Reduced Cardiac Uptake and Enhanced Washout of ^{123}I-MIBG in Pure Autonomic Failure Occurs Conjointly with Parkinson's Disease and Dementia with Lewy Bodies

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The purpose of this study was to investigate myocardial uptake of ^{123}I-metaiodobenzylguanidine (MIBG) in patients with pure autonomic failure (PAF), which has pathologic features in common with idiopathic Parkinson's disease (IPD) and dementia with Lewy bodies (DLB). **Methods:** Six patients with PAF, 130 with IPD, 21 with DLB, 9 with corticobasal degeneration (CBD), 11 with progressive supranuclear palsy (PSP), and 11 with multiple-system atrophy (MSA) underwent myocardial ^{123}I-MIBG scintigraphy, as did 16 control patients. **Results:** Resulting heart-to-mediastinum (H/M) ratios were significantly lower in patients with PAF, IPD, or DLB than in patients with CBD, PSP, or MSA and in the controls. H/M ratios were lower for delayed images than for early ones in patients with PAF, IPD, or DLB, whereas the ratios were higher for delayed images in patients with CBD and in the controls. **Conclusion:** Cardiac sympathetic denervation and enhanced washout of ^{123}I-MIBG from sympathetic nerve terminals may develop in parallel in patients with PAF, IPD, or DLB.

Key Words: Parkinson's disease; myocardial MIBG scintigraphy; dementia with Lewy bodies; pure autonomic failure

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Evidence indicates that cardiac uptake of ^{123}I-metaiodobenzylguanidine (MIBG) is reduced in patients with Parkinson's disease (PD) or dementia with Lewy bodies (DLB) (*1–4*). Reduced cardiac uptake may occur even during the early stage and offers a sensitive tool with which to differentiate PD and DLB from other disorders with rigid akinetic symptoms and dementia (*2–4*). PD, DLB, and pure autonomic failure (PAF) have Lewy bodies as a common pathologic feature (*5,6*) and are considered to be 3 phenotypes of a single disorder that may be called Lewy body disease. Yoshida et al. (*7*) reported 2 patients with PAF who had reduced myocardial ^{123}I-MIBG uptake. We performed myocardial ^{123}I-MIBG scintigraphy on 6 patients with PAF and compared the results with those for patients with PD, DLB, or other neurodegenerative disorders presenting extrapyramidal symptoms and with those for the control patients.

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MATERIALS AND METHODS

With their informed consent, we studied 130 patients with idiopathic PD (IPD), 21 with DLB, 6 with PAF, 9 with corticobasal degeneration (CBD), 11 with progressive supranuclear palsy (PSP), and 11 with multiple-system atrophy (MSA) who had visited our hospital and undergone ^{123}I-MIBG myocardial scintigraphy from August 1, 2002, to December 31, 2005. The probable-PD diagnosis was based on the criteria of the United Kingdom Brain Bank (*8*). If patients with PD had no family history of that disease, they were categorized in the IPD group. The respective diagnoses of probable DLB, CBD, PSP, and MSA were based on the criteria of McKeith et al. (*6*), Kumar et al. (*9*), Litvan et al. (*10*), and Gilman et al. (*11*). PAF was diagnosed when patients presented with orthostatic hypotension combined with repeated fainting spells and severe reduction of systolic blood pressure (>30 mm Hg) within 3 min after standing and showed no sign of central nervous system degeneration. The controls were 16 patients with neurologic diseases who had no neurodegenerative disorder. None of these patients had a previous history of a heart disease detectable on electrocardiography or of diabetes mellitus, and none had been taking tricyclic antidepressant medication. This study was approved by the Ethical Committee of Okayama Kyokuto Hospital.

The severity of patients' motor impairment was assessed by Hoehn and Yahr staging. Patients' cognitive functions were measured by the Mini-Mental State Examination (MMSE). Head-up tilt tests were performed on a motor-driven tilt table, and maximum reduction of systolic blood pressure (δBP) was determined within 3 min after standing.

^{123}I-MIBG Myocardial Imaging

After a 30-min resting period, patients and controls received an intravenous injection of 111 mBq of ^{123}I-MIBG (Daiichi Radioisotope Laboratories Co.). A planar image of the chest was obtained in an anterior view for 5 min with a double-head Starcam 400AC/T γ-camera (GE Healthcare) after 15 min for the early image and after 4 h for the delayed one (Fig. 1). Photopeak energy

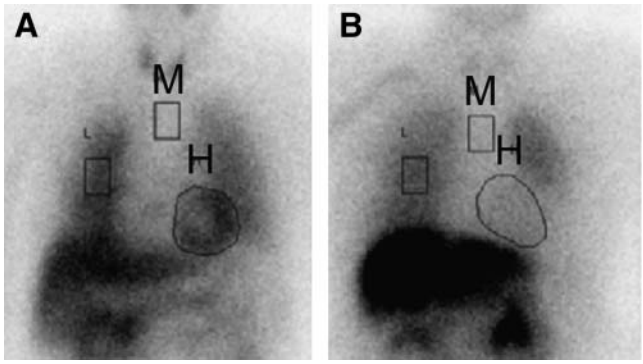

FIGURE 1. Early anterior planar images of myocardial ^{123}I-MIBG scintigraphy in control patient (A) and patient with IPD (B). Regions of interest enclosing ^{123}I-MIBG uptake were placed in mediastinum and heart (labeled with M and H, respectively). Average counts per pixel of mediastinal and cardiac regions were 55.4 and 132.7, respectively, for control patient and 56.6 and 78.8, respectively, for patient with IPD. Uptake of heart differs considerably. L = region of interest enclosing lung.

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.

Statistical Analysis

Intergroup differences in age, disease duration, H/M ratio, and δBP on the head-up tilt test were evaluated by 1-way ANOVA followed by the Scheffé test post hoc. Intergroup differences in the Hoehn and Yahr stages and MMSE scores were determined by the Kruskal–Wallis and Mann–Whitney *U* tests. The paired *t* test was used to evaluate differences in H/M ratios obtained from early and delayed images of the same group.

RESULTS

Patients' characteristics are listed in Table 1. Age did not significantly differ between any of the patient groups and the controls. Of the diseases with Lewy body formation, disease duration was significantly shorter in patients with PAF and DLB than in those with IPD. Hoehn and Yahr stages were the same for IPD and DLB. The mean MMSE score was lower for patients with DLB than for those with IPD and was lower for patients with IPD than for those with PAF. Reduction of systolic blood pressure on standing was more marked in patients with PAF than in those with IPD or DLB.

Patients' H/M ratios for each disease are listed in Table 1 and Figure 2. Patients with PAF, IPD, or DLB had a significantly lower H/M ratio for both the early and the delayed images than did those with CBD, PSP, or MSA and the controls. H/M ratios for the controls were considered to be normal, and the lower limits (mean – 2 SDs) were set at 1.84 and 1.78 for the early and delayed images, respectively. Thus, no decrease was found for patients with CBD, PSP, or MSA.

In each type of Lewy body disease, the H/M ratio was significantly lower for the delayed image than for the early one (PAF, value of $t = 4.3$; IPD, $t = 19.7$; DLB, $t = 7.9$; $P < 0.01$). This tendency was preserved in all 27 patients with Lewy body diseases (IPD, 21; DLB, 6) who showed early H/M ratios higher than 1.84. The mean ± SD of their early and delayed H/M ratios were 2.16 ± 0.25 and 1.86 ± 0.25, respectively. The decrease also was significant ($t = 9.1$, $P < 0.01$). Patients with CBD and the controls had significantly higher H/M ratios for the delayed image than for the early image (CBD, $t = -2.6$; controls, $t = -4.0$; $P < 0.05$).

DISCUSSION

Our findings clearly show that patients with PAF had the same degree of reduced myocardial ^{123}I-MIBG uptake as did those with IPD or DLB. Taking into account the shorter disease duration for patients with PAF than for those with IPD, the PAF H/M ratio may decrease earlier during the disease. Sympathetic dysfunction determined from the

TABLE 1
Patients' Clinical Characteristics and Myocardial ^{123}I-MIBG Scintigraphy Results

Patient group	*n*	Age (y)	Disease duration (y)	Hoehn and Yahr stage		MMSE	δBP	H/M ratio	
				On	Off			Early	Delayed
Control	16	75.4 ± 6.8				ND	ND	2.26 ± 0.21	2.48 ± 0.35
IPD	130	72.3 ± 8.2	7.0 ± 5.9	3.1 ± 1.0	3.4 ± 1.1	22.5 ± 6.5	27.5 ± 23.2	1.63 ± 0.29‡	1.37 ± 0.27‡
DLB	21	75.3 ± 6.0	2.8 ± 2.8*	3.3 ± 1.2	3.4 ± 1.3	17.7 ± 6.1*	21.6 ± 23.3	1.69 ± 0.44‡	1.47 ± 0.37‡
PAF	6	71.3 ± 6.6	1.1 ± 1.1*	0†	0†	28.5 ± 1.9†	63.5 ± 18.8†	1.47 ± 0.19‡	1.32 ± 0.16‡
CBD	9	66.2 ± 7.4	3.1 ± 3.1	3.4 ± 1.0	3.4 ± 1.0	22.9 ± 6.9	ND	2.51 ± 0.44	2.75 ± 0.51
PSP	11	74.6 ± 4.6	2.5 ± 1.7	3.3 ± 0.6	3.3 ± 0.6	25.8 ± 3.0	ND	2.45 ± 0.37	2.57 ± 0.38
MSA	11	67.8 ± 7.8	2.3 ± 1.3	3.0 ± 1.0	3.0 ± 1.0	29.3 ± 1.0	20.7 ± 25.7	2.54 ± 0.29	2.53 ± 0.41

*Values for IPD, DLB, and PAF differ significantly from values for IPD ($P < 0.05$).
†Values for IPD, DLB, and PAF differ significantly from values for IPD and DLB ($P < 0.05$).
‡Values for IPD, DLB, PAF, CBD, PSP, MSA, and controls differ significantly from values for CBD, PSP, MSA, and controls ($P < 0.05$).
δBP = maximum reduction of systolic blood pressure within 3 min of standing after motor-driven tilt-table test; ND = not determined.
Data are mean ± SD.

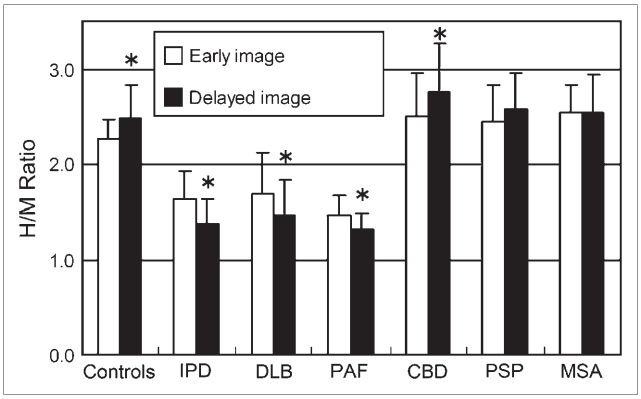

FIGURE 2. H/M ratios of patients with IPD, DLB, PAF, CBD, PSP, or MSA and of controls. *Significantly different from H/M ratio for early image of same group.

decrease in blood pressure on standing was greater (more than 2 times) in PAF than in IPD. The predominant involvement of sympathetic nerve terminals in PAF may result in the earlier reduction in myocardial ^{123}I-MIBG uptake during the disease.

PD, DLB (*12*), or MSA may develop in patients with PAF. Two of the 11 MSA patients in our study had predominant autonomic dysfunction, and Shy-Drager syndrome could be diagnosed. Their H/M ratios were within the normal range (2.50 and 2.60 for the early image, 2.71 and 2.64 for the delayed one). In our patients with PAF, therefore, IPD or DLB might later develop, but not MSA.

A reduced H/M ratio was more marked for the delayed image than for the early image in patients with PAF, IPD, or DLB, but not in those with CBD, PSP, or MSA or in the controls. By contrast, patients with CBD and the controls had significantly higher delayed than early H/M ratios. Early uptake of myocardial ^{123}I-MIBG may reflect presynaptic sympathetic system integrity and distribution, whereas delayed uptake in addition may reflect the functional status or washout of norepinephrine from sympathetic nerve terminals (*13*). Our findings suggest that patients with Lewy body diseases have in common not only decreased cardiac sympathetic nerve terminals but also enhanced spillover of, or reduced ability to preserve, ^{123}I-MIBG or norepinephrine in their cardiac sympathetic nerve terminals. The enhanced washout was observed even in patients with Lewy body diseases who showed no reduction in early H/M ratios. Dysfunction of cardiac sympathetic nerve terminals may therefore precede their loss. An enhanced washout of ^{123}I-MIBG on the delayed image may be more sensitive than a reduced uptake of ^{123}I-MIBG for differentiating Lewy body disorders from other neurodegenerative diseases.

CONCLUSION

Myocardial ^{123}I-MIBG uptake is reduced, and washout enhanced, from sympathetic nerve terminals in PAF and in other Lewy body diseases, including IPD and DLB. Because this reduction and enhanced washout occur earlier during these diseases, their time of appearance may prove a sensitive way to differentiate PAF and other Lewy body diseases from MSA and other neurodegenerative disorders that present with extrapyramidal or autonomic dysfunction.

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