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FULL PAPER

^{123}I -MIBG myocardial scintigraphy for the evaluation of Lewy body disease: are delayed images essential? Is visual assessment useful?

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Objective: We performed ^{123}I -meta-iodobenzylguanidine (^{123}I -MIBG) myocardial scintigraphy for the diagnosis of Lewy body disease (LBD) and assessed whether the early heart-to-mediastinum (H/M) ratio was diagnostic and whether visual image analysis was useful.

Methods: Our study included 453 patients with clinically suspected LBD who had undergone ^{123}I -MIBG myocardial scintigraphy. We evaluated semi-quantitative values (early and delayed H/M ratio, washout rate) and performed visual image analysis. The sensitivity, specificity, accuracy, positive-predictive value (PPV) and negative-predictive value (NPV) of both analyses were calculated.

Results: The early H/M ratio exhibited the best diagnostic ability. Its overall sensitivity, specificity, accuracy, PPV and NPV were 72.2%, 93.1%, 84.3%, 88.5% and 82.2%,

respectively (cut-off value 2.2 or less). However, there was no significant difference from the delayed H/M ratio or the results of visual assessment.

Conclusion: ^{123}I -MIBG myocardial scintigraphy accurately differentiates between patients with and without LBD and a correct diagnosis can be established based on the early H/M ratio. We also document that visual evaluation of scintigrams is useful. Therefore, patients may benefit from the single performance of the procedure because a correct diagnosis can be obtained early in the disease process and their prognosis and appropriate treatment can be determined.

Advances in knowledge: ^{123}I -MIBG myocardial scintigraphy on the early H/M ratio makes it possible to differentiate between patients with LBD and patients without LBD.

INTRODUCTION

Dementia with Lewy bodies (DLB), Parkinson's disease (PD), Parkinson's disease with dementia and pure autonomic failure are overlapping diseases;¹ Lewy body disease (LBD) is a general term for these diseases. Patients with LBD usually present with impairment of the sympathetic nervous system and abnormalities on ^{123}I -meta-iodobenzylguanidine (^{123}I -MIBG) myocardial scintigraphy studies.^{2,3} As the ^{123}I -MIBG uptake is correlated with the function of the adrenergic nervous system, involvement of the myocardial postganglionic sympathetic nerves may account for the decrease in the ^{123}I -MIBG uptake on myocardial scintigraphs in patients with LBD.^{4,5} Progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and corticobasal degeneration (CBD) are seen in parkinsonism. In the early stage of PD, its differentiation from other neurodegenerative diseases is difficult. As the prognosis differs among these disorders, the selection of

the proper treatment strategy is highly important. Therefore, the early differentiation between PD and other neurodegenerative parkinsonisms is crucial and the diagnostic accuracy must be improved. ^{123}I -MIBG myocardial scintigraphy is useful for distinguishing between LBD and non-LBD including Alzheimer disease, PSP, MSA, vascular dementia, CBD and other neurodegenerative diseases,⁶ and the role of myocardial sympathetic imaging in the early diagnosis of LBD and in the differentiation between LBD and other neurodegenerative diseases has been studied.^{2,3}

While the diagnostic accuracy of ^{123}I -MIBG myocardial scintigraphy is high,^{2,3} nevertheless, 3–4 h is required for the completion of scintigraphy. This places a burden on patients and medical staff. Also, exacerbation of the behavioural and psychological symptoms of dementia may force a halt in the examination. Early-phase imaging of ^{123}I -MIBG myocardial scintigraphy may help to support

the clinical diagnosis of LBD. Early images have been reported to be as accurate as delayed images for the differential diagnosis between LBD and other neurodegenerative diseases.^{2,3,7} Moreover, if early ¹²³I-MIBG myocardial scintigraphy yields accurate diagnostic information, the treatment of more patients with clinically suspected LBD can be started earlier. To our knowledge, there are no reports that compared the diagnostic performance of the heart-to-mediastinum (H/M) rate statistically between early and delayed imaging. Therefore, the utility of early H/M imaging was not established.

The H/M ratio reflects the ratio of the heart to the background. However, selection of the regions of interest (ROIs) may vary among institutions, and the H/M ratio is higher on medium-energy collimators than on low-energy (LE) collimators.⁸ Also, even if the H/M ratio is not used for quantitative evaluations, in the presence of LBD, the cardiac uptake on early-phase planar images may be markedly decreased.

In the present study, we investigated the utility of early ¹²³I-MIBG myocardial scintigraphy in a large population of patients with suspected LBD. We evaluated whether the early or the delayed H/M ratio was more diagnostically useful and whether visual image assessment can help to differentiate LBD from non-LBD.

METHODS AND MATERIALS

Patients

This retrospective study was approved by our institutional ethics board. Patient informed consent was waived owing to its retrospective, purely observational nature.

We included 453 patients with clinically suspected LBD who had undergone ¹²³I-MIBG myocardial scintigraphy at Kumamoto University Hospital between January 2008 and December 2013. The diagnosis was LBD in 191 patients (78 males, 113 females; mean age $\pm$ standard deviation, 73.6 ± 9.6 years; range,

34–89 years) and non-LBD in 262 patients (108 males, 154 females; mean age $\pm$ standard deviation, 73.2 ± 9.0 years; range, 77–89 years). We excluded patients with congestive heart failure, ischaemic heart disease, cardiomyopathy and diabetes and patients taking antipsychotic drugs (tricyclic antidepressants, reserpine) that would clearly affect the results of ¹²³I-MIBG scintigraphy. The final diagnosis of LBD was made by neurologists or psychiatrists who took into account the patient history, clinical symptoms and each guideline. The presence of hydrocephaly or an arteriosclerotic disease was investigated by MRI.

As shown in Table 1, of the 191 patients in the LBD group, 98 patients had probable DLB, 15 patients had possible DLB, 74 patients had PD and 4 patients had Parkinson's disease with dementia. Among patients in the non-LBD group ($n = 262$), 73 patients had Alzheimer disease, 41 patients had vascular dementia, 26 patients each had MSA or PSP, 20 patients had CBD and the remaining 76 patients were diagnosed with other diseases. There was no significant difference in the age and gender of the two groups.

¹²³I-MIBG myocardial scintigraphy

Anterior planar images were obtained 15 min (early images) and 3 h (delayed images) after the i.v. injection of 111 MBq (3 mCi) of ¹²³I-MIBG (FUJIFILM RI Pharma Co., Ltd, Tokyo, Japan). The images were acquired with a double-head gamma camera equipped with a medium-energy general-purpose collimator (Millennium VG, GE Healthcare). The image acquisition time was 5 min, a 256×256 matrix format, zoom was 1.33 and the energy window was set at 159 keV ($\pm 10\%$). The pixel size was 1.64 mm. Using the ROI method, we calculated the early and delayed ¹²³I-MIBG H/M ratios on the anterior views of the planar images. An irregular circular ROI was manually drawn on the left ventricle and a square ROI was drawn in the upper mediastinum. The ¹²³I-MIBG washout rate (%) was calculated with the formula:

Table 1. Diagnoses of 453 patients included in this study

Characteristics	LBD	Non-LBD	<i>p</i> -value
<i>n</i>	191	262	
Age (years)	73.6 ± 9.6	73.1 ± 9.0	0.629
Gender (male:female)	78:113	108:154	0.923
Details of diagnosis	Probable DLB 98 Possible DLB 15 PD 74 PDD 4	AD 73 VaD 41 MSA 26 PSP 26 CBD 20 iNPH 11 FTLD 7 FAP 4 Depression 27 Others 27	

AD, Alzheimer disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; FAP, familial amyloid polyneuropathy; FTLD, frontotemporal lobar degeneration; iNPH, idiopathic normal pressure hydrocephalus; LBD, Lewy body disease; MSA, multiple system atrophy; PD, Parkinson's disease; PDD, Parkinson's disease with dementia; PSP, progressive supranuclear palsy; VaD, vascular dementia.

Figure 1. For visual image analysis in impairment of the sympathetic nervous system, we categorized into five grades from 1 to 5: Score 1 = defective, Score 2 = severely decreased (slight uptake, but not clear), Score 3 = moderately decreased (clear uptake, but slightly), Score 4 = mildly decreased (clear uptake, but lower than normal pattern) and Score 5 = normal pattern.

Score	1	2	3	4	5
visual assessment	Defect	Severe	Moderate	Mild	Normal
lung uptake positive
lung uptake negative

$$\frac{[(\text{early heart counts} - \text{early background counts}) - (\text{delayed heart counts} - \text{delayed background counts})]}{(\text{early heart counts} - \text{early background counts})} \times 100$$

Visual image analysis

We separated images that did and did not show lung uptake and evaluated the myocardial uptake on early and delayed planar images. We categorized the uptake as 1 = defective, 2 = severely decreased (slight uptake, but not clear), 3 = moderately decreased (clear uptake, but slight), 4 = mildly decreased (clear uptake, but lower than normal pattern) and 5 = normal pattern (Figure 1). Visual image analysis was performed independently by two nuclear medicine specialists.

Statistical analysis

Our objective was to differentiate between LBD and non-LBD by using relevant variables. Differences between patients with LBD and without LBD with respect to their age and gender were determined with the Mann-Whitney *U*-test. The results of ¹²³I-MIBG myocardial scintigraphy (early and delayed H/M ratio and washout rate) and visual image analyses were tested as predictors of a conversion from LBD to non-LBD. The diagnostic value of our quantitative and visual assessments was evaluated by calculating the area under the receiver-operating characteristic (ROC) curve in patients with LBD and patients without LBD. Diagnostic accuracy was evaluated by calculating the sensitivity, specificity, positive-predictive value, negative-predictive value and accuracy. The cut-off

Figure 2. Scatterplots of the striatal early heart-to-mediastinum (H/M) ratio (a), the delayed H/M ratio (b) and the washout rate (%) (c) in patients with Lewy body disease (LBD) and patients without LBD. The horizontal bars indicate the median.

Figure 3. Scatterplots of the results of striatal image analysis in all patients. H/M, heart to mediastinum.

value for each index was based on the ROC curve with the highest accuracy for differentiating between LBD and non-LBD. All statistical calculations were performed using the SPSS statistics software program v. 17.0 (SPSS Inc., Chicago, IL). Differences of $p < 0.05$ were considered statistically significant.

RESULTS

As shown in the scattergram (Figure 2), the early and delayed H/M ratio and the washout rate were significantly lower in the LBD group than in the non-LBD group. The washout rate was not significantly different between the two groups. The H/M ratio of the LBD group ranged from 1.2 to 3.6 (median 1.76) in the early phase of imaging and from 1.0 to 4.6 (median 1.46) in the delayed phase. The H/M ratio of non-LBD subjects ranged from 1.4 to 5.9 (median 2.70) on early images and from 1.0 to 5.8 (median 3.11) on the delayed images.

The scatterplots in Figure 3 represent the striatal visual assessment of images from all patients and compare the visual score and the mean H/M ratio. Although there was overlap, the H/M ratio increased with the visual score. The average early H/M ratio and the delayed H/M ratio for a visual score of 1 were 1.56 and 1.44 and for a visual score of 2, they were 1.75 and 1.73, respectively,

suggesting that these values reflect the H/M ratios of an LBD pattern. In many patients with a visual score of 3 or higher, the H/M ratio was within the normal range, suggesting non-LBD.

The summarized results are shown in Table 2. By the Mann–Whitney *U*-test, the early and delayed H/M ratios were significantly lower ($p < 0.001$) in the LBD group (early: 1.97 ± 0.62 ; delayed: 1.78 ± 0.77) than in the non-LBD group (early: 2.95 ± 0.59 ; delayed: 3.04 ± 0.80). While the ^{123}I -MIBG washout rate was not significantly different ($p = 0.850$), the early and the delayed visual scores were significantly lower ($p < 0.001$) in the LBD group (early: 2.24 ± 1.27 ; delayed: 1.94 ± 1.30) than in the non-LBD group (early: 3.84 ± 0.87 ; delayed: 3.73 ± 1.01).

Figure 4 shows the ROC curves for discriminating between LBD and non-LBD based on the early and delayed H/M ratios and the early and delayed visual scores. The cut-off values for differentiating LBD from non-LBD were <2.2 [area under the curve (AUC), 0.868; 95% confidence interval (CI), 0.831–0.904] for the early H/M ratio and <2.1 (AUC, 0.865; 95% CI, 0.829–0.901) for the delayed H/M ratio. They were 2 or less (AUC, 0.827; 95% CI, 0.784–0.869) for the early visual score and 2 or less (AUC, 0.832; 95% CI, 0.790–0.874) for the delayed visual score.

Table 2. Results of ^{123}I -meta-iodobenzylguanidine (^{123}I -MIBG) myocardial scintigraphy

Parameters	LBD	Non-LBD	<i>p</i> -value
Early H/M ratio	1.97 ± 0.62	2.95 ± 0.59	<0.001
Delayed H/M ratio	1.78 ± 0.77	3.04 ± 0.80	<0.001
Washout rate	45.20 ± 14.00	43.20 ± 172.23	0.850
Early visual score	2.24 ± 1.27	3.84 ± 0.87	<0.001
Delayed visual score	1.94 ± 1.30	3.73 ± 1.01	<0.001

H/M, heart to mediastinum; LBD, Lewy body disease.

Figure 4. Receiver-operating characteristic (ROC) curves for discriminating between Lewy body disease (LBD) and non-LBD based on the early heart-to-mediastinum (H/M) ratio, the delayed H/M ratio and the early and delayed visual scores. AUC, area under the curve.

Table 3 presents the diagnostic performance of the cut-off values selected for the early and the delayed H/M ratio and the early and delayed visual scores. In ROC analysis of the diagnostic performance for LBD, the early H/M ratio yielded the highest AUC value, but the difference for AUC values among the early and delayed H/M ratio and the early and delayed visual scores was not statistically significant.

Table 4 shows the % LBD at the cut-off value for the early H/M ratio and the early visual score. When the H/M ratio was <2.0, 92% of the cases had LBD and at 2.0–2.5, this value was 38%; it was 15% or more at an H/M ratio of 2.5. On the other hand, LBD was present in 88% of patients with a visual score of 1 or 2, in 32% of patients with a score of 3 and in 17% of patients with a score of 4 or 5.

Figures 5 and 6 present cases in which the H/M ratio was 2.2 or less. We found that when the H/M ratio was 2.1–2.2, the visual score was 1 or 2 and on planar images, there was no myocardial uptake or a low degree of myocardial uptake.

DISCUSSION

Usefulness of the early heart-to-mediastinum ratio

The ¹²³I-MIBG uptake in early-phase imaging mainly reflects the density of the presynaptic cardiac sympathetic nerve endings; the delayed phase imaging also reflects the presynaptic functional tone of the cardiac sympathetic nerve. Early images show the integrity of the presynaptic nerve terminals, while delayed images reflect the integrity of the neuronal function.⁹ The protocols for early and delayed images were developed for the evaluation of heart failure and were based on the protocol for the evaluation of nervous function in patients with heart failure. Therefore, in LBD, as a consequence of the degeneration of the cardiac muscle sympathetic nerve, assessment of the distribution of this nerve on early images was considered useful.^{10–12} Orimo et al¹³ suggested that a decrease in myocardial ¹²³I-MIBG uptake in the early stage of LBD, a neurodegenerative disease, reflects the degeneration of the cardiac muscle sympathetic nerve.

In an effort to reduce the burden on patients subjected to ¹²³I-MIBG myocardial scintigraphy, we evaluated the utility of early imaging for differentiating between LBD and non-LBD. Interestingly, in patients with LBD, there was no statistically significant difference in the diagnostic performance of the early and delayed H/M ratios. Our findings suggest that an LBD diagnosis can be obtained by using ¹²³I-MIBG myocardial scintigraphy and that acquisition of only the early H/M ratio is sufficient. Generally, it takes about 3–4 h to complete the procedure because patients have to wait for imaging until the delayed phase. However, we found that early-phase imaging could change the protocol for patients suspected of LBD. Early-phase imaging makes it possible to test patients who cannot tolerate long examination hours because of their parkinsonism, behavioural and psychological symptoms of dementia or dementia.

Our investigation yielded some false-positive results and some false-negative results. First, Sakata et al¹⁴ reported that the myocardial ¹²³I-MIBG uptake decreases significantly as the patient age increases. Spiegel et al¹⁵ reported that 8–17%

Table 3. Diagnostic performance of four variables in the patients with Lewy body disease (LBD) and patients without LBD

Parameters	Cut-off	AUC (95% CI)	Sensitivity	Specificity	Accuracy	PPV	NPV
Early H/M ratio	<2.2	0.868	72.2	93.1	84.3	88.5	82.2
Delayed H/M ratio	<2.1	0.865	75.9	89.7	83.9	84.3	83.6
Early visual score	≤2	0.827	67.0	93.5	82.3	88.3	79.5
Delayed visual score	≤2	0.832	74.9	88.9	83.0	83.1	82.9

AUC, area under the curve; CI, confidence interval; H/M, heart to mediastinum; NPV, negative-predictive value; PPV, positive-predictive value.

Early H/M ratio vs delayed H/M ratio; $p \geq 0.05$.

Early H/M ratio vs early visual score; $p \geq 0.05$.

Early H/M ratio vs delayed visual score; $p \geq 0.05$.

Table 4. Percent Lewy body disease (LBD) at the cut-off value for early heart-to-mediastinum (H/M) ratio and the early visual score

	Cut-off	LBD	Non-LBD	%LBD
Early H/M ratio	<2.0	125	11	92
	2.0–2.5	31	50	38
	>2.5	35	201	15
Early visual score	1 or 2	127	17	88
	3	24	51	32
	4 or 5	40	194	17

of neurologically normal autopsied subjects older than 60 years harboured Lewy bodies, a phenomenon termed incidental LBD. Therefore, we posit that our false-positive findings are attributable to age-related—rather than LBD-related—postsynaptic noradrenergic degeneration. Studies that include age-matched controls are needed to address this issue. Second, Nagayama *et al*¹⁶ reported a patient with a clinical diagnosis of MSA whose myocardial ¹²³I-MIBG uptake was reduced. Post-mortem pathology studies confirmed LBD in addition to MSA, suggesting that LBD affects ¹²³I-MIBG findings. Thus, some patients diagnosed as non-LBD may in fact have LBD. We considered this possibility but were unable to obtain pathological evidence. Third, Spiegel *et al*¹⁵ found that in some patients with early-stage PD subjected to ¹²³I-MIBG scintigraphy, the H/M ratio was within the normal range. In patients with LBD with a short disease duration, ¹²³I-MIBG myocardial scintigraphy may return false-negative results.

Although our observation period was at least 12 months, cases with early LBD may have returned a false-negative result.

The availability of visual assessment

Nakajima,¹⁷ who collected data from Japanese standard ¹²³I-MIBG databases, reported that the normal values obtained on different types of collimators showed significant differences. When an LE collimator was used, the H/M ratio was lower owing to scattered radiation. In addition, the ROI

may be placed at different sites at different institutions, and this also affects the reported H/M ratio. Therefore, we performed not only a semi-quantitative evaluation of the H/M ratio but also a visual assessment.

We assigned 5 scores to the myocardial uptake and compared the results with the uptake in the liver. Taking into account the possibility of error due to uptake by the lung, we subdivided our findings into those that did and did not reveal lung uptake. Lung uptake of ¹²³I-MIBG is a potential marker of pulmonary endothelial cell function in the lung.^{18,19} PD is reported to cause endothelial dysfunction *via* elevated plasma homocysteine levels, and hyperhomocysteinaemia is related to treatment with L-dopa.^{20,21} It is necessary to examine the relationship between ¹²³I-MIBG and lung uptake.

ROC analysis showed that the differentiation between LBD and non-LBD was possible when the cut-off value for early-phase and delayed phase images and for the early and delayed H/M ratios was set at <2. No statistically significant difference was seen between the early and delayed visual score.

To the best of our knowledge, this is the first comparison of the diagnostic accuracy of ¹²³I-MIBG myocardial scintigraphy and image analysis in a mixed patient population with suspected LBD. Even in the absence of semi-quantitative evaluation, when the myocardial uptake is defective or severely decreased on early planar images, the possibility of LBD is high.

Our study has some limitations. First, as the diagnoses were not confirmed by autopsy but were based on the careful interpretation of clinical and imaging findings, we may have misdiagnosed some patients. Second, we assigned a slightly higher cut-off value (2.2 or less) for the H/M ratio than others.^{7,22,23} We used a medium-energy rather than an LE collimator, but there appears to be no difference in the results yielded by these instruments. Because the reported H/M ratio obtained by ¹²³I-MIBG myocardial scintigraphy varied among institutions, scintiscamera-collimator combinations should be standardized.

Figure 5. Patients with Lewy body disease (LBD) with a heart-to-mediastinum (H/M) ratio of 2.1–2.2. (a) A 58-year-old female with Parkinson's disease. The lung uptake was positive. The visual score was 1 and the early and delayed H/M ratios were 2.1 and 2.0, respectively. (b) A 78-year-old female with dementia with LBD. The lung uptake was negative. The visual score was 1 and the early and delayed H/M ratios were 2.2 and 1.9, respectively.

Figure 6. Patients without Lewy body disease with a heart-to-mediastinum (H/M) ratio of 2.1–2.2. (a) A 48-year-old male with familial amyloidotic polyneuropathy. The lung uptake was positive. The visual score was 1 and the early and delayed H/M ratios were 2.2 and 1.8, respectively. (b) A 52-year-old male with multiple system atrophy. The lung uptake was negative. The visual score was 1 and the early and delayed H/M ratios were 2.1 and 1.5, respectively.

CONCLUSION

¹²³I-MIBG myocardial scintigraphy makes it possible to differentiate between patients with LBD and patients without LBD. Our findings indicate that as the early and delayed H/M ratios are not significantly different, acquisition of the early H/M ratio is sufficient for an accurate diagnosis.

We also document that visual evaluation of scintigrams is useful. We expect that a shorter examination time will ease the burden on patients, their family and care providers.

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