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ORIGINAL ARTICLE

Usefulness of rCBF analysis in diagnosing Parkinson's disease: supplemental role with MIBG myocardial scintigraphy

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Abstract
^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy is a useful tool for differentiating idiopathic Parkinson's disease (PD) from parkinsonism (PS) caused by other disorders. However, cardiac MIBG uptake is affected by various causes. Alternatively, hypoperfusion in the occipital lobe of PD is reported recently.
Objective The objective is to clarify the correlation between regional cerebral blood flow (rCBF) alteration and cardiac MIBG uptake in PD. In addition, we examined whether additional brain perfusion analysis improved the differential diagnostic ability for PD from PS when compared with MIBG scintigraphy alone.
Methods Forty-nine patients with PD (27 mild groups: Hoehn and Yahr stages I, II; 22 severe groups: Hoehn and Yahr stages III, IV) and 28 patients with PS participated. We compared absolute rCBF values between PD and PS. In addition, we determined correlation between MIBG parameters and each rCBF value. Finally, we compared the diagnostic ability for the differentiation of PD from PS between two diagnostic criteria, each MIBG index abnormality alone [heart-to-mediastinum ratio, H/M (E) < 1.9, H/E (D) < 1.7, washout rate > 40%] and each MIBG index abnormality or occipital lobe hypoperfusion (<36 ml/100 g per min).
Results Absolute rCBF value of occipital lobe was significantly lower in severe PD as compared with PS or mild PD. In the correlation analysis, rCBF of occipital lobe correlated positively with MIBG parameters (H/M). Regarding the diagnostic ability, sensitivity improved by accounting for occipital hypoperfusion as compared with MIBG indices alone. In contrast, neither specificity nor accuracy improved by adding occipital lobe analysis.
Conclusions MIBG parameters (H/M) correlated positively with occipital hypoperfusion in PD. In the differential diagnosis between PD and PS, although its usefulness might be limited, analysis of rCBF in the occipital lobe added to ^{123}I-MIBG myocardial imaging can be recommended.

Keywords ^{123}I-MIBG · ^{99m}Tc-HMPAO · 3D-SSP · 3D-SRT · Parkinson's disease

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Introduction

Idiopathic Parkinson's disease (PD) is characterized by several cardinal symptoms, including resting tremor, rigidity, bradykinesia, and postural instability. However, there are no absolute indicators for diagnosing PD because the initial symptoms of PD may change with the onset, and the clinical diagnosis is sometimes difficult [1, 2].

In addition to the aforementioned characteristic symptoms, autonomic abnormalities have frequently

been noted in PD [3]. Earlier, [^{123}I] metaiodobenzylguanidine (MIBG) myocardial scintigraphy was used as an imaging method to evaluate sympathetic nerve terminals [4]. Recently, MIBG myocardial uptake is reported to be decreased in patients with PD regardless of the presence of orthostatic hypotension [5–8]. Clinically, MIBG myocardial scintigraphy is a useful tool for differentiating PD from parkinsonism (PS) caused by other disorders [5, 9]. However, cardiac MIBG uptake is known to be decreased in various diseases other than PD [10–13]. Other effective imaging methods, therefore, are necessary to overcome such drawbacks. One of the alternative imaging methods is measuring the concentration of striatal dopamine reuptake transporters such as ^{123}I-β-CIT single-photon emission computed tomography (SPECT) [14, 15]. However, such pharmaceuticals are commercially available in only a few countries, and are not commonly available in Japan.

Recently, regional cerebral blood flow (rCBF) alteration of PD using brain perfusion SPECT has been reported [16–21]. PD with autonomic nerve impairment showed hypometabolism in the parieto-occiptal lobe [22–24]. Bohnen et al. [20] reported a correlation between glucose metabolism and the severity of motor impairment. Notably, Abe et al. [25] reported occipital and posterior parietal hypoperfusion in PD patients without dementia using *N*-isopropyl-*p*-[(^{123}) I] iodoamphetamine rCBF SPECT.

Here, we investigated the correlation between rCBF distribution and MIBG indices in PD. In addition, we examined whether additional brain perfusion SPECT analysis could improve the ability to differentiate PD from PS as compared with ^{123}I-MIBG myocardial scintigraphy alone.

Materials and methods

Patients

Fifty patients with PS were recruited for the present study. Finally, we studied 49 idiopathic PD patients and 28 patients with PS owing to other diseases. The final diagnosis of those with PS was 14 multiple system atrophy (MSA-P), 5 progressive supranuclear palsy, 4 corticobasal degeneration, 3 drug-induced PS, and 2 essential tremor. PS with cerebrovascular disease was excluded.

Parkinson's disease was diagnosed if a patient had resting tremor, cogwheel rigidity, and bradykinesia. The PD patients did not have a supranuclear gaze abnormality, myoclonus, automatic dysfunction, apraxia, or dementia. No patients showed pseudopsia clinically. The severity of patients' motor impairment was graded according to the Hoehn and Yahr (H&Y) staging system [26]. All PD patients were categorized into two groups, severe stage (H&Y III, IV) and mild stage (H&Y I, II). Patients' cognitive functions were evaluated by Mini-Mental State Examination to exclude Parkinson's disease with dementia (PDD) or diffuse Levy body disease (DLB) [27–29].

None of the participants had any cardiac symptoms including bradycardia, tachycardia, chest oppression and pain, or significant arrhythmia. Electrocardiography, chest roentgenography, ultrasonic cardiography, and blood examinations including thyroid function were also performed and none of the patients showed any abnormality including diabetes mellitus on these examinations.

^{123}I-MIBG myocardial imaging

Following a 20-min resting period, patients received an intravenous injection of 111 MBq of ^{123}I-MIBG (FUJIFILM RI Pharma, Tokyo, Japan). A planar image of the chest view was obtained in an anterior view for 5 min with a dual-head eCAM r-camera (Siemens, New York, NY, USA) after 15 min for the early image and after 4 h for the delayed examination. The photopeak energy was centered at 159 keV with a 20% window. Relative ^{123}I-MIBG organ uptake was determined by setting the region of interest on the anterior view. Average counts per pixel in the heart and mediastinum were used to calculate the heart-to-mediastinum (H/M) ratio. Cardiac MIBG washout rate (WR) was defined as the percent change in activity from the early image to the delayed image within the left ventricle.

We previously performed cardiac MIBG imaging in normal subjects ($n = 20$, mean age 58.8 ± 5.2, range 43–66). In these patients, the mean early H/M was 2.3 ± 0.3, the mean delayed H/M was 2.1 ± 0.2, and the mean WR was 25 ± 5.3%.

^{99m}Tc-HMPAO-SPECT

Prior to undergoing SPECT, all subjects received an intravenous line while lying down with their eyes closed. Each subject received a 600-MBq intravenous injection of ^{99m}Tc-HMPAO (PAO). A dynamic study was done for calculating the absolute rCBF value using graphic analysis; 10 min following this injection, a brain SPECT was performed using a triple-head gamma camera (Prism 3000: Marconi) equipped with a high-resolution fan-beam collimator. For each camera, projection data were obtained in a 128 × 128 format for 24 angles of 120° at 50 s per angle. A Shepp and Logan Hanning filter was

used for SPECT image reconstruction at 0.7 cycles per centimeter. Attenuation correction was performed using Chang's method.

The global CBF was non-invasively measured using graphic analysis as described earlier without blood sampling [30]. The SPECT data were transferred to a personal computer with the interface software via the network for both 3D-SSP and 3D-SRT analyses. In 3D-SSP analysis, we used adjusted rCBF images (normalization of global CBF for each subject to 50 ml/100 g per minute with proportional scaling) to compare the relative rCBF in each group. Each of three groups was compared using unpaired *t* test. The areas whose *Z* score exceed 4.53 were defined as areas showing abnormal rCBF distribution. We also demonstrated decreased rCBF distribution with *Z* score over 2. In addition, absolute rCBF values of each cerebral cortex and basal ganglia were calculated using 3D-SRT [31]. We compared those absolute rCBF values respectively between three groups. And we examined which regions' rCBF abnormality was specific for PD.

To clarify the association between cardiac sympathetic nerve involvement and rCBF alteration, we analyzed the correlation between MIBG parameters and each cortical rCBF value.

Finally, we compared the diagnostic ability to differentiate PD from PS between two diagnostic criteria, patient is PD when each MIBG index is abnormal [H/M (E) <1.9, H/M (D) <1.7, WR > 40%] and that patient is PD when each MIBG index is abnormal or rCBF alteration (<36.0 ml/100 g per minute) existed. We determined the cut-off values of MIBG parameters and rCBF when accurate in differentiating PD from PS.

Statistical analysis

Correlations were analyzed using Spearman's and Pearson's correlation coefficients and expressed using linear regression curves. The Bonferroni–Dunn test was used for intergroup differences of rCBF or MIBG parameters among PD subgroup and PS.

Results

Patients' characteristics are listed in Table 1. Neither age nor sex was statistically significantly different among the three groups. In PD, both H/M (E) and H/M (D) were significantly lower than those of PS. WR of PD with severe stage was significantly higher than that of PS. Within the PD group, both H/M (E) and H/M (D) in the severe stage group were significantly lower than those of the mild stage group. Although the value of WR in the severe stage group was markedly increased in the severe stage group as compared with the mild stage group, the difference was not statistically significant (Table 1, Fig. 1).

The 3D-SSP analyses demonstrated that the severe PD group showed prominently decreased rCBF in the occipital lobe when compared with the PS group. A decrease in rCBF was also noted in the occipital lobe and in a part of the parietal lobe in severe PD as compared with the mild stage group (Figs. 2, 3).

According to the results of 3D-SRT analysis, the absolute rCBF value of the bilateral occipital lobes was significantly lower in the severe stage PD group as compared with PS or mild stage PD. Absolute values of rCBF in the other regions did not differ significantly. In contrast, rCBF of mild stage PD was almost equal to that of PS (Table 2).

In the correlation analysis, rCBF of both occipital lobes significantly correlated positively with H/M parameters in PD. However, there was no significant correlation between WR and rCBF of the bilateral occipital lobes. Although rCBF of other regions also correlated positively with H/M, their correlation coefficients were

Table 1 Comparison of clinical characteristics and ^{123}I-metaiodobenzylguanidine (MIBG) indexes

	PD (*n* = 49)		PS (*n* = 28)	*P*
	HY I or II (*n* = 27)	HY III or IV (*n* = 22)		
Age	66.0 ± 9.3	71.6 ± 7.7	64.5 ± 7.2	NS
Sex (M : F)	12 : 15	11 : 11	12 : 16	NS
Duration (y) (MIBG indices)	6.1 ± 5.2	9.6 ± 5.3	7.4 ± 2.1	NS
H/M (E)	1.81 ± 0.43*,**	1.36 ± 0.49*	2.36 ± 0.52	<0.01
H/M (D)	1.61 ± 0.56*,**	1.13 ± 0.51*	2.42 ± 0.85	<0.01
WR (%)	40.7 ± 12.7***	47.5 ± 17.3***	26.3 ± 12.2	<0.01

PD Parkinson's disease, *PS* parkinsonism, *H/M* heart-to-mediastinum ratio, *WR* washout rate
* Statistically significantly lower than PS
** Statistically significantly higher than HY III or IV
*** Statistically significantly higher than PS

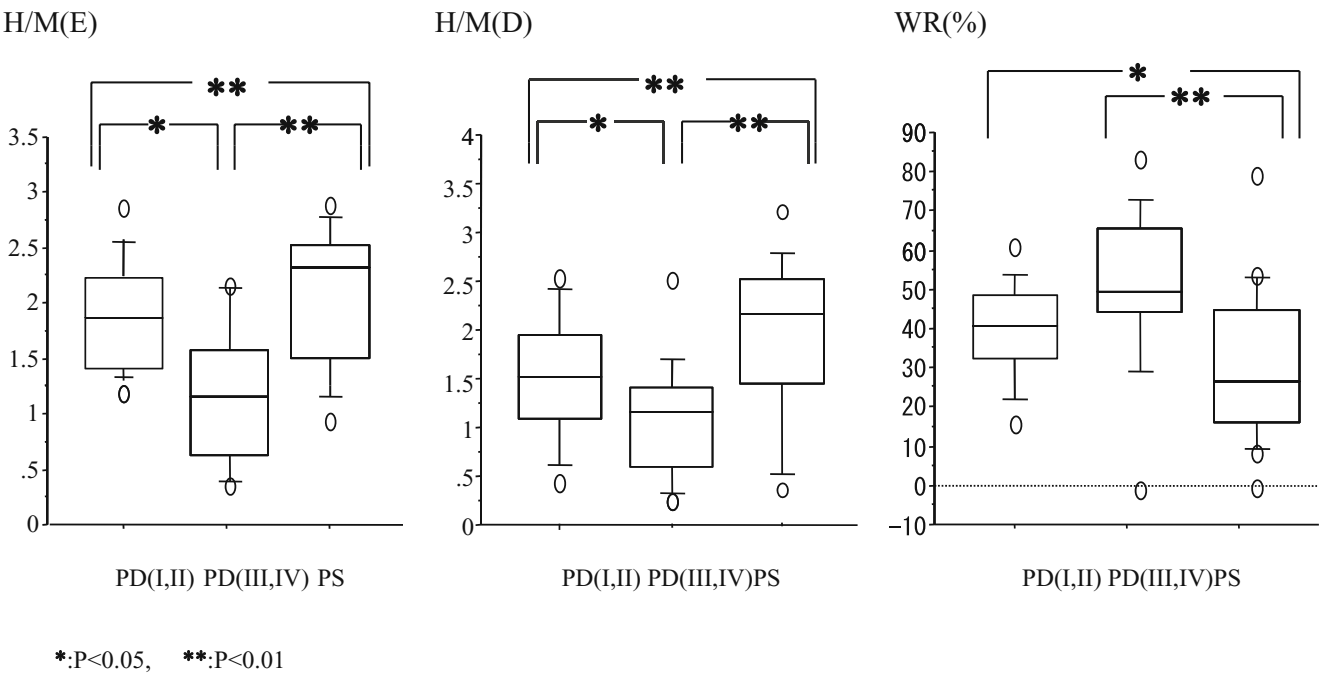

Fig. 1 Comparison of ^{123}I-metaiodobenzylguanidine (MIBG) indices among parkinsonism (PS) and Parkinson disease (PD) subgroups were demonstrated. Both PD subgroups showed significantly low heart-to-mediastinum ratio (H/M) and high washout rate as compared with those of the PS group

Table 2 Comparison of regional cerebral blood flow (rCBF; absolute value, ml/100 g per minute)

	PD HY (I, II) (n = 27)	PD HY (III, IV) (n = 22)	PS (n = 28)
Occipital (R)	39.9 ± 8.2	34.4 ± 6.8*	41.1 ± 11.2
Occipital (L)	39.7 ± 8.5	34.5 ± 7.2*	41.2 ± 12.8
Frontal (R)	42.8 ± 8.6	39.9 ± 8.8	42.5 ± 8.2
Frontal (L)	41.8 ± 11.0	38.9 ± 9.3	42.7 ± 9.0
Temporal (R)	40.1 ± 12.3	38.5 ± 9.2	40.9 ± 11.2
Temporal (L)	40.7 ± 11.7	38.7 ± 9.3	40.5 ± 9.4
Parietal (R)	41.6 ± 10.2	38.6 ± 10.2	41.7 ± 7.6
Parietal (L)	41.6 ± 11.8	39.2 ± 9.8	42.8 ± 8.0
Basal ganglia (R)	40.6 ± 10.7	39.2 ± 6.8	39.8 ± 7.2
Basal ganglia (L)	40.4 ± 11.0	39.3 ± 6.6	40.2 ± 8.7

*Statistically significantly lower than PS or PD HY (I, II)

relative weak when compared with those of rCBF in the occipital lobe (Table 3).

Regarding the ability to differentiate PD from PS, sensitivity improved by accounting for occipital lobe hypoperfusion in comparison with MIBG parameters analysis alone (81.6% vs. 75.5%, 81.6% vs.77.6%, and 87.8% vs. 71.6%). However, neither specificity nor accuracy improved (Table 4). When comparing severe PD with PS, the values of each diagnostic parameter improved. They also showed some improvement in the sensitivity (95.5% vs. 90.1%, 100% vs. 95.5%, and 95.5% vs. 86.3%) by combining MIBG and rCBF analysis, respectively. Neither specificity nor accuracy improved (Table 5).

Table 3 Correlation coefficient between absolute rCBF and MIBG indexes in PD

Region	H/M (E)	H/M (D)	WR
Rt occipital	0.61	0.64	0.35
Lt occipital	0.62	0.61	0.32
Rt frontal	0.51	0.53	0.20
Lt frontal	0.52	0.56	0.22
Rt temporal	0.36	0.45	0.12
Lt temporal	0.37	0.45	0.13
Rt parietal	0.49	0.52	0.15
Lt parietal	0.49	0.52	0.16
Rt basal ganglia	0.51	0.54	0.24
Lt basal ganglia	0.53	0.57	0.29

WR washout rate

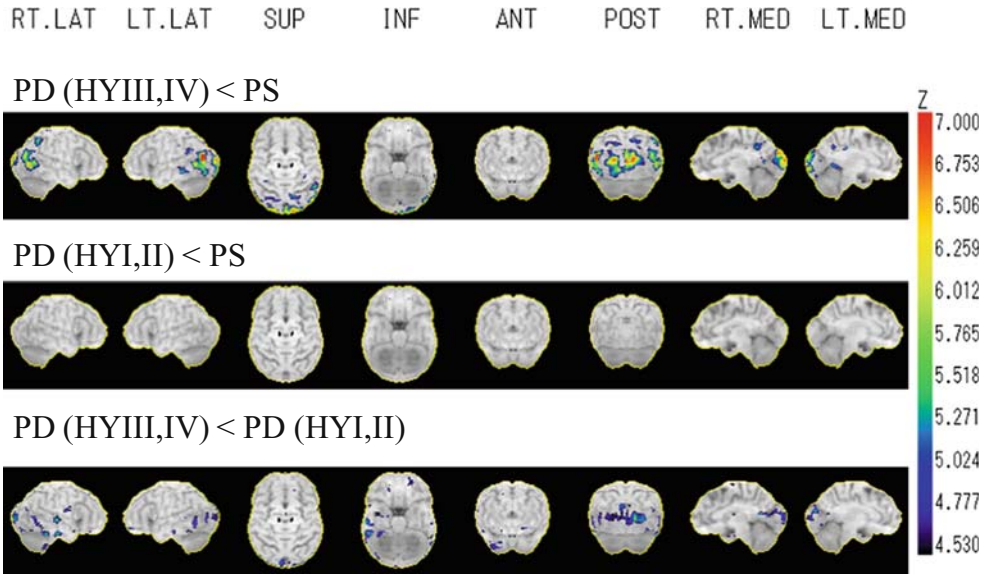

Fig. 2 Results of two-group comparison between PS and PD subgroups by 3D-SSP analysis. The regions with *Z* score over 4.53. *Upper row* The results of two-group comparison between severe PD and PS. Severe PD demonstrated significant decreased occipital perfusion. *Middle row* The results of two-group comparison between mild PD and PS. No significant rCBF difference is noted. *Lower row* The results of two-group comparison between severe PD and mild PD. Significant regional cerebral blood flow (rCBF) decrease of occipital lobe is noted in severe PD

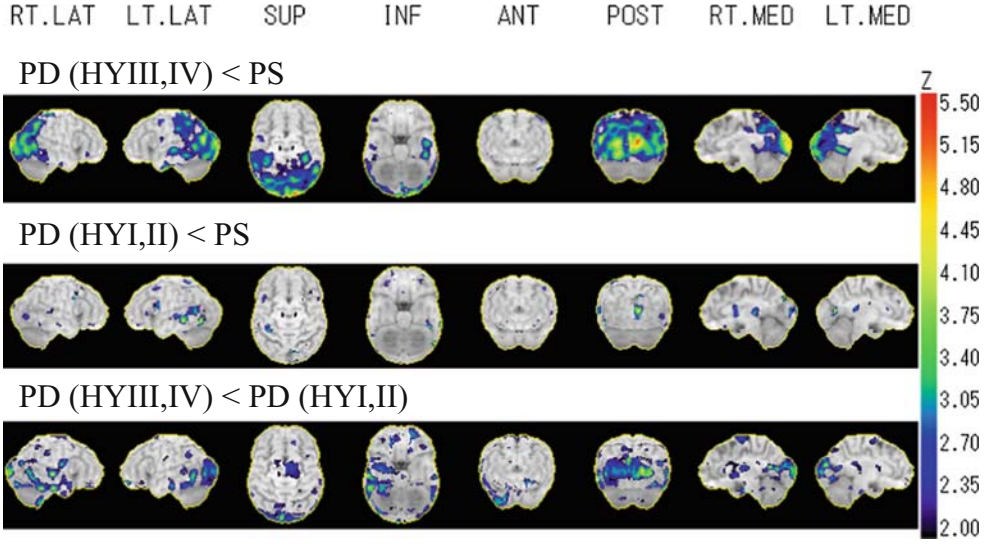

Fig. 3 Results of two-group comparison between PS and PD subgroups using 3D-SSP analysis. Abnormal rCBF areas with *Z* score over 2.0. *Upper row* The results of two-group comparison between severe PD and PS. Severe PD demonstrated prominent occipital hypoperfusion. *Middle row* The results of two-group comparison between mild PD and PS. Localized hypoperfusion of occipital lobe is noted. *Lower row* The results of two-group comparison between severe PD and mild PD. Prominent rCBF decrease in occipital lobe is noted in severe PD

Table 4 Comparison of differential diagnostic ability for PD (whole patients) from PS

	Sensitivity	Specificity	Accuracy
Low H/M (E) (<1.9)	75.5	89.3	80.5
Low H/M (E) or low-occi rCBF	81.6	82.1	80.5
Low H/M (D) (<1.7)	77.6	85.7	80.5
Low H/M (D) or low-occi rCBF	81.6	75.0	79.1
High WR (>40%)	81.6	89.3	84.4
High WR or low-occi rCBF	87.8	75.0	83.1
Low-occi rCBF	55.2	85.7	67.5

Low occipital rCBF: <36 ml/100 g per minute

Table 5 Comparison of differential diagnostic ability for PD (HY III, IV) from PS

	Sensitivity	Specificity	Accuracy
Low H/M (E) (<1.9)	90.1	89.3	90.0
Low H/M (E) or low-occi rCBF	95.5	78.5	86.0
Low H/M (D) (<1.7)	95.5	85.7	90.0
Low H/M (D) or low-occi rCBF	100.0	71.4	84.0
High WR (>40%)	86.3	89.3	88.0
High WR or low-occi rCBF	95.5	75.0	84.0
Low occipital rCBF	77.3	85.7	82.0

Low occipital rCBF: <36.0 ml/100 g per minute

Discussion

In PD, the entire autonomic nervous system is affected, including the hypothalamus, parasympathetic system, and sympathetic system [32]. Evidence indicates that cardiac uptake of MIBG is reduced in PD, even early in the clinical course [33, 34]. Early uptake of myocardial MIBG likely reflects presynaptic sympathetic system integrity and distribution, whereas delayed uptake in addition may reflect the functional status or washout of norepinephrine from sympathetic nerve terminals given the presence of pathological changes [9]. MIBG myocardial scintigraphy, therefore, has been found to contribute to the differential diagnosis between PD and other forms of PS [9, 32]. Our results supported these earlier reports, and the phenomenon was observed in the severe PD group in particular. However, one limitation is that we cannot use the examination in the presence of abnormal cardiac function, such as in patients with heart failure or diabetes mellitus.

Alternatively, although not specific, rCBF analysis is known to be helpful in characterizing PD [16, 35]. An earlier study reported that global CBF in PD was uniformly lower than that in healthy volunteers [35]. Regarding the connection with H&Y staging, rCBF in the severe stage (H&Y III, IV) is lower than in the mild stage (H&Y I, II) [35]. The results of the present study using 3D-SRT analysis agreed with the earlier report. In addition, recent studies showed that both hypometabolism and hypoperfusion of the occipital lobe are the characteristics of PD [22–24]. Arahata et al. [22, 36] reported that PD with autonomic nerve disturbance represents occipital lobe hypoperfusion. This study also agreed well with the results of a report on the use of statistical parametric imaging method (3D-SSP). Moreover, absolute occipital rCBF correlated positively with H/M. On the basis of these results, occipital lobe low perfusion is likely to reflect the seriousness of the pathological condition of PD. The reason for the modest correlation coefficient may be that occipital lobe disability does not always coexist with cardiac sympathetic nerve disorder. Aggravation of the severity of the two conditions seems not to accord in the early stages of PD.

Thus, occipital rCBF analysis seemed to have a meaningful role in diagnosing PD, whereas there were no significant differences in rCBF in the frontal lobe, basal ganglia parietal lobe, or temporal lobe between PD and PS. ^{18}F-DOPA-PET studies have described decreased uptake in the caudate nucleus or frontal cortex in PD [37, 38]. Dysfunction of the dopamine nervous system including striatal region is well known. However, in the present study by 3D-SRT analyses, selective rCBF decrease in these areas was not observed. This discordance between rCBF and dysfunction of caudate nucleus has also been reported [36].

As described earlier [9], when using MIBG scintigraphy analysis alone, the differential diagnostic ability is quite good, with the diagnostic ability of every index being around 80–90% in severe PD. When we use combined diagnosing criteria, abnormal MIBG indices or occipital lobe hypoperfusion, only sensitivity improved. However, both specificity and accuracy deteriorated or remained unchanged. One of the possible reasons is the disease severity of PD. As rCBF in the occipital cortex is usually higher physiologically than that in other cortices [39, 40], it is difficult to identify occipital lobe hypoperfusion in mild cases [41, 42]. Hence, the selective hypoperfusion of the occipital lobe when compared with PS was noted mainly in severe stage PD. This phenomenon seemed to be observed dependent on the stage of the disease. Another influential factor is disorders included in the PS group. In this study, all false-positive cases with low occipital rCBF were composed of MSA-P. Differential diagnosis between MSA-P and IPD is known to be very difficult and the final diagnosis in some cases is made only at autopsy [43]. Although Matsui et al. [23] reported a similar result by 3D-SSP with small patient numbers; the diagnostic capability was not addressed [23]. We should take into account that there is a significant overlap of cerebral blood flow values between the two groups.

Thus, additional occipital lobe rCBF analysis did not always improve diagnostic capability in comparison with that by MIBG alone after all. Therefore, the clinical implication of additional occipital lobe rCBF analysis is considered as follows, it would be effective, having recognized that possible MSA-P cannot be always excluded from the differential diagnosis. In addition, in cases with complicating cardiac disease such as heart failure or diabetic autonomic neuropathy which disturbs MIBG interpretation, rCBF analysis might be helpful for either screening or ruling out a diagnosis. Thus, additional rCBF analysis might be restrictive and should be chosen dependent on limited conditions. However, as the occipital lobe rCBF is associated with the severity of PD, it might be useful for monitoring disease progression.

The precise mechanism of the hypoperfusion in occipital lobe had not been clarified yet. One explanation is that visual cognitive function is disturbed earlier than other cognitive functions in PD [40]. Retinal dopamine nerve deletion is also present [34]. Hypoperfusion of the occipital lobe is likely to be related to these clinical background factors. In PDD, hypoperfusion or hypometabolism of the occipital lobe, parietal lobe and cingulate gyrus are known [34]. Because all our subjects in severe stage PD were free from dementia, occipital hypo-

perfusion was not considered to be associated with dementia. Pathologically, DLB, PDD, and PD constitute a part of a pathological continuum [43]. Glucose metabolism in DLB is similar to that in PDD [44]. Therefore, the differential diagnosis of these Lewy body diseases is difficult and also is the most important problem. There is still a possibility that we might detect a case of PD progressing to PDD in the near future. Serial follow-up studies should preferably be done by these two methods to resolve these issues in future.

Conclusions

The MIBG parameters, both H/M (E) and H/M (D), were positively correlated with occipital lobe hypoperfusion in PD. In the differential diagnosis between PD and PS, although the utility might be limited, the analysis of rCBF in the occipital lobe in addition to ^{123}I-MIBG myocardial imaging would be helpful.

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