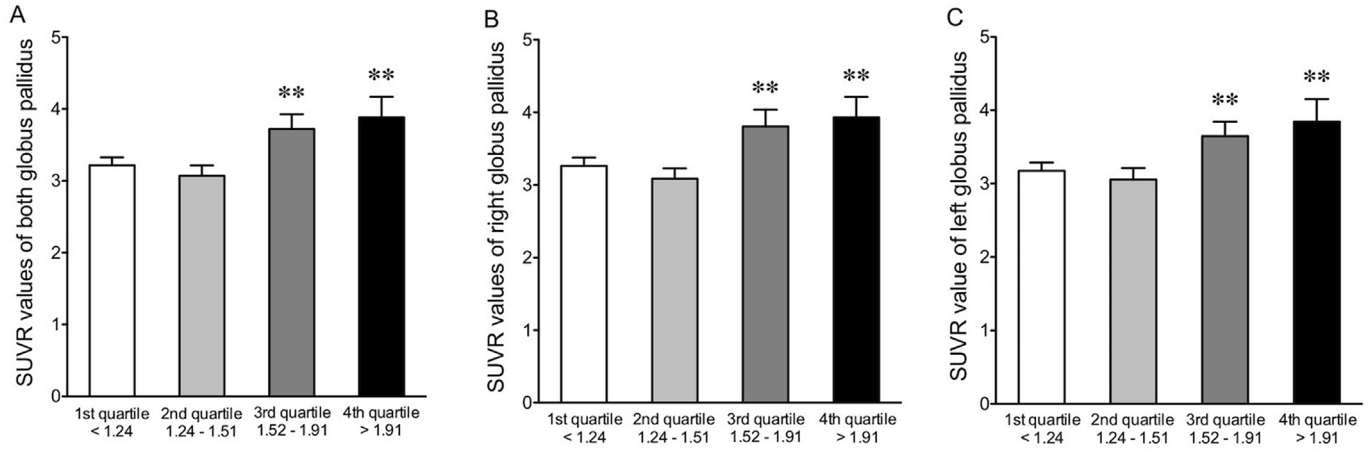

Fig. 2. Comparison between the delayed heart-to-mediastinum ratio by quartile and the standardized uptake value ratios (SUVRs) of (A) the globus pallidus, (B) right globus pallidus, and (C) left globus pallidus. The two lower quartiles showed lower SUVRs than the two higher quartiles.

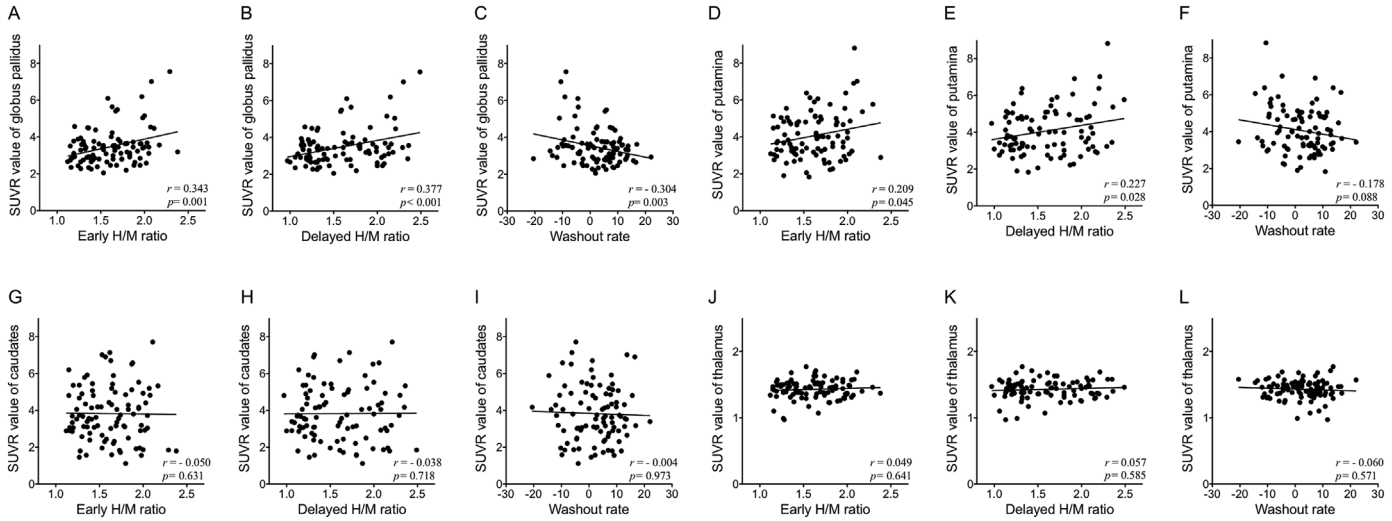

Fig. 3. Scatterplot graph and partial correlation analysis result between the heart-to-mediastinum (H/M) ratio and washout rate on myocardial ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy and the standardized uptake value ratios (SUVRs) of the striatal subregions. The SUVR values of the globus pallidus (A–C) were correlated with the early and delayed H/M ratios, and washout rate as well. The SUVRs of the putamen (D, E) were marginally associated with both the early and delayed H/M ratios. There was no relation between ^{123}I-MIBG uptakes and SUVR values of caudate nucleus (G–I) and thalamus (J–L).

dominant PD subjects [26]. Therefore, the relatively higher dopamine transporter uptake in the globus pallidus of patients with normal ^{123}I-MIBG uptake might contribute to motor manifestations.

PD is a multisystem disorder with progressive degeneration of the nigrostriatal dopaminergic systems and widespread extranigral pathology affecting different anatomical structures and neurotransmitters [27]. A postmortem analysis of incidental and symptomatic PD suggested that the appearance of α-synuclein-positive Lewy bodies occurred in a progressive and anatomical way from the dorsal motor nucleus of the vagus and the olfactory system with an ascending pattern [28]. Recent studies have suggested that Lewy body pathologies in the locus coeruleus and sympathetic ganglia precede those in the substantia nigra [29]. On the contrary, retrospective clinicopathologic studies have suggested that up to 47% of cases did not follow an ascending progression of Lewy bodies [30,31]. The subjects of our study showed decreased dopamine transporter uptake in the striatum, mainly in the posterior putamen. Among them, some had decreased ^{123}I-MIBG uptake, which suggest unequivocally early cardiac involvement, and others had normal ^{123}I-MIBG uptake due to the heterogeneous evolution of Lewy body pathology in the myocardium. Therefore, we can speculate that the threshold of the heart for pathological functional changes would vary in PD [32]. This cellular pathology thus spreads in parallel at similar rates with an ascending pattern, although the threshold for functional changes varies [32]. The cardiac sympathetic denervation influenced neuronal transmission in the brainstem. In the midbrain, complex circuitry was responsible for the innervation of dopaminergic neurons in the globus pallidus and substantia nigra. This parallel degeneration of the central and peripheral nervous systems and their functional thresholds for the emergence of symptoms could account for the association we found between myocardial ^{123}I-MIBG uptake and central dopaminergic activity in our patients.

The strength of this study is that we enrolled only newly diagnosed patients with relatively mild diseases who had never taken any drugs affecting dopaminergic and autonomic systems. In addition, we tried to minimize the confounding biases by squaring the motor symptom status. It has been well known that the correlation between disease severity and dopamine loss appears linear as the disease progresses [1]. Moreover, standardized quantitative analyses could minimize the image noise and sampling errors resulted during the visual or semi-quantitative method.

However, this study has several limitations. First, because all subjects were enrolled at the early stage of PD, atypical parkinsonism could not be completely excluded. In addition, we did not carry out neuropathological investigations, to confirm Lewy body pathology. In this study, we attempted to reduce selection bias by including patients who fulfilled UK brain bank criteria for PD and excluding suspected cases with MSA and PSP using each diagnostic criteria. Second, because this study had a cross-sectional design, we did not assess combined interactions on parkinsonian motor symptoms or further motor deterioration over time and temporal changes of striatal dopamine activity and myocardial ^{123}I-MIBG uptake.

To our knowledge, this is the first investigation of subregional differences in dopamine transporter uptake according to ^{123}I-MIBG uptake in patients with PD. Normal ^{123}I-MIBG uptake in early PD patients

Table 3
Multiple linear regression model for clinical and subregional dopamine transporter activities for contributors of myocardial ^{123}I-metaiodobenzylguanidine uptake in patients with Parkinson's disease.

Characteristics	Unstandardized B	Coefficients Standard Error	Standardized Coefficients Beta	t	p	95% confidence interval
Constant	1.783	0.613		2.907	0.005	0.564, 3.001
Age	- 0.010	0.005	- 0.235	- 1.817	0.073	- 0.021, 0.001
Disease duration	- 0.018	0.037	- 0.049	- 0.481	0.631	- 0.091, 0.055
UPDRS part III	- 0.002	0.005	- 0.035	- 0.329	0.743	- 0.012, 0.009
SUVR value of caudate nucleus	- 0.045	0.050	- 0.172	- 0.898	0.372	- 0.145, 0.055
SUVR value of putamen	0.020	0.066	0.064	0.303	0.762	- 0.111, 0.151
SUVR value of globus pallidus	0.143	0.068	0.371	2.105	0.038	0.008, 0.279
SUVR value of thalamus	0.088	0.339	0.032	0.260	0.795	- 0.586, 0.762

Abbreviations: SUVR = standardized uptake value ratio.

showed a lower reduction in dopamine transporter uptake in the globus pallidus. This finding suggests that patients with normal ^{123}I-MIBG uptake have a relatively preserved dopamine reserve. Further longitudinal studies will be needed to verify the combined impact of ^{123}I-MIBG uptake and dopamine transporter activity on the motor symptoms of PD.

Conflict of interest disclosures

All authors declare no competing interests.

Funding/support

This research was supported by Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT and Future Planning (NRF-2017R1D1A1B06028086).

Role of the funder/sponsor

The funder had no role in study design, data collection and analysis, the decision to publish or manuscript preparation.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.02.012.

References

[1] V. Kaasinen, T. Vahlberg, Striatal dopamine in Parkinson disease: a meta-analysis of imaging studies, Ann. Neurol. 82 (2017) 873–882.
[2] R. Djaldetti, A. Rigbi, L. Greenbaum, J. Reiner, M. Lorberboym, Can early dopamine transporter imaging serve as a predictor of Parkinson's disease progression and late motor complications? J. Neurol. Sci. 390 (2018) 255–260.
[3] S.J. Chung, Y. Lee, J.S. Oh, J.S. Kim, P.H. Lee, Y.H. Sohn, Putaminal dopamine depletion in de novo Parkinson's disease predicts future development of wearing-off, Park. Relat. Disord. 53 (2018) 96–100.
[4] F. Ba, W.R. Martin, Dopamine transporter imaging as a diagnostic tool for parkinsonism and related disorders in clinical practice, Park. Relat. Disord. 21 (2015) 87–94.
[5] S. Orimo, M. Suzuki, A. Inaba, H. Mizusawa, 123I-MIBG myocardial scintigraphy for differentiating Parkinson's disease from other neurodegenerative parkinsonism: a systematic review and meta-analysis, Park. Relat. Disord. 18 (2012) 494–500.
[6] S. Orimo, M. Yogo, T. Nakamura, M. Suzuki, H. Watanabe, 123)I-meta-iodobenzylguanidine (MIBG) cardiac scintigraphy in alpha-synucleinopathies, Ageing Res. Rev. 30 (2016) 122–133.
[7] S.J. Brandl, S. Braune, Sensitivity and specificity of cardiac metaiodobenzylguanidine scintigraphy in the early diagnosis of Parkinson's disease, Clin. Auton. Res. (2018), https://doi.org/10.1007/s10286-018-0534-y.
[8] K. Hamada, M. Hirayama, H. Watanabe, et al., Onset age and severity of motor impairment are associated with reduction of myocardial 123I-MIBG uptake in Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 74 (2003) 423–426.
[9] J. Spiegel, D. Hellwig, G. Farmakis, et al., Myocardial sympathetic degeneration correlates with clinical phenotype of Parkinson's disease, Mov. Disord. 22 (2007) 1004–1008.
[10] K. Tsujikawa, Y. Hasegawa, S. Yokoi, et al., Chronological changes of 123I-MIBG myocardial scintigraphy and clinical features of Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 86 (2015) 945–951.
[11] M. Watanabe, T. Takeda, K. Nakamagoe, et al., Sequential imaging analysis using MIBG scintigraphy revealed progressive degeneration of cardiac sympathetic nerve in Parkinson's disease, Eur. J. Neurol. 18 (2011) 1010–1013.
[12] D.W. Ryu, J.S. Kim, J.E. Lee, et al., Initial versus follow-up sequential myocardial ^{123}I-MIBG scintigraphy to discriminate Parkinson disease from atypical parkinsonian syndromes, Clin. Nucl. Med. (2019), https://doi.org/10.1097/RLU.0000000000002424.
[13] J.S. Kim, H.E. Park, I.S. Park, et al., Normal 'heart' in Parkinson's disease: is this a distinct clinical phenotype? Eur. J. Neurol. 24 (2017) 349–356.
[14] J.E. Lee, J.S. Kim, D.W. Ryu, Y.S. Oh, I.R. Yoo, K.S. Lee, Cardiac sympathetic denervation can predict the wearing-off phenomenon in patients with Parkinson's disease, J. Nucl. Med. 59 (2018) 1728–1733.
[15] W.R. Gibb, A.J. Lees, The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease, J. Neurol. Neurosurg. Psychiatry 51 (1988) 745–752.
[16] R.B. Postuma, D. Berg, M. Stern, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (2015) 1591–1601.
[17] S. Gilman, G.K. Wenning, P.A. Low, et al., Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (2008) 670–676.
[18] G.U. Höglinger, G. Respondek, M. Stamelou, et al., Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria, Mov. Disord. 32 (2017) 853–864.
[19] D. Agostini, I. Carrio, H.J. Verberne, How to use myocardial ^{123}I-MIBG scintigraphy in chronic heart failure, Eur. J. Nucl. Med. Mol. Imaging 36 (2009) 555–559.
[20] E.J. Chung, S.J. Kim, 123)I-metaiodobenzylguanidine myocardial scintigraphy in Lewy body-related disorders: a literature review, J Mov Disord 8 (2015) 55–66.
[21] J.S. Kim, H. Cho, J.Y. Choi, et al., Feasibility of computed tomography-guided methods for spatial normalization of dopamine transporter positron emission tomography image, PLoS One 10 (2015) e0132585.
[22] K. Nakajima, J. Taki, N. Tonami, et al., Decreased 123I-MIBG uptake and increased clearance in various cardiac diseases, Nucl. Med. Commun. 15 (1994) 317–323.
[23] F. Yoshii, M. Ryo, Y. Baba, T. Koide, J. Hashimoto, Combined use of dopamine transporter imaging (DAT-SPECT) and (123)I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy for diagnosing Parkinson's disease, J. Neurol. Sci. 375 (2017) 80–85.
[24] A. Chiaravalloti, A. Stefani, D. Di Biagio, et al., Cardiac sympathetic denervation is not related to nigrostriatal degeneration in Parkinson's disease, Ann. Nucl. Med. 27 (2013) 444–451.
[25] J.Y. Lee, N.P. Lao-Kaim, J. Pasquini, G. Deuschl, N. Pavese, P. Piccini, Pallidal dopaminergic denervation and rest tremor in early Parkinson's disease: PPMI cohort analysis, Park. Relat. Disord. 51 (2018) 101–104.
[26] A.H. Rajput, H.H. Sitte, A. Rajput, M.E. Fenton, C. Pifl, O. Hornykiewicz, Globus pallidus dopamine and Parkinson motor subtypes: clinical and brain biochemical correlation, Neurology 70 (2008) 1403–1410.
[27] L. Klingelhoefer, H. Reichmann, Parkinson's disease as a multisystem disorder, J. Neural. Transm. 124 (2017) 709–713.
[28] H. Braak, K. Del Tredici, et al., Staging of brain pathology related to sporadic Parkinson's disease, Neurobiol. Aging 24 (2003) 197–211.
[29] Y. Vermeiren, P.P. De Deyn, Targeting the norepinephrinergic system in Parkinson's disease and related disorders: the locus coeruleus story, Neurochem. Int. 102 (2017) 22–32.
[30] M.E. Kalaitzakis, M.B. Graeber, S.M. Gentleman, R.K. Pearce, The dorsal motor nucleus of the vagus is not an obligatory trigger site of Parkinson's disease: a critical analysis of alpha-synuclein staging, Neuropathol. Appl. Neurobiol. 34 (2008) 284–295.
[31] K.A. Jellinger, A critical reappraisal of current staging of Lewy-related pathology in human brain, Acta Neuropathol. 116 (2008) 1–16.
[32] S. Engelender, O. Isacson, The threshold theory for Parkinson's disease, Trends Neurosci. 40 (2017) 4–14.