Original article

Comparison of the diagnostic performance of H/M ratio between early and delayed phases for Lewy body disease

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Objectives The aim of the study was to compare the diagnostic performance of early-phase ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy with that of delayed-phase imaging in Lewy body disease (LBD).

Methods A retrospective cohort study of ^{123}I-MIBG scintigraphy was carried out in 192 patients who were suspected of having LBD. Clinical diagnosis was obtained using the UK Parkinson's Disease Brain Bank Criteria in some cases or the third report of the Dementia with Lewy bodies Consortium in others. The participants consisted of 81 patients with LBD and 111 nondiseased patients. An injection of 111 MBq of ^{123}I-MIBG was used. Planar images were obtained in an early phase and again in a delayed phase and the heart to mediastinum count ratio was calculated for both phases. Diagnostic performance was compared using a receiver-operator characteristic analysis. The cutoff value was chosen to maximize the Youden index. The sensitivity and specificity of each phase were calculated from the optimal cutoff value.

Results The heart to mediastinum ratio of the LBD group (median 1.8 and 1.45 for early and delayed phases, respectively) was significantly lower than that of the nondiseased group (median 2.93 and 3.18 for early and

delayed phases, respectively). The area under the receiver-operating characteristic curve was not significantly different between the early and delayed phases (0.871 vs. 0.893; $P = 0.0914$). Sensitivity and specificity were 80.2 and 91% for early-phase imaging (cutoff value at 2.28) and 81.5 and 95.5% (cutoff value at 1.91) for delayed-phase imaging, respectively.

Conclusion The diagnostic performance of ^{123}I-MIBG scintigraphy was not significantly different between early-phase and delayed-phase imaging. *Nucl Med Commun* 36:477–480 Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

Parkinsonism is a common symptom, but early diagnosis of Parkinson's disease (PD) and dementia with Lewy bodies (DLB) is very difficult even for neurologists because clinical history or physical examination is nonspecific. Metaiodobenzylguanidine (MIBG) is a physiological analog of noradrenaline (norepinephrine) and has been used to evaluate postganglionic cardiac sympathetic innervation. Many studies have reported that cardiac MIBG uptake is reduced in the case of Lewy body disease (LBD). Examples are PD and DLB [1]. The studies have proven that the heart to mediastinum (H/M) ratio of ^{123}I-MIBG cardiac scintigraphy is a useful diagnostic tool for indicating the significant reduction in myocardial MIBG uptake in LBD as compared with a control group.

MIBG scintigraphy is performed twice – in the early phase (from 10 to 30 min after injection of the radioisotope) and in the delayed phase (from 3 to 4 h after injection of the

radioisotope). All previous studies on LBD examined the patients twice, and the H/M average count ratio was obtained for both early and delayed images mainly using planar imaging. However, only the delayed H/M ratio was used to evaluate the diagnostic performance in most of the previous studies [2]. To our knowledge, there are no reports comparing the diagnostic performance of H/M ratio statistically between early and delayed phases [3,4]. Therefore, the potential role of early H/M ratio has not been established. The aim of our study was to compare the diagnostic performance of the H/M ratio in early-phase ^{123}I-MIBG scintigraphy with that in delayed-phase imaging. If the diagnostic performance of the H/M ratio in the early phase is found comparable to that of the delayed phase, the total time taken by the examination to evaluate LBDs would be much shorter.

Methods

Patients

This is a single-center retrospective case–control study. Our institutional review board approved the study and the need for informed consent was waived. Between April 2012 and December 2013, 217 consecutive patients

Table 1 Patient characteristics

	Nondiseased	Lewy body disease	P
Number	111	81	
Sex (male : female)	54 : 57	38 : 43	0.8121[a]
Age (median)	38–90 (75)	49–88 (74)	0.59[b]
Duration of symptom (median)	Not available	0 − 240 months (13)	
Hoehn and Yahr classification (median)	–	0–5 (3)	

[a]χ^2-test.
[b]Mann–Whitney test.

with suspected degenerative parkinsonism underwent ^{123}I-MIBG cardiac scintigraphy. The exclusion criteria for this study were a history of tricyclic antidepressive medication or heart disease. The latter included coronary heart disease, infarction, and heart failure. All of these conditions could influence the cardiac uptake. Application of the exclusion criteria resulted in the identification of 192 patients for analysis. The final diagnosis of LBD – that is, PD or DLB – was made by neurologists who took into account the patient's history, the clinical presentation of key features, and a diagnostic brain MRI to exclude symptomatic parkinsonism such as multiple arteriosclerotic changes or hydrocephalus. The UK PD Society Brain Bank Criteria [5] were used for the clinical diagnosis of PD, and the third report of the DLB Consortium [3] was used to make the clinical diagnosis of DLB. Thereby, 81 patients were diagnosed as having LBD. The characteristics of the patients are listed in Table 1.

MIBG myocardial scintigraphic imaging
All patients underwent ^{123}I-MIBG myocardial scintigraphy after an intravenous injection of 111 MBq of ^{123}I-MIBG (Fujifilm RI Pharma Co. Ltd, Tokyo, Japan). Energy discrimination was centered on 159 keV with a 15% window. Anterior images of the chest were obtained after 15 min and again after 4 h using a dual-headed gamma camera (Toshiba E.CAM duet; Toshiba Medical Systems, Kawasaki, Japan) equipped with low-to medium-energy general-purpose collimators. The imaging data were acquired for 4 min in a 256×256 matrix. The cardiac uptake of ^{123}I-MIBG was determined by manually drawing a region of interest (ROI) that encircled the left ventricle. The mediastinal uptake was determined by setting a rectangular ROI drawn by a skilled medical radiation technologist in the upper mediastinum. The H/M ratio was calculated as the ratio of the average counts per pixel in the heart ROI divided by that in the mediastinum ROI. We used software for transport and analysis of myocardial planar images (STAMP ver1.3; Fujifilm RI Pharma Co. Ltd) to calculate the H/M ratio.

Statistical analysis
Normality of the H/M ratios of the early and delayed images was examined by means of the Shapiro–Wilk test.

The difference in H/M ratios between the early and delayed images was examined for statistical significance using the Mann–Whitney U-test. We conducted conventional receiver-operating characteristic (ROC) analysis for assessing the diagnostic performance of the H/M ratio in the early and delayed phases. The area under the curve (AUC) was calculated for each phase and the difference in AUC was analyzed. The optimal cutoff value of the H/M ratio for both early and delayed phases was chosen to maximize the Youden index (sensitivity + specificity − 1). Thereafter, the sensitivity and specificity were obtained at each cutoff value. The software used was JMP Pro11 (SAS Institute Inc., Cary, North Carolina, USA). Significance was assumed at a P value less than 0.05.

Results
The H/M ratios of the early and delayed images did not show a normal distribution. The H/M ratio of the LBD group ranged from 1.1 to 3.88 (median 1.8) in the early phase and from 0.97 to 4.7 (median 1.45) in the delayed phase. The H/M ratio of the nondiseased group ranged from 1.17 to 4.18 (median 2.93) in the early phase and from 0.85 to 4.77 (median 3.18) in the delayed phase. Both early and delayed H/M ratios of the LBD group were significantly lower than those of the nondiseased group ($P < 0.0001$) (Fig. 1). These results were consistent with those of previous studies [6,7]. There was no normality in the H/M ratios in the early and delayed images.

The ROC curves for both phases are shown in Fig. 2. The AUC for the early phase was 0.871 and that for the delayed phase was 0.893. The difference between them was not significant ($P = 0.0914$). The optimal cutoff value of the H/M ratio for the early and delayed phases was 2.28 and 1.91, respectively. These are higher because our collimator and the way of drawing ROIs were different from the past report. The sensitivity and specificity of the early phase were 80.2% (65/81) and 91% (101/111), respectively. The sensitivity and specificity for the delayed phase were 81.4% (66/81) and 96.7% (106/111), respectively. One patient with LBD was identified only in the delayed phase. In contrast, five nondiseased participants were classified correctly as nondiseased only with the early phase (their H/M ratio was greater than the cutoff value).

Discussion
To our knowledge, this is the first research to statistically compare the diagnostic performance of early and delayed phases. Although previous studies [8–10] have reported the sensitivity and specificity of early and delayed phases, they did not compare the difference statistically. Our results reveal that the diagnostic performance of ^{123}I-MIBG scintigraphy was not significantly different between early and delayed phases.

The results for ^{123}I-MIBG cardiac scintigraphy in the evaluation of LBD have been obtained both in the early

Fig. 1
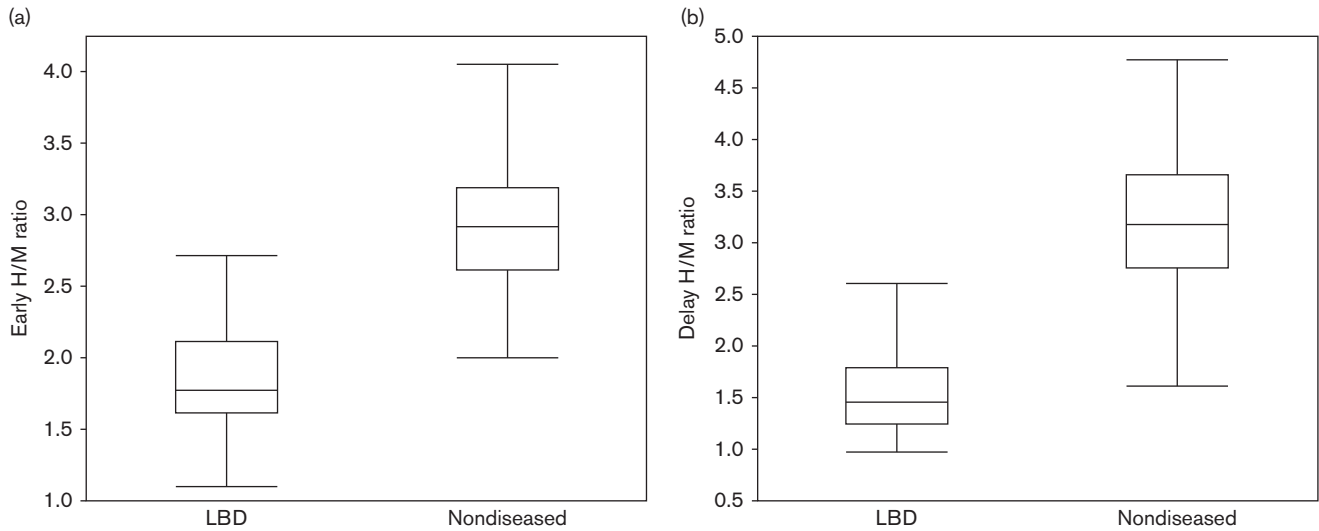
(a) The comparison of early H/M ratio for LBD and nondiseased patients. Early H/M ratios of LBD were significantly lower than those of the nondiseased group ($P < 0.0001$). (b) The comparison of delayed H/M ratio for LBD and nondiseased patients. Delayed H/M ratios of LBD were significantly lower than those of the nondiseased group ($P < 0.0001$). The boxes are bound on the top by the third quartile, and on the bottom by the first quartile. The middle horizontal line of the box represents the median. The upper whisker extends from the third quartile to the third quartile $+ 1.5 \times$ IQR (interquartile range), and the other extends downward from the first quartile to the first quartile $- 1.5 \times$ IQR. H/M, heart to mediastinum ratio; IQR, interquartile range; LBD, Lewy body disease.

Fig. 2
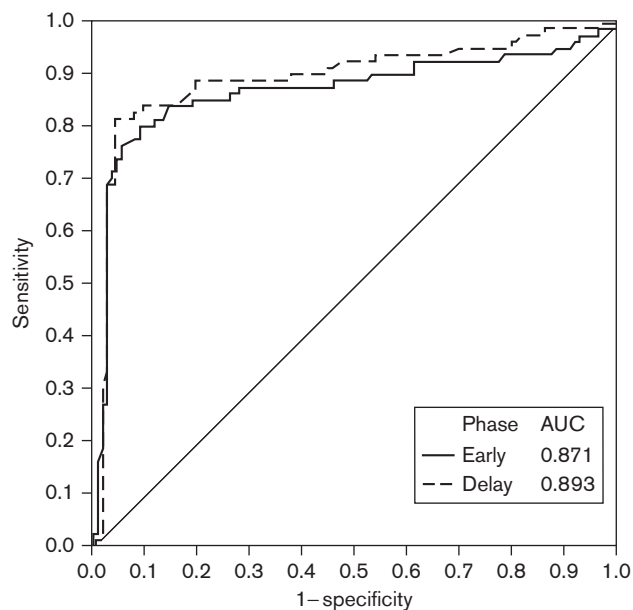
Receiver operating characteristic curves of the H/M ratio in the early and delayed phases. The AUC for the early phase was 0.871 and that for the delayed phase was 0.893. The difference between them was not significant ($P = 0.0914$). AUC, area under the curve; H/M, heart to mediastinum ratio.

(15–30 min) phase and in the delayed (3–5 h) phase. However, the delayed phase was weighted heavily in the meta-analysis part of a previous study [2]. The authors cited some reasons for this. Early myocardial uptake of MIBG reflects the integrity and distribution of the pre-synaptic sympathetic system [11]. However, the neuronal accumulation of MIBG uptake reaches its peak 3–4 h after injection and the delayed uptake may reflect the functional status such as the relative level of neuronal uptake or the degree of washout of norepinephrine from sympathetic nerve terminals [8]. Thus, the delayed phase has been recommended for diagnostic studies. In addition, Kashihara *et al.* [12] reported that the H/M ratio in the LBD group was significantly lower in the delayed phase than in the early one, and the H/M ratio in the control group was higher in the delayed phase than in the early one. This means that the difference in H/M ratio between the LBD and control groups was larger for the delayed phase than for the early one. Regardless of these explanations, the previous studies actually revealed that the H/M ratio in the early phase was also significantly lower in the LBD group than in the control group [1,9, 11]. Sawada *et al.* [8] conducted an ROC analysis for each of the two phases and showed similar AUCs (0.86 for the early phase and 0.85 for the delayed phase), although they were not statistically compared. This trend is similar to our results. Therefore, once the optimal cutoff value of the H/M ratio for the early phase is determined, early-phase imaging can provide comparable diagnostic performance to delayed-phase imaging.

The comparable diagnostic performance of early-phase imaging could change the protocol for patients suspected of having LBD. At present, it takes about 4 h to complete

the procedure because patients have to wait to undergo delayed-phase imaging. Early-phase imaging would shorten the time from injection to completion of imaging to less than 1 h and would make testing available to patients who cannot tolerate long hours because of their parkinsonism or dementia.

Nowadays, ^{123}I-Ioflupan dopamine transporter visualization using single photon emission computed tomography (SPECT) is being increasingly used to assist in the evaluation of parkinsonism. Low dopamine transporter uptake in the basal ganglia is one of the suggestive features of parkinsonism according to the third report of the DLB Consortium, whereas abnormally low uptake in MIBG scintigraphy is only a supportive feature [3]. This means that ^{123}I-Ioflupan SPECT is a more specific examination for LBD compared with ^{123}I-MIBG cardiac scintigraphy. The sensitivity and specificity of ^{123}I-Ioflupan SPECT for PD were 86.5 and 93.6%, respectively, and that for DLB were 98 and 67% [13,14]. Therefore, the diagnostic performance of ^{123}I-Ioflupan SPECT for LBD relative to that of ^{123}I-MIBG cardiac scintigraphy may be somewhat superior but not overwhelmingly so. Second, setting ROIs on ^{123}I-Ioflupan SPECT images has not been standardized and the optimal cutoff value for diagnosis has not been established. Third, it is reported that MIBG can differentiate LBD from multiple systemic atrophy or progressive supranuclear palsy, but ^{123}I-Ioflupan cannot [13,14]. In addition, ^{123}I-Ioflupan SPECT takes longer than early-phase ^{123}I-MIBG scintigraphy; that is, the data of ^{123}I-Ioflupan are usually collected from 3 to 6 h after injection of the radioisotope. Therefore, we believe that cardiac ^{123}I-MIBG scintigraphy will not be completely replaced by ^{123}I-Ioflupan SPECT.

There are a couple of limitations to our study. It is retrospective in nature and the results of ^{123}I-MIBG scintigraphy could have affected the clinician's diagnosis. Second, the ROI was placed manually by encircling the uptake of the heart. Currently, an ROI is placed automatically over the heart by the new software smart MIBG (Fujifilm RI Pharma Co. Ltd). Although an experienced technician placed the ROI in this study, the reproducibility of placing the ROIs was not confirmed. Third, the patients were referred to the university hospital, and hence pretest probability may be high.

Conclusion
Early H/M ratio has almost the same diagnostic performance as delayed H/M ratio. Early-phase ^{123}I-MIBG scintigraphy may be optional for patients who cannot tolerate a long interval from injection to completion of imaging.

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