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ORIGINAL COMMUNICATION

Appropriate assessment method of ^{123}I-MIBG myocardial scintigraphy for the diagnosis of Lewy body diseases and idiopathic REM sleep behavior disorder

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Abstract

Background In ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy, the early heart-to-mediastinum (H/M) ratio is considered to reflect the density of the cardiac sympathetic nerve endings, washout rate (WR) is an indicator of the cardiac sympathetic tone, and the delayed H/M ratio reflects both. The Delayed H/M ratio is usually used to support the diagnosis of Lewy body diseases (LBDs) and idiopathic REM sleep behavior disorder (iRBD); however, which values should be used have not been specified. Here, we hypothesized that the combination of these values is appropriate for the diagnostic purpose.

Methods In this single-center retrospective cohort study, we recruited 106 patients with LBDs or iRBD and 33 patients without those diseases, of whom we reviewed the ^{123}I-MIBG myocardial scintigraphy results.

Results Sensitivity/specificity to diagnose LBDs and iRBD were 0.77/0.94 for the early H/M ratio (≤ 2.0), 0.82/0.94 for the delayed H/M ratio (≤ 2.0), and 0.89/0.91 for WR (≥ 23.0). When patients were considered positive if at least either the early H/M ratio or WR was abnormal, the sensitivity significantly increased to 0.97, whereas the specificity remained similar at 0.91. Furthermore, our subgroup analyses revealed that WR enhancement preceded H/M ratio reduction, but, in patients with a severely reduced early H/M ratio, paradoxically normal WR could be observed.

Conclusion We propose the highly sensitive, combined early H/M ratio and WR assessments for ^{123}I-MIBG myocardial scintigraphy. The temporal precedence of cardiac sympathetic dysfunction over denervation and the floor effect in ^{123}I-MIBG uptake may underlie the sensitivity improvement.

Keywords ^{123}I-MIBG myocardial scintigraphy · Lewy body diseases · Idiopathic REM sleep behavior disorder

Introduction

Differentiation of each Parkinsonian syndrome poses a huge challenge for clinicians. In fact, postmortem pathological studies revealed that the clinical diagnosis made even by experienced neurologists is often inaccurate [1–6]. Therefore, tools to aid the differential diagnosis are of prominent importance. Among them, ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy has been consistently reported as a powerful tool to distinguish Lewy body diseases [LBDs; i.e. pure autonomic failure (PAF), Parkinson's disease (PD), and dementia with Lewy bodies (DLB)] and idiopathic REM sleep behavior disorder (iRBD) from other mimicking diseases since its first application to neurological diseases in the 1990s [7–16]. Recently, reduced cardiac ^{123}I-MIBG uptake was employed as one of supportive criteria in the clinical diagnostic criteria of PD [1] and as one of

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indicative biomarkers in that of DLB [17]. However, these criteria do not specify which quantification values obtained in ^{123}I-MIBG myocardial scintigraphy, namely, the early heart-to-mediastinum (H/M) ratio, delayed H/M ratio, and wash-out rate (WR), should be used for diagnosis, although the delayed H/M ratio is empirically preferred [10, 12].

The early H/M ratio is considered to primarily reflect the density of the cardiac sympathetic nerve endings, WR is an indicator of the cardiac sympathetic tone, and the delayed H/M ratio reflects both [18–22]. A recent longitudinal imaging study using ^{18}F-dopamine positron emission tomography suggested that dysfunction precedes denervation in the cardiac sympathetic nerves [23]; therefore, WR should theoretically be more sensitive than the delayed H/M ratio. However, the floor effect in radioisotope uptake can produce paradoxically normal WR in patients with severe cardiac sympathetic denervation and reduce the sensitivity of WR [24, 25]. Considering these two opposing facts, we hypothesized that the combined early H/M ratio and WR assessments of ^{123}I-MIBG myocardial scintigraphy would be best suited for the diagnoses of LBDs and iRBD.

Methods

Patients

This was a single-center retrospective cohort study conducted at the Department of Neurology and Center for Sleep-related Disorders of Kansai Electric Power Hospital, a regional referral hospital in Osaka, Japan. The institutional review board approved the study protocol. Among 157 consecutive patients who underwent ^{123}I-MIBG myocardial scintigraphy from May 2013 to February 2019, 11 patients with diabetes, peripheral neuropathy, and/or a history of heart failure were firstly excluded because ^{123}I-MIBG uptake has been reported to decrease in these conditions. Seven more patients were also excluded because their definite final diagnosis could not be obtained. Finally, we included 106 patients with a final diagnosis of LBDs or iRBD and 33 patients with a final diagnosis of other diseases. Patients with LBDs included 63 PD, 8 DLB, and 3 PAF patients, all of whom were diagnosed according to the established clinical criteria at the last follow-up visit (follow-up duration 3.37 ± 1.96 years) [1, 17, 26], as well as 32 iRBD patients who underwent all-night polysomnography and were diagnosed as described in the International Classification of Sleep Disorders, third edition [27]. All-night polysomnography equipped with the standard montage for scoring sleep stages was conducted and scored according to the manual by the American Academy of Sleep Medicine [28]. Patients with other diseases included 3 multiple system atrophy (MSA), 4 progressive supranuclear palsy (PSP), 4 corticobasal syndrome (CBS), 5 Alzheimer disease (AD), 4 drug-induced parkinsonism, 5 idiopathic normal pressure hydrocephalus (iNPH), 2 essential tremor (ET), and 2 psychogenic movement disorder patients, all of whom were diagnosed clinically at the last follow-up visit (follow-up duration 3.87 ± 1.75 years) [29–31], as well as 4 obstructive sleep apnea syndrome (OSAS) patients who were diagnosed in accordance with the International Classification of Sleep Disorders, third edition [27]. Study flowchart is represented in Fig. 1. For background characteristics, the age, sex, and disease duration were gathered for all participants. Hoehn-Yahr stage, initial motor symptom (tremor or not), and the presence of dream enactment behavior (DEB) were investigated only for PD patients.

^{123}I-MIBG myocardial scintigraphy

Medications that are well known to affect ^{123}I-MIBG uptake, such as serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, reserpine, and labetalol, were temporally stopped [32]. At rest in the supine position, 111 MBq of ^{123}I-MIBG (Fujifilm Toyama Chemical, Co. Ltd, Tokyo, Japan) was intravenously injected. Using a dual-head γ camera (GE healthcare, Tokyo, Japan) with low-energy collimators, the anterior planar image of the chest was acquired 20 min (early phase) and 3 h (delayed phase) after injection. The photopeak of ^{123}I was centered at 159 keV with a 20% energy window. Acquisition time was 3 min and a 256 × 256 matrix was used. For quantification of the result, regions of interests (ROIs) were drawn around the heart and the mediastinum. Average counts per pixel in the ROI of the heart (H) were divided by those in the ROI of the mediastinum (M) to calculate the H/M ratio. The H/M ratio in the early phase was designated as the early H/M ratio and that in the delayed phase was designated as the delayed H/M ratio. WR was calculated by the following formula: $\{[(\text{early H}) - (\text{early M}) - (\text{delayed H}) + (\text{delayed M})] \times 0.5^{3/13}\}/[(\text{early H}) - (\text{early M})] \times 100$ [33]. The institutional cut-off values were predetermined from normal controls as "mean—[2 × standard deviation (SD)]" for the early and delayed H/M ratios, and as "mean + (2 × SD)" for WR in 1992 when the clinical use of ^{123}I-MIBG myocardial scintigraphy was approved in Japan, and were 2.0, 2.0, and 23.0 for the early H/M ratio, delayed H/M ratio, and WR, respectively, which is similar to the value obtained in the previous study using similar collimators [33].

Statistical analysis

The statistical software R (version 3.4.0, freely available at https://www.R-project.org) was used for analyses. We used the Mann–Whitney *U* test for comparing the distribution of two-groups, the Kruskal–Wallis test followed by the the

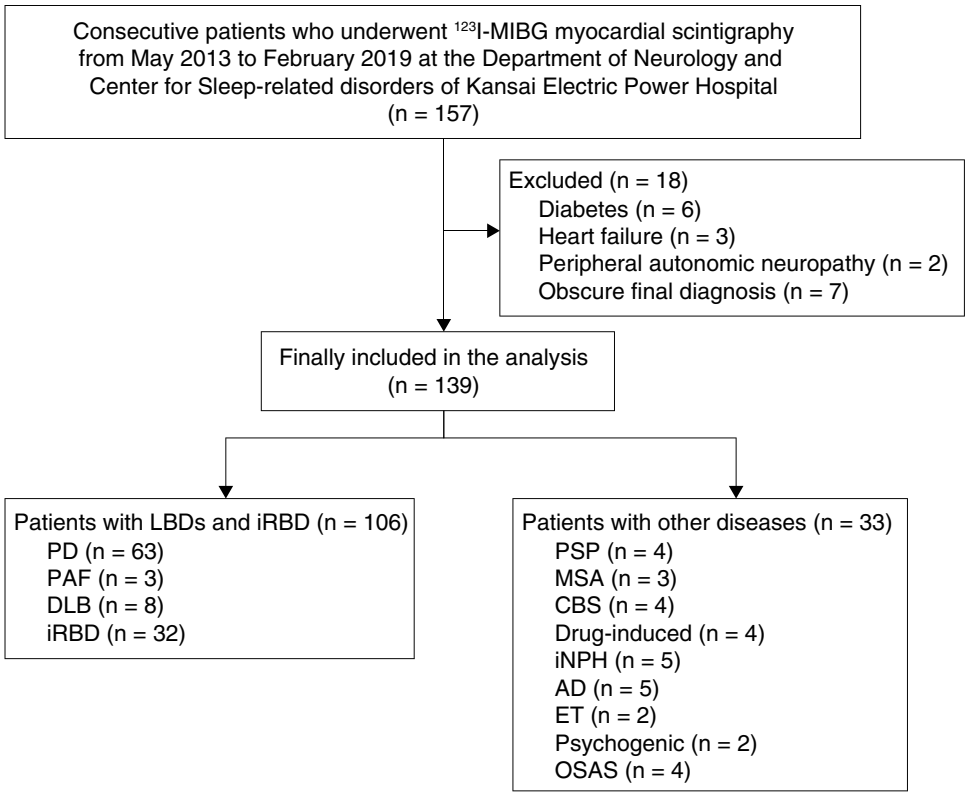

Fig. 1 Study flowchart. *123I-MIBG* 123I-metaiodobenzylguanidine, *LBDs* Lewy body diseases, *PD* Parkinson's disease, *PAF* pure autonomic failure, *DLB* dementia with Lewy bodies, *iRBD* idiopathic REM sleep behavior disorder, *PSP* progressive supranuclear palsy, *MSA* multiple system atrophy, *CBS* corticobasal syndrome, *iNPH* idiopathic normal pressure hydrocephalus, *AD* Alzheimer disease, *ET* essential tremor, *OSAS* obstructive sleep apnea syndrome

Steel–Dwass test for comparing the distribution of multiple-groups, and Spearman's rank correlation coefficients (Rs) for correlation analyses. We also used Fisher's exact test for the analyses of contingency tables and McNemar's test for comparisons of the sensitivity and specificity. Receiver operating characteristic (ROC) analyses were performed to assess the diagnostic accuracy. To compare the area under the ROC curve (AUC) of ROC curves, we used the method described in DeLong et al. [34]. Data are expressed as mean ± SD. *P* value of less than 0.05 was considered statistically significant.

Results

The clinical characteristics are summarized in Table 1. The representative 123I-MIBG myocardial scintigraphy images of each disease were represented in Fig. 2.

The 123I-MIBG myocardial scintigraphy results are summarized in Table 2. Both early and delayed H/M ratios were significantly lower in LBDs (i.e. PD, PAF, and DLB) and iRBD than in other diseases [early, 1.70 ± 0.41 (LBDs and iRBD) vs. 2.32 ± 0.38 (other diseases), $p < 0.01$; delayed, 1.55 ± 0.40 (LBDs and iRBD) vs. 2.32 ± 0.35 (other diseases), $p < 0.01$] (Fig. 3a, b), and WR was significantly enhanced in LBDs and iRBD than in other diseases [31.08 ± 6.44 (LBDs and iRBD) vs. 20.00 ± 3.85 (other diseases), $p < 0.01$] (Fig. 3c). Among LBDs and iRBD, the early H/M ratio, the delayed H/M ratio and WR were not significantly different between each disease [early, 1.56 ± 0.30 (iRBD) vs. 1.77 ± 0.46 (PD) vs. 1.73 ± 0.06 (PAF) vs. 1.65 ± 0.27 (DLB), $p = 0.21$; delayed, 1.39 ± 0.24 (iRBD) vs. 1.65 ± 0.46 (PD) vs. 1.44 ± 0.15 (PAF) vs. 1.42 ± 0.22 (DLB), $p = 0.09$; WR, 32.42 ± 5.74 (iRBD) vs. 29.94 ± 6.60 (PD) vs. 33.55 ± 10.66 (PAF) vs. 33.73 ± 5.36 (DLB), $p = 0.08$] (Fig. 3d–f). However, when compared between iRBD and LBDs, the early H/M ratio and delayed H/M ratios were significantly lower in iRBD than in LBDs [early, 1.56 ± 0.30 (iRBD) vs. 1.76 ± 0.43 (LBDs), $p = 0.04$; delayed, 1.39 ± 0.24 (iRBD) vs. 1.62 ± 0.44 (LBDs), $p = 0.02$] but WR were not significantly different [32.42 ± 5.74 (iRBD) vs. 30.50 ± 6.68 (LBDs), $p = 0.10$]. Among diseases other than LBDs and iRBD, the early H/M ratio, delayed H/M ratio, and WR were similar between each disease [early, 2.60 ± 0.52 (MSA) vs. 2.48 ± 0.13 (PSP) vs. 2.48 ± 0.43 (CBS) vs. 2.14 ± 0.15 (AD) vs. 2.10 ± 0.59 (drug-induced) vs. 2.06 ± 0.27 (iNPH) vs. 2.25 ± 0.21 (ET) vs. 2.70 ± 0.57 (psychogenic) vs. 2.4 ± 0.29 (OSAS), $p = 0.15$; delayed, 2.71 ± 0.46 (MSA) vs. 2.43 ± 0.11 (PSP) vs. 2.47 ± 0.38 (CBS) vs. 2.18 ± 0.12 (AD) vs. 2.08 ± 0.58 (drug-induced) vs. 2.18 ± 0.39 (iNPH) vs. 2.24 ± 0.33 (ET) vs. 2.54 ± 0.39 (psychogenic) vs. 2.32 ± 0.16 (OSAS), $p = 0.32$; WR, 18.56 ± 3.50 (MSA) vs. 18.33 ± 1.11 (PSP) vs. 20.49 ± 4.84 (CBS) vs. 20.58 ± 0.97 (AD) vs. 23.01 ± 5.12

Table 1 Characteristics of the enrolled subjects

	PD ($n=63$)	PAF ($n=3$)	DLB ($n=8$)	iRBD ($n=32$)	Other diseases ($n=33$)	p value
Age (years)	73.1 ± 8.4	71.7 ± 1.53	68.6 ± 9.3	70.1 ± 7.8	54.8 ± 7.0	0.05[A]
Male	22 (35%)	3 (100%)	6 (75%)	25 (78%)	19 (58%)	< 0.01[Ba]
Disease duration (years)	3.5 ± 1.8	4.7 ± 1.5	3.9 ± 1.4	7.7 ± 4.4	4.5 ± 7.0	< 0.01[A,b]
Tremor-onset	28 (44%)	–	–	–	–	–
Hoen-Yahr stage	2.3 ± 0.6	–	–	–	–	–
Dream enactment behavior	14 (26%)[c]	–	–	–	–	–

Data are expressed as mean ± standard deviation or number (percentage)

PD Parkinson's disease, *PAF* pure autonomic failure, *DLB* dementia with Lewy bodies, *iRBD* idiopathic REM sleep behavior disorder

[A]Kruskal–Wallis test

[B]Fisher's exact test

[a]Fisher's exact test with Bonferroni correction revealed that the percentage of male participants were significantly higher in iRBD patients than in PD patients

[b]Tukey–Kramer test revealed that disease duration was significantly longer in iRBD patients than in PD, DLB, and other disease patients

[c]The presence of dream enactment behavior was unclear in 9 PD patients

(drug-induced) vs. 19.98 ± 6.26 (iNPH) vs. 15.47 ± 1.20 (ET) vs. 21.59 ± 0.85 (psychogenic) vs. 20.03 ± 3.31 (OSAS), $p=0.31$] (Supplementary Fig. 1). Both in PD and iRBD, the early and delayed H/M ratios had significant negative correlations with the disease duration (PD, early, Rs = − 0.33, $p<0.01$; PD, delayed, Rs = − 0.28, $p=0.02$; iRBD, early, Rs = − 0.37, $p=0.04$; iRBD, delayed, Rs = − 0.46, $p<0.01$) (Supplementary Fig. 2A and 2B). It was also observed that the early and delayed H/M ratios were significantly reduced in PD patients with DEB than in those without DEB [early, 1.44 ± 0.28 (PD with DEB) vs. 1.88 ± 0.47 (PD without DEB), $p<0.01$; delayed, 1.33 ± 0.28 (PD with DEB) vs. 1.75 ± 0.47 (PD without DEB), $p<0.01$] (Supplementary Fig. 3A and 3B) but WR were not significantly different [31.11 ± 6.19 (PD with DEB) vs. 29.45 ± 7.06 (PD without DEB), $p=0.29$]. The Hoehn-Yahr stage and initial motor symptom (tremor or not) were not associated with the early or delayed H/M ratio in PD patients.

AUCs were 0.86 [95% confidence interval (CI) 0.79–0.92] for the early H/M ratio, 0.90 (95% CI 0.84–0.96) for the delayed H/M ratio, and 0.93 (95% CI 0.87–0.97) for WR (Fig. 4a). No statistically significant differences were found among these 3 AUCs [early vs. delayed, $p=0.34$; early vs. WR, $p=0.11$; delayed vs. WR, $p=0.35$]. ROCs also demonstrated that pre-determined institutional cut-offs for the early H/M ratio (2.0), delayed H/M ratio (2.0), and WR (23.0) were reasonable (Fig. 4a). Using these cut-offs, sensitivity and specificity of the early H/M ratio for the diagnosis of LBD and iRBD were 0.77 and 0.94, respectively, of the delayed H/M ratio were 0.82 and 0.94, respectively, and of WR were 0.89 and 0.91, respectively (Fig. 4a, b). No statistically significant differences in sensitivity or specificity were found among the early H/M ratio, delayed H/M ratio, and WR [sensitivity and specificity, $p=0.54$ and $p=1.00$ (early vs. delayed); $p=0.07$ and $p=1.00$ (early vs. WR); $p=0.28$ and $p=1.00$ (delayed vs. WR)]. When patients were considered positive if at least either the early H/M ratio was ≤ 2.0 or WR was ≥ 23.0 (combined assessment), the sensitivity became significantly higher than individual assessments [0.97, $p<0.01$ (vs. the early H/M ratio), $p<0.01$ (vs. the delayed H/M ratio), $p=0.04$ (vs. WR)] whereas the specificity remained similar [0.91, $p=1.00$ (vs. the early H/M ratio), $p=1.00$ (vs. the delayed H/M ratio), $p=1.00$ (vs. WR)] (Fig. 4b).

To further assess the physiological background of the improvement in sensitivity with this combined assessment, we conducted serial subgroup analyses. First, the disease duration was compared between LBDs and iRBD patients with a normal early H/M ratio but an enhanced WR (subgroup 1–1), and those with *a* reduced early H/M ratio and an enhanced WR (subgroup 1–2) (Supplementary Fig. 4A). The disease duration was significantly shorter in subgroup 1–1 compared with subgroup 1–2 [2.71 ± 1.01 (subgroup 1–1) vs 5.58 ± 3.72 (subgroup 1–2) years, $p<0.01$] (Supplementary Fig. 4B), suggesting that WR enhancement precedes early H/M ratio reduction. Restricting the analysis only to PD patients did not alter the result [2.63 ± 1.01 (PD in subgroup 1–1) vs 3.86 ± 1.01 (PD in subgroup 1–2) years, $p<0.01$]. Next, the disease duration was compared between LBDs and iRBD patients with a normal delayed H/M ratio but an enhanced WR (subgroup 2–1), and those with a reduced delayed H/M ratio and an enhanced WR (subgroup 2–2) (Fig. 5a). The disease duration was significantly shorter in subgroup 2–1 than in subgroup 2–2 [2.87 ± 1.13 (subgroup 2–1) vs. 5.33 ± 3.68 (subgroup 2–2) years, $p<0.01$]

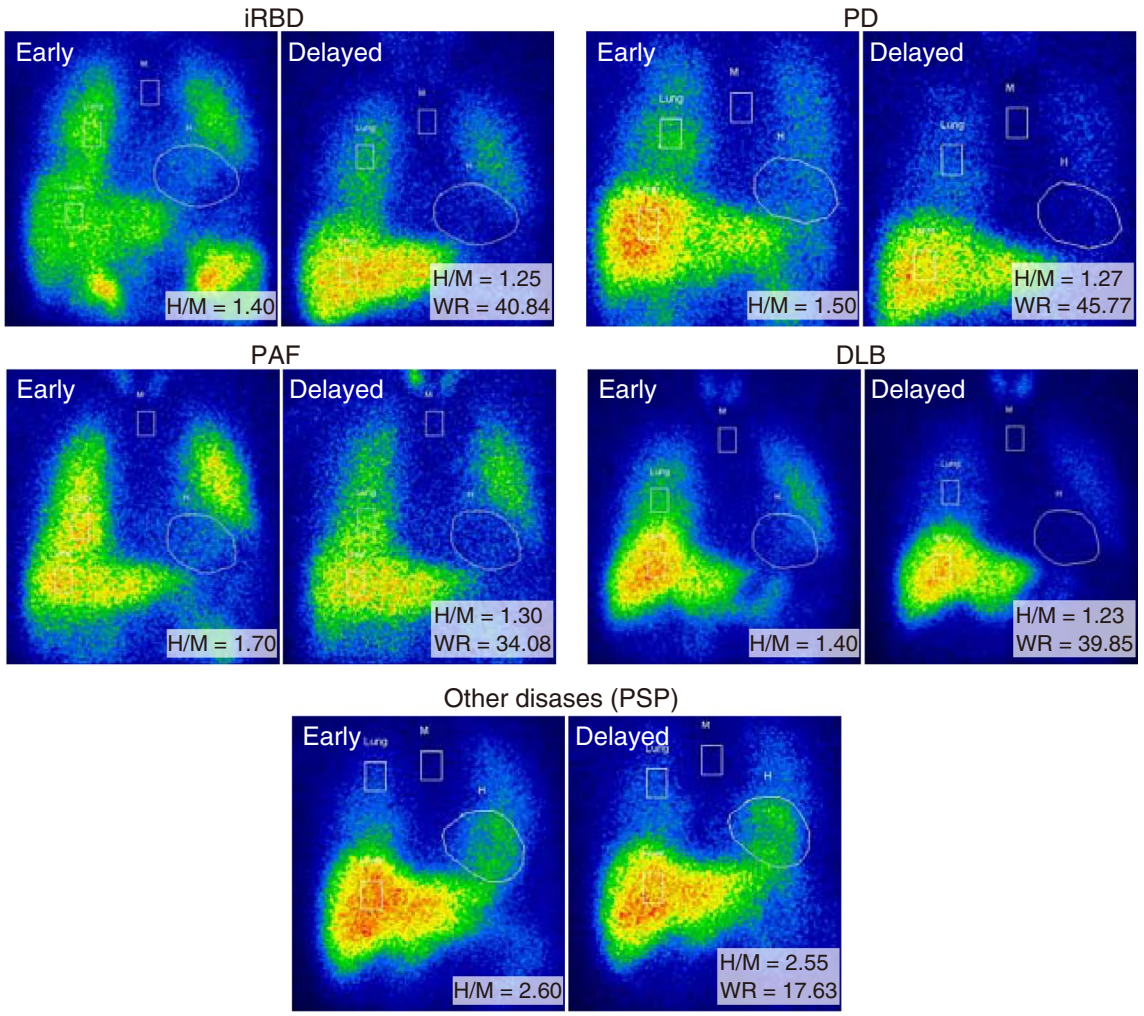

Fig. 2 Representative ^{123}I-metaiodobenzylguanidine myocardial scintigraphy images in each disease. *H/M ratio* heart-to-mediastinum ratio, *WR* washout rate, *iRBD* idiopathic REM sleep behavior disorder, *PD* Parkinson's disease, *PAF* pure autonomic failure, *DLB* dementia with Lewy bodies, *PSP* progressive supranuclear palsy

(Fig. 5b), suggesting that WR enhancement even precedes delayed H/M ratio reduction. Restricting the analysis only to PD patients did not alter the result [2.77 ± 1.17 (PD in subgroup 2–1) vs 3.65 ± 1.88 (PD in subgroup 2–2) years, $p = 0.04$]. Finally, the early H/M ratio was compared between LBDs and iRBD patients with a reduced early H/M ratio and an enhanced WR (subgroup 3–1), and those with a reduced early H/M ratio but a normal WR (subgroup 3–2) (Fig. 5c). The early H/M ratio was significantly reduced in subgroup 3–2 than in subgroup 3–1 [1.53 ± 0.23 (group 3–1) vs. 1.34 ± 0.14 (group 3–2), $p < 0.01$] (Fig. 5d), showing that WR can return to normal value in patients with severe cardiac sympathetic nerve denervation supposedly because of the floor effect in ^{123}I-MIBG uptake.

Discussion

In this study, we have shown that the combined early H/M ratio and WR assessments yielded significantly higher sensitivity than individual assessments of the early H/M ratio, delayed H/M ratio, and WR without an associated reduction in specificity. Furthermore, our subgroup analyses revealed that temporal precedence of WR enhancement over H/M ratio reduction and the floor effect in ^{123}I-MIBG uptake may underlie the sensitivity improvement in our combined assessment.

MIBG, an analog of guanethidine, behaves similarly to noradrenaline in terms of uptake and storage by the cardiac sympathetic nerve endings, and radiolabeling of

Table 2 Summary of the ^{123}I-MIBG myocardial scintigraphy results in this study

	LBDs ($n=74$)					
	PD ($n=63$)	PAF ($n=3$)	DLB ($n=8$)	iRBD ($n=32$)	Other diseases ($n=33$)	p value
LBDs and iRBD vs. other diseases						
The early H/M ratio	1.70 ± 0.41				2.32 ± 0.38	< 0.01[a]
The delayed H/M ratio	1.55 ± 0.40				2.32 ± 0.35	< 0.01[a]
WR	31.08 ± 6.44				20.00 ± 3.85	< 0.01[a]
iRBD vs. LBDs						
The early H/M ratio	1.76 ± 0.43			1.56 ± 0.30	–	0.04[a]
The delayed H/M ratio	1.62 ± 0.44			1.39 ± 0.24	–	0.02[a]
WR	30.50 ± 6.68			32.42 ± 5.74	–	0.10[a]
Among LBDs						
The early H/M ratio	1.77 ± 0.46	1.73 ± 0.06	1.65 ± 0.27	–	–	0.87[b]
The delayed H/M ratio	1.65 ± 0.46	1.44 ± 0.15	1.42 ± 0.22	–	–	0.48[b]
WR	29.94 ± 6.60	33.55 ± 10.66	33.73 ± 5.36	–	–	0.17[b]
PD with DEB vs. PD without DEB						
The early H/M ratio	1.44 ± 0.28 vs. 1.88 ± 0.47	–	–	–	–	< 0.01[a]

Data are expressed as mean ± standard deviation

LBDs Lewy body diseases, *PD* Parkinson's disease, *PAF* pure autonomic failure, *DLB* dementia with Lewy bodies, *iRBD* idiopathic REM sleep behavior disorder, *H/M* heart-to-mediastinum, WR, washout rate

[a]Mann–Whitney *U* test

[b]Kruskal–Wallis test

MIBG with iodine-123 enables us to clinically evaluate the integrity of the cardiac sympathetic nervous system. Originally, in the 1980s, ^{123}I-MIBG myocardial scintigraphy was shown to have a prognostic value in heart failure [35, 36]. Subsequently, in the 1990s, ^{123}I-MIBG myocardial scintigraphy was applied to LBDs and shown to have a diagnostic value for LBDs [7, 8]. Evidences have accumulated from then on, and a meta-analysis revealed that pooled sensitivity and specificity were 82.6% and 89.2%, respectively, for the early H/M ratio, and 89.7% and 82.6%, respectively, for the delayed H/M ratio to differentiate PD from other neurodegenerative parkinsonian syndromes [11]. Another meta-analysis revealed that pooled sensitivity and specificity were 98% and 94%, respectively, for the delayed H/M ratio to differentiate DLB from other types of dementia [37]. Patients with iRBD, a large proportion of whom eventually developed LBDs [38], have also been shown to demonstrate reduced ^{123}I-MIBG uptake [9, 39–44]; therefore, reduced ^{123}I-MIBG uptake has been considered as a good biomarker to support the diagnoses of LBDs and iRBD. Previous studies revealed that independent assessments of the early H/M ratio, delayed H/M ratio, and WR produce a similar diagnostic accuracy [45]; however, considering the reported fact that reduced ^{123}I-MIBG uptake usually begins in the delayed phase and progresses longitudinally [22], the delayed H/M ratio is empirically preferred for the diagnostic purpose. It have also been observed that WR enhancement could precede delayed H/M ratio reduction [19]; however, supposedly because of a paradoxical normal WR in severely denervated patients which was observed in our study, WR is usually avoided for diagnoses of LBDs and iRBD. Our combinational assessment is therefore a totally reasonable approach to overcome this disadvantage of WR and should be preferred in clinical practice to raise the diagnostic accuracy of ^{123}I-MIBG myocardial scintigraphy.

Although beyond the scope of this study, our study also revealed that both early and delayed H/M ratios were significantly reduced in iRBD than in LBDs, and in PD patients with DEB than in those without DEB. Although an earliest study reported that the magnitude of ^{123}I-MIBG uptake reduction was similar between iRBD and PD [9], subsequent reports showed that iRBD patients display significantly lower ^{123}I-MIBG uptake than PD patients [40, 42]. Furthermore, previous studies with small participants also revealed that PD patients with clinical symptoms of RBD display significantly lower ^{123}I-MIBG uptake than those without clinical symptoms of RBD [43, 46]. Therefore, our data and those previous data altogether suggest that the lesion responsible for RBD links closely to the cardiac sympathetic denervation and that the presence of RBD only mirrors a distinct pathological subtype in PD. This hypothesis is important especially because iRBD recently gathers a lot of attention as prodromal PD for developing a disease modification

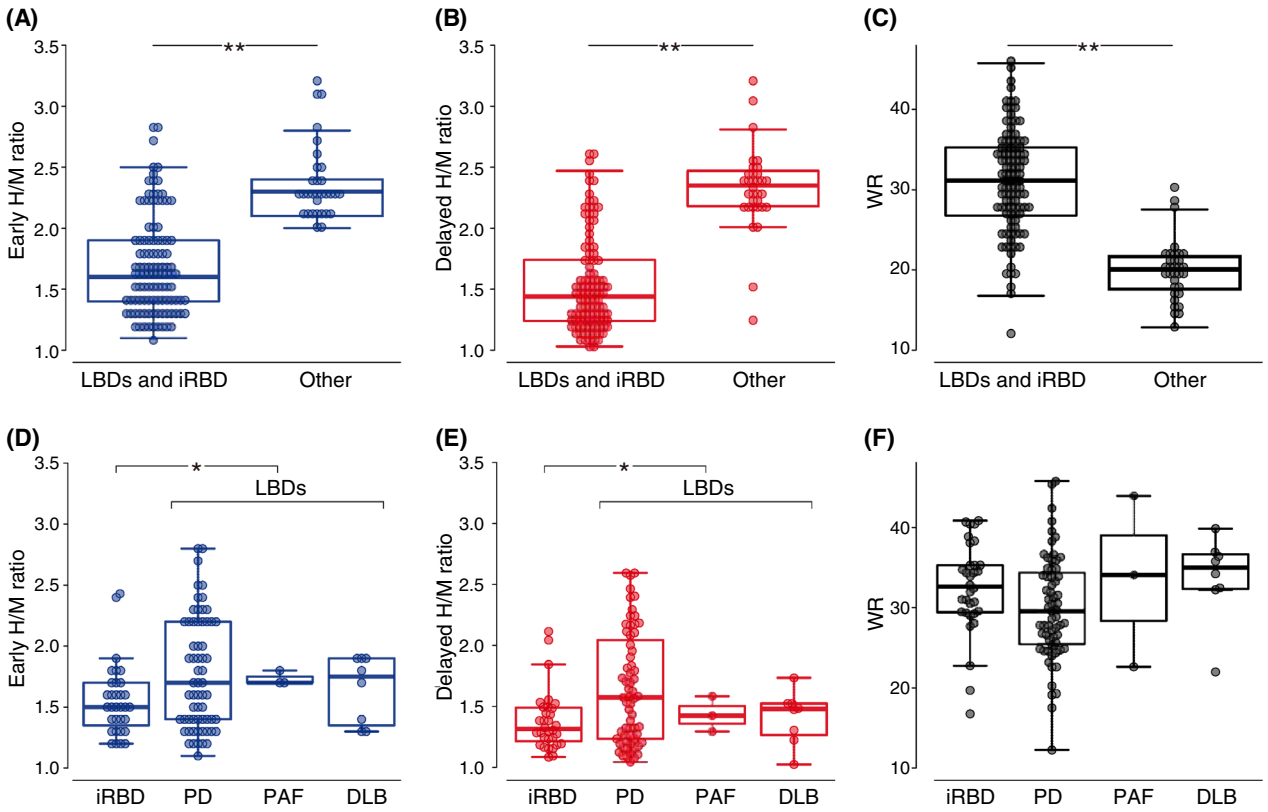

Fig. 3 Box plots with dot plots showing the early heart-to-mediastinum (H/M) ratio, delayed H/M ratio, and washout rate (WR). The early (**a**) and delayed (**b**) heart-to-mediastinum (H/M) ratios were significantly reduced in Lewy body diseases (LBDs) and idiopathic REM sleep behavior disorder (iRBD). WR (**c**) was significantly enhanced in LBDs and iRBD. Among LBDs and iRBD, there were no statistically significant differences between each disease in the early H/M ratio (**d**), delayed H/M ratio (**e**), and WR (**f**); however, when compared between iRBD and LBDs, the early H/M ratio and the delayed H/M ratios were significantly lower in iRBD than in LBDs. *PAF* pure autonomic failure, *DLB* dementia with Lewy bodies. $^{**}p<0.01$, $^{*}p<0.05$

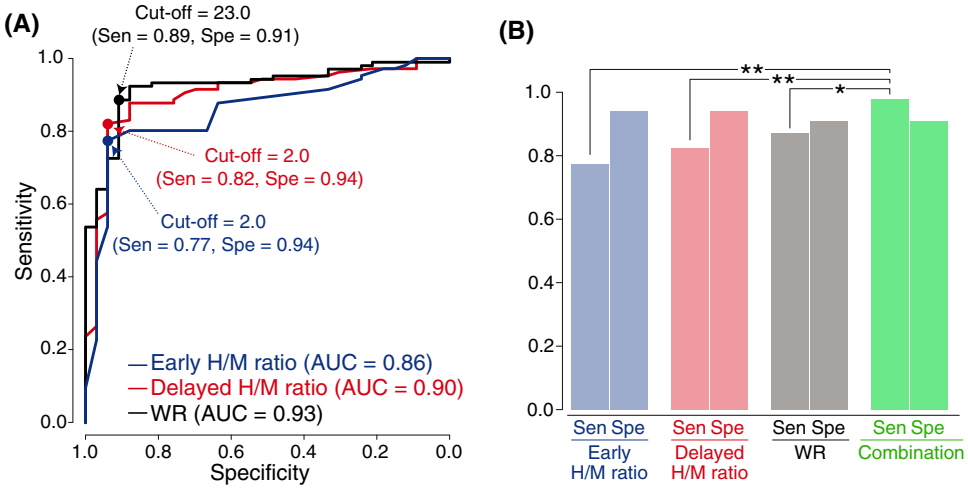

Fig. 4 Diagnostic accuracy of our combined assessment. **a** Receiver operating characteristic (ROC) analysis of individual assessments of the early heart-to-mediastinum (H/M) ratio, delayed H/M ratio, and washout rate (WR). Sensitivity (Sen) and specificity (Spe) obtained from our pre-determined cut-off values were also presented. **b** Bar plots showing the significant improvement in sensitivity with our combined assessment. *AUC* area under the ROC curve. $^{**}p<0.01$, $^{*}p<0.05$

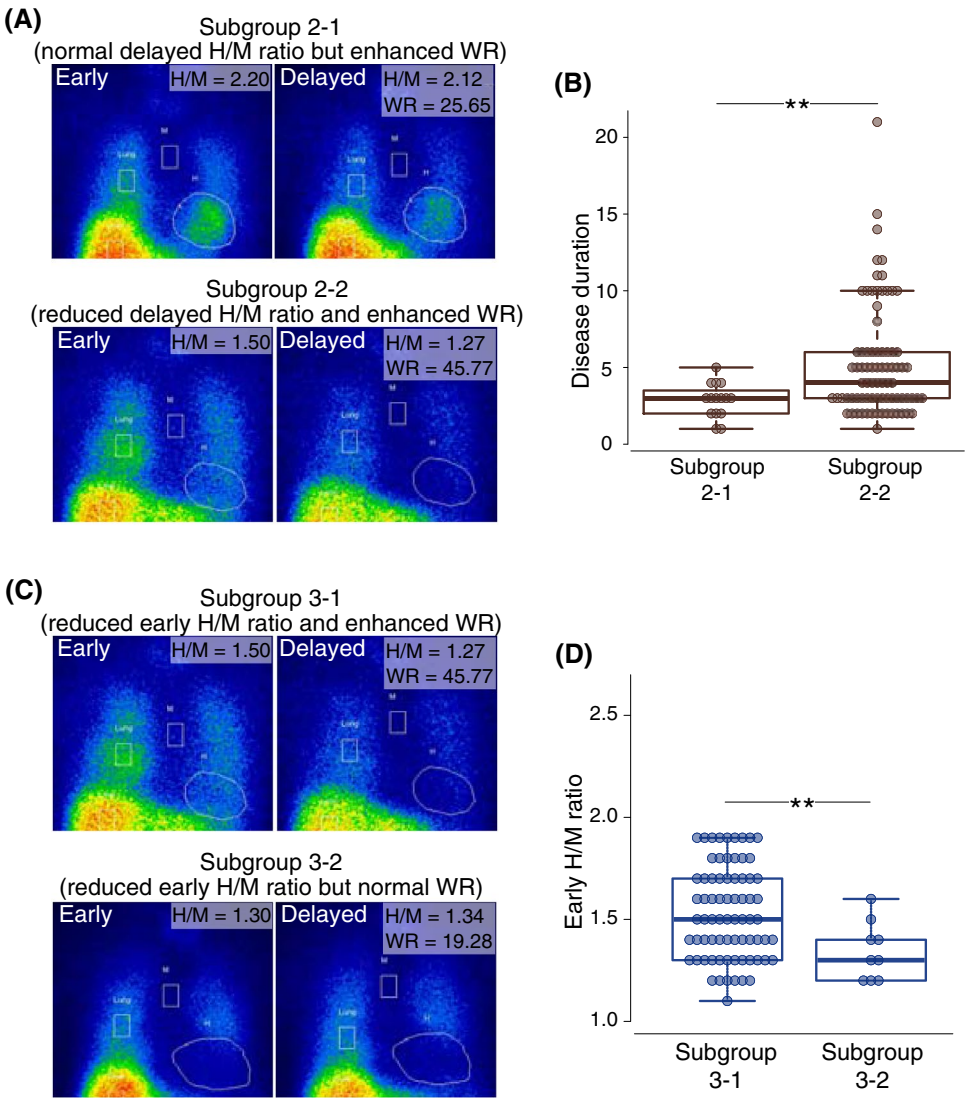

Fig. 5 Subgroup analyses in Lewy body diseases and idiopathic REM sleep disorder. **a** Representative ^{123}I-metaiodobenzylguanidine myocardial scintigraphy images in subgroup 2–1 and subgroup 2–2. **b** Box plots with dot plots showing the disease duration was significantly shorter in subgroup 2–1 than in subgroup 2–2. **c** Representative ^{123}I-metaiodobenzylguanidine myocardial scintigraphy images in subgroup 3–1 and subgroup 3–2. **d** Box plots with dot plots showing the early heart-to-mediastinum (H/M) ratio was significantly reduced in subgroup 3–2 than in subgroup 3–1. *WR* washout rate, $^{**}p < 0.01$

therapy [47]; therefore, future studies with larger cohorts are definitely warranted to examine this hypothesis.

There are several limitations to this study. First, although we took a long follow-up period, it would be unfeasible to totally eliminate a diagnostic bias due to the established usefulness of ^{123}I-MIBG myocardial scintigraphy for the diagnosis of LBDs [1, 17]. Second, only the clinical diagnosis was employed as a reference standard. Finally, the number of patients without LBDs and iRBD was relatively small. Nevertheless, our study has a high clinical relevance in that we proposed a reasonable, easily-feasible approach of combined early H/M ratio and WR assessments, which showed significantly higher sensitivity without an associated reduction of specificity.

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Author contributions KT, NT, and TH contributed to the study conception, study design, and data acquisition. KT primarily analyzed the data and did the statistical analyses. The first draft of the manuscript was written by KT. NT and TH revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest concerning this study. Outside

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Ethics approval This study was approved by the institutional review board of Kansai Electric Power Hospital and conducted according to the ethical standards issued by the Declaration of Helsinki.

Consent to participate and consent for publication The details of this study was posted up in our hospital with our contact information. All patients were exempt by the institutional review board of Kansai Electric Power Hospital from providing written informed consent due to the retrospective design of this study; however, all patients had the chance to request the detailed explanation from us and opt out at any time.

Code availability Not applicable.

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