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FULL PAPER

Diagnosis of dementia with Lewy bodies: can ^{123}I -IMP and ^{123}I -MIBG scintigraphy yield new core features?

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Objective: Since the clinical symptoms of different types of dementia frequently overlap, especially in the earlier stages at onset, it is difficult to distinguish dementia with Lewy bodies (DLB) from other neurodegenerative dementias based on their clinical manifestations alone. Nuclear medicine imaging has been reported as a high-value index for the objective evaluation and diagnosis of DLB. The aim of this study was to evaluate whether nuclear medicine imaging findings may yield core features to be added to the diagnosis of DLB.

Methods: We enrolled 332 patients with suspected DLB. All were evaluated by both ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) myocardial scintigraphy and ^{123}I -labelled N-isopropyl-p-iodoamphetamine (^{123}I -IMP). brain perfusion single-photon emission CT. The final clinical diagnosis indicated probable DLB in 92 patients (40 males, 52 females; mean age $\pm$ standard deviation, 77.4 ± 6.4 years; range, 56–89 years); 240 patients (98 males, 142 females; mean age, 75.5 ± 9.0 years; range, 70–87 years) were recorded as being without DLB. The accepted core features used for clinical evaluations were fluctuating cognition, visual hallucinations and Parkinsonism. The nuclear medicine evaluation indices were the severity score of cerebral blood flow on ^{123}I -IMP scintigraphs of the posterior cingulate and praecuneus and a reduction in the blood flow in the occipital lobe.

For ^{123}I -MIBG evaluation, we recorded the early and delayed heart-to-mediastinum (H/M) ratios and the washout rate.

Results: Univariate and multivariate analyses of fluctuating cognition, visual hallucinations, Parkinsonism and early H/M ratio in patients with probable and without DLB revealed significant differences. Parameters based on ^{123}I -IMP studies did not show any significant differences by multivariate analysis. The area under the curve for the early H/M ratio was 0.918; for fluctuating cognition, visual hallucinations and Parkinsonism, it was 0.693, 0.760 and 0.611, respectively, by receiver-operating characteristic analysis. The early H/M ratio of <2.0 on ^{123}I -MIBG scintigraphs was of the highest diagnostic accuracy. The sensitivity, specificity and accuracy for the diagnosis of probable DLB were 82.4%, 96.3% and 92.5%, respectively.

Conclusion: The early H/M ratio obtained by ^{123}I -MIBG myocardial scintigraphy can serve as a reliable diagnostic index for the core clinical features of DLB. It can be used for the early diagnosis and treatment of DLB.

Advances in knowledge: ^{123}I -MIBG myocardial scintigraphy performed at the initial clinical examination can facilitate the early identification or exclusion of DLB and the early H/M ratio may be a diagnostic biomarker for DLB.

INTRODUCTION

Worldwide, 47.5 million people have dementia and there are 7.7 million new cases reported every year. As societies continue to age, the number of such patients is likely to increase and is estimated to reach 131.5 million by 2050. Dementia has physical, psychological, social and economical impact on caregivers, families and society. Dementia is marked by degeneration of both the mind and body. Alzheimer's disease (AD) is the most common cause of dementia. Dementia with Lewy bodies (DLB) is the second biggest common cause of neurodegenerative dementia.¹

DLB is characterized by a progressive cognitive decline with fluctuations in cognition and alertness, recurrent visual hallucinations and mild to severe Parkinsonism.² DLB progresses more rapidly than other dementia disorders and these patients have a poor prognosis owing to worsening cognitive impairment and Parkinsonism. Therefore, the early diagnosis and treatment of this debasing disease is crucial. However, the clinical symptoms of different types of dementia frequently overlap and it is difficult to distinguish DLB from other neurodegenerative dementias based on clinical manifestations alone. As there is no

conclusive pathological evidence, the possibility of a wrong clinical diagnosis remains a concern and a functional imaging evaluation that would offer objective and consistently reliable information is needed. To increase the accuracy of *ante mortem* differential diagnosis of DLB, current criteria include findings from ^{123}I -metaiodobenzylguanidine (^{123}I -MIBG) cardiac scintigraphy, CT, MRI, single-photon emission CT (SPECT) and positron emission tomography (PET).^{3,4} In the latest practice guidelines issued for the accurate diagnosis of DLB, abnormal ^{123}I -N-omega-fluoropropyl-2beta-carbomethoxy-3beta-(4-iodo-phenyl) nortropane (^{123}I -FP-CIT) (DaTSCAN) SPECT findings are listed as suggestive of DLB.⁵ The relative preservation of medial temporal lobe structures compared with other atrophic changed lobes on CT or MRI scans is also supportive of a diagnosis of DLB. In addition, they play the role of excluding cerebrovascular disorders and brain tumours. However, CT or MRI do not yield views specific to DLB. The index used by nuclear medicine in the guidelines for the diagnosis of DLB consists of three items, namely (1) a low dopamine transporter uptake in the basal ganglia demonstrated by SPECT or PET imaging; (2) a generalized low uptake on SPECT/PET perfusion scans with reduced occipital activity; and (3) abnormal (low uptake) metaiodobenzylguanidine (MIBG) myocardial scintigraphy. On the other hand, the health insurance system adopted in Japan does not cover the diagnosis of DLB when using PET. But, as the practice guidelines were published in January 2014, ^{123}I -FP-CIT-SPECT is considered to be a relatively new index. When we started this study, ^{123}I -FP-CIT-SPECT was not availed of as an evaluation index, since national health insurance coverage was not yet approved.

To the best of our knowledge, the core features of DLB have not been compared on radioisotope studies such as ^{123}I -MIBG myocardial scintigraphy and ^{123}I -IMP brain perfusion SPECT. Therefore, we performed a retrospective study to determine whether the diagnostic performance of nuclear medicine imaging studies is as high as that of the current core features of DLB.

METHODS AND MATERIALS

Subjects

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

We enrolled 332 patients with clinically suspected DLB who had undergone both ^{123}I -IMP brain perfusion SPECT and ^{123}I -MIBG myocardial scintigraphy at Kumamoto University Hospital between January 2008 and March 2014. Based on the criteria promulgated by the Consortium on DLB International Workshop,⁵ 92 patients (40 males, 52 females; mean age $\pm$ standard deviation, 77.4 ± 6.4 years; range, 56–87 years) were recorded as with probable DLB and the other 240 patients (98 males, 142 females; mean age, 75.5 ± 9.0 years; range, 72–89 years) as being without DLB. All underwent structural neuroimaging (MRI or CT) studies. We excluded patients with congestive heart failure, ischaemic heart disease, cardiomyopathy and diabetes, and patients taking antipsychotic drugs

(tricyclic antidepressants, reserpine) that affect the results of ^{123}I -MIBG scintigraphy.⁶ As shown in Table 1, of the 240 patients diagnosed as being without DLB, 99 patients had AD and 75 patients had vascular dementia; the remaining patients had other diseases. There was no significant difference in the age or gender of patients with probable and without DLB.

Guidelines for the diagnosis of dementia with Lewy bodies

Table 2 shows the latest guidelines for the diagnosis of DLB.^{7,8} The core features include fluctuating cognition, visual hallucinations and Parkinsonism. A decrease in the myocardial uptake of MIBG and the cerebral blood flow in the occipital lobe on SPECT or PET scans is listed under supportive features.

^{123}I -IMP brain perfusion single-photon emission CT

^{123}I -IMP brain perfusion SPECT studies were performed using a dual-detector variable angle gamma camera with a 16-slice CT scanner (Symbia T16; Siemens Healthcare, Erlangen, Germany) equipped with a low-medium-energy general purpose collimator. Projection data were acquired for approximately 20 min after the i.v. injection of ^{123}I -IMP (167 MBq in 1.5 ml). The image acquisition time (continuous mode, 3.0 min/rotation $\times$ 8 rotations, 128×128 matrix) was 24 min. The energy peak was set at 159 keV with a 20% energy window. Transaxial images were reconstructed with filtered back projection using a Butterworth filter. A Butterworth filter (cut-off frequency: $0.35 \text{ cycles cm}^{-1}$, order: 8) was used for SPECT image reconstruction as a post-processing filter. The reconstructed slice thickness was 3.3 mm. Chang's method was used for attenuation correction and the scatter correction was not performed. The reconstructed ^{123}I -IMP SPECT images were analyzed with Neurostat (three-dimensional stereotactic surface projection) using image analysis software (iSSP v. 3.5, Ann Arbor, MI, USA).^{9,10} data were normalized to the mean global activity. Further analysis was with stereotactic extraction estimation software.⁴ Using the stereotactic extraction estimation method, we divided the whole brain into segments (Level 3, gyrus level classification) and assessed the severity of hypoperfusion in the occipital lobe, precuneus and posterior cingulate.

^{123}I -metaiodobenzylguanidine myocardial scintigraphy

All patients underwent ^{123}I -MIBG studies after the i.v. injection of 111 MBq (3 mCi) (Fuji Film RI Pharma Co. Ltd, Tokyo, Japan). Early and delayed planar imaging was performed 15 min and 3 h after the injection, respectively. The images were acquired with a dual-head gamma camera (Symbia T16), equipped with a medium-energy general purpose collimator. The image acquisition time was 5 min, the matrix size was 256×256 , the magnification factor was 1.33 and the energy window was set at 159 keV with a 20% energy window. The pixel size was 1.64 mm. The myocardial uptake of ^{123}I -MIBG was determined by drawing a region of interest that encircled the left ventricle and a rectangular region of interest in the upper mediastinum on anterior views of the planar images. The ^{123}I -MIBG washout rate (%) from the heart was calculated with the formula:

Table 1. Diagnosis of 332 patients included in this study

Index	Probable DLB	Without DLB	<i>p</i> -value
<i>n</i>	92	240	
Age (years)	77.4 ± 6.4	75.5 ± 9.0	0.42
Gender (male : female)	40 : 52	98 : 142	0.79
		AD 99	
		VaD 75	
		MSA 15	
		PSP 15	
		CBD 10	
		Others 26	

AD, Alzheimer's disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PSP, progressive supranuclear palsy; VaD, vascular dementia.

$$\text{Washout rate} = \left[\frac{(\text{early heart counts} - \text{early background counts}) - (\text{delayed heart counts} - \text{delayed background counts})}{(\text{early heart counts} - \text{early background counts})} \right] \times 100\%$$

Data analysis

Differences in the age and gender of patients with probable and without DLB were determined with the Mann–Whitney *U*-test (a non-parametric alternative to the *t*-test). The clinical core features included fluctuating cognition, visual hallucinations and Parkinsonism. Using these features and nuclear medicine imaging indices, we compared patients with probable and without DLB.

Multivariate backward stepwise logistic regression analysis was performed to examine the effect of all key features. Variables we considered were fluctuating cognition, visual hallucinations, Parkinsonism, the ratio of hypoperfusion on ¹²³I-IMP SPECT images, the early and delayed heart-to-mediastinum (H/M) ratio and the washout ratio on ¹²³I-MIBG scintigraphs. Conventional receiver-operating characteristic (ROC) analysis was performed to assess the diagnostic performance of indices exhibiting a significant difference between patients with probable and without DLB. The area under the curve (AUC) was calculated for each index and the difference in the AUC was analyzed. Diagnostic accuracy was evaluated by calculating the sensitivity, specificity, positive-predictive value, negative-predictive value and accuracy. Differences of *p* < 0.05 were considered statistically significant. All statistical calculations were performed using the SPSS statistics software program (SPSS®, v. 22) (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL).

RESULTS

There was no significant difference in the age (*p* < 0.42) and sex (*p* < 0.79) of patients with probable and without DLB (Table 1). Of the 92 patients with probable DLB, 55 (60.0%) patients manifested fluctuating cognition, 74 (80.4%) patients manifested visual hallucinations and 62 (67.4%) patients manifested Parkinsonism. These core features differed significantly between patients with probable and without DLB (*p* < 0.01) (Table 3).

By univariate analysis, on the severity score ¹²³I-IMP brain perfusion SPECT images, cerebral blood flow in the occipital lobe, praecuneus and posterior cingulate were significantly lower (*p* < 0.001) in patients with probable DLB. Also, on ¹²³I-MIBG myocardial scintigraphic images, their early and delayed H/M ratios were also significantly lower (early: 1.79 ± 0.53; delayed: 1.56 ± 0.63) than those in patients without DLB (early: 2.91 ± 0.61; delayed: 3.11 ± 0.81) (*p* < 0.001). Only the washout rate showed no statistically significant difference (*p* = 0.64).

Subsequent multivariate forward stepwise regression analysis identified four factors, *i.e.* fluctuating cognition, visual hallucinations, Parkinsonism and early H/M ratio. They were independent predictors of probable DLB (*p* < 0.001). Parameters based on ¹²³I-IMP studies were not significantly different between patients with probable and without DLB (Table 3).

Figure 1 shows the ROC curves for differences between probable and without DLB based on fluctuating cognition, visual hallucinations, Parkinsonism and early H/M ratio. The AUC for the early H/M ratio was the highest at 0.918 [95% confidence interval (CI) 0.877–0.959]; for fluctuating cognition, visual hallucinations and Parkinsonism, it was 0.693 (95% CI, 0.625–0.760), 0.760 (95% CI, 0.701–0.818) and 0.611 (95% CI, 0.543–0.678), respectively.

The diagnostic performance of four variables (fluctuating cognition, visual hallucinations, Parkinsonism and early H/M ratio) in patients with probable DLB is presented in Table 4. The highest diagnostic value of the early H/M ratio on ¹²³I-MIBG scintigraphs was 82.4% for sensitivity, 96.3% for specificity, 89.3% for positive-predictive value, 93.5% for negative-predictive value and 92.5% for accuracy.

Figure 2 shows a DLB case seen as positive on both MIBG scintigraphy and brain perfusion SPECT imaging, and Figure 3 shows a DLB case seen as positive on MIBG scintigraphy but negative on the brain perfusion SPECT.

Table 2. Guidelines for the diagnosis of dementia with Lewy bodies (DLB)

Guidelines for the diagnosis of DLB	
1. Central feature	
	Dementia, defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function
2. Core features	
	Fluctuating cognition
	Recurrent visual hallucinations
	Spontaneous parkinsonism
3. Suggestive features	
	REM sleep behaviour disorder
	Severe neuroleptic sensitivity
	Low dopamine transporter uptake in the basal ganglia demonstrated by SPECT or PET imaging
4. Supportive features	
	Repeated falls and syncope
	Transient, unexplained loss of consciousness
	Severe autonomic dysfunction, <i>e.g.</i> orthostatic hypotension, urinary incontinence
	Hallucinations in other modalities
	Systematized delusions
	Depression
	Relative preservation of medial temporal lobe structures on CT/MRI scan
	Generalized low uptake on SPECT/PET perfusion scan with reduced occipital activity
	Abnormal (low uptake) MIBG myocardial scintigraphy
	Prominent slow wave activity on EEG with temporal lobe transient sharp waves

EEG, electroencephalogram; MIBG, metaiodobenzylguanidine; PET, positron emission tomography; REM, rapid eye movement; SPECT, single-photon emission CT.

DISCUSSION

As DLB is a progressive disease, an early and accurate diagnosis is essential. The latest guidelines for the diagnosis of DLB include fluctuating cognition, visual hallucinations and Parkinsonism as core features.⁸ Approximately 65–70% of patients with DLB experience visual hallucinations^{11,12} and Parkinson symptoms are seen in approximately 70–90% of patients with DLB.⁸ Similar to these, we found that the accuracy of clinical symptoms with respect to fluctuating cognition, visual hallucinations and Parkinsonism was 74.7%, 74.7% and 59.3%, respectively. However, in the early stages of the disease, these criteria are not specific for DLB. In earlier reports, the incidence of fluctuating cognition in DLB ranged from 13% to 85%.¹¹ The differential diagnosis of dementia cannot rely on clinical symptoms alone because they tend to overlap in different types of dementia, especially in the initial clinical stages. Suspected DLB cases may include patients with not only AD but also

Parkinsonism [*e.g.* Parkinson's disease (PD); progressive supranuclear palsy; multiple system atrophy; corticobasal degeneration] and other neurological diseases. Some characteristics observed in the brain pathology of AD are also found in DLB; this renders a differential diagnosis of AD and DLB difficult.^{9,12} Because pathological confirmation is not possible, morphological and functional imaging studies yield objective information that can be used for the diagnosis and treatment of these complex neurological disorders.

Lewy body-related disorders are characterized by the presence of Lewy bodies and Lewy neurites, which have abnormal aggregations of α -synuclein in the nigral and extranigral areas, including in the heart. The ¹²³I-MIBG scintigraphy is a tool widely used to evaluate cardiac sympathetic denervation in the Lewy body-related disorders,¹³ with ¹²³I-MIBG scintigraphy showing a low uptake of MIBG in the Lewy body-related disorders, including PD, DLB, pure autonomic failure and rapid eye movement sleep behaviour disorder. Also, ¹²³I-MIBG scintigraphy has been used to discriminate DLB from AD and to predict the conversion to probable DLB.^{13–17} The value of ¹²³I-MIBG myocardial scintigraphy in the early diagnosis of DLB and in the differential diagnosis between DLB and other dementias has been studied; scintigraphic findings are reported to yield independent diagnostic predictors of DLB.^{18–21} In their meta-analysis, Treglia and Cason²² demonstrated that MIBG scintigraphy is an accurate diagnostic imaging method to differentiate DLB from other dementias; they reported a pooled sensitivity and specificity of 98% and 94%, respectively. In addition, ¹²³I-MIBG scintigraphy appears to be of higher sensitivity than brain perfusion SPECT for the diagnosis of DLB.¹⁹

Combining these methods may increase the accuracy of the clinical diagnosis of DLB.²³ However, according to the current guidelines, they yield supportive rather than diagnostic features because their diagnostic specificity has not been confirmed. We found that the early H/M ratio was a significant indicator for the diagnosis of probable DLB and equivalent to or better than the currently accepted core features. Our ROC analysis showed that the AUC of the early H/M ratio was higher than that of the core features. Therefore, we contend that besides the clinical symptoms, the addition of ¹²³I-MIBG scintigraphy findings should lead to an earlier diagnosis and would improve the clinical course and prognosis of patients with DLB and, consequently, that such findings should be considered as core features of DLB.

Different perfusion patterns have been associated with different types of dementia. In the absence of cerebrovascular disease, hypoperfusion detected in SPECT images might be related to impaired cerebral function, and a hyperperfused area could be related to increased neuronal activity.²⁴ In the case of DLB, in addition to the temporoparietal association area and posterior cingulate gyrus, the hypoperfusion and glucose metabolism of the occipital lobe seen on SPECT and PET images are said to reflect visual hallucination.^{21,23,25,26} Two ^{99m}Tc-labelled radiopharmaceuticals have become available: ^{99m}Tc-labelled hexamethylpropyleneamine oxime (Ceretic; Nycomed-Amersham, Little Chalfont, UK) and ^{99m}Tc-labelled ethylcysteinate dimer bisate (Neurolite; Dupont-Pharma, Stevenage, UK). By using

Table 3. Variables associated with probable and without dementia with Lewy bodies (DLB) by univariate and multivariate analysis

Variables	Univariate analysis			Multivariate analysis
	Probable DLB	Without DLB	<i>p</i> -value	<i>p</i> -value
<i>n</i>	92	240		
Core features				
Fluctuating cognition	55 (60.0%)	44 (18.3%)	<0.001	<0.001
Visual hallucination	74 (80.4%)	64 (26.7%)	<0.001	<0.001
Parkinsonism	62 (67.4%)	103 (42.9%)	<0.001	<0.001
¹²³ I-IMP brain perfusion				
Posterior cingulate	0.84 ± 0.53	0.65 ± 0.50	<0.001	
Praecuneus	1.08 ± 0.84	0.68 ± 0.61	<0.001	
Occipital lobe	0.79 ± 0.67	0.57 ± 0.60	<0.001	
¹²³ I-MIBG scintigraphy				
Early H/M ratio	1.79 ± 0.53	2.91 ± 0.61	<0.001	<0.001
Delayed H/M ratio	1.56 ± 0.63	3.11 ± 0.81	<0.001	
Washout rate	49.9 ± 14.6	44.5 ± 17.9	0.64	

H/M, heart-to-mediastinum; ¹²³I-MIBG, ¹²³I-metaiodobenzylguanidine.

these chemical agents, the peak brain activity can be reached faster (within 2 min after injection) and there is no re-distribution; so, the initial tracer uptake and distribution, which are proportional to regional cerebral blood flow (rCBF) at the time of injection, remain unchanged up to at least 2 h, independent of rCBF variations occurring after the time set. The properties of quick uptake and prolonged stability enable the acquisition of the so-called frozen or shoot images and make interventional SPECT tests clearly feasible.²⁴ Among the initially

used ¹²³I-labelled amines, ¹²³I-IMP (IK-3; CIS Bio-International, Gif-sur-Yvette, France) has been most frequently used.²⁷ In our investigations, since the first-pass extraction fraction of ¹²³I-IMP was higher and the contrast of the blood-stream drop area was clearer when compared with ^{99m}Tc-labelled preparation, it was ¹²³I-IMP that we mostly used as a normal database in three-dimensional stereotactic surface projection analyses at our facilities. Tatenio et al⁷ reported that the sensitivity of brain perfusion SPECT for the diagnosis of

Figure 1. Receiver-operating characteristic curves for discriminating between probable and without dementia with Lewy bodies based on fluctuating cognition, visual hallucinations and Parkinsonism, and the early heart-to-mediastinum (H/M) ratio. AUC, area under the curve.

Table 4. Diagnostic performance of variables in patients with probable dementia with Lewy bodies

Variables	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
Fluctuating cognition		56.5	81.7	54.2	83.1	74.7
Visual hallucination		78.3	73.3	52.9	89.8	74.7
Parkinsonism		65.2	57.1	36.8	81.1	59.3
Early H/M ratio	<2.0	82.4	96.3	89.3	93.5	92.5

H/M, heart-to-mediastinum; PPV, positive-predictive value; NPV, negative-predictive value.

DLB was about 68%. Pasquier *et al*,¹⁸ who used ^{99m}Tc-labelled ethylcysteinate dimer as a tracer in their brain perfusion SPECT study, found that the sensitivity for the diagnosis of DLB was 65% and specificity was 71%. Similarly, each hypoperfusion of

the posterior cingulate, praecuneus and occipital lobe was a meaningful index in the univariate analysis in our study. This finding was in accordance with the results that we reported previously.²³ But, in subsequent multivariate forward stepwise regression analysis, occipital hypoperfusion as based on ¹²³I-IMP evaluations did not differ significantly between the patients with probable DLB and without DLB. This was a result which differed from previous reports. One reason for this outcome is that when occipital hypoperfusion is seen, frequently visual hallucinations may also be considered as being present.

Figure 2. A dementia with Lewy bodies (DLB) case seen as positive on both metaiodobenzylguanidine (MIBG) scintigraphy and brain perfusion single-photon emission CT (SPECT) imaging: an 83-year-old female diagnosed with probable DLB. Fluctuating cognition, visual hallucination and Parkinsonism were all seen among the core features. Early heart-to-mediastinum ratio was 1.3 on ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) myocardial scintigraphy, and significant hypoperfusion of the occipital lobe was recognized on ¹²³I-IMP brain perfusion SPECT. In a three-dimensional stereotactic surface projection (3D-SSP) image based on the global lobe brain (GLB), a statistically significant hypoperfusion in the occipital lobe is seen on images with a Z-score value >2. Both MIBG and IMP show typical probable DLB diagnosis. (a) An ¹²³I-MIBG planar image (an anterior view), (b) an ¹²³I-IMP SPECT image (a section including the frontal lobe, basal ganglia, thalamus and occipital lobe) and (c) 3D-SSP images (an enlarged 3D-SSP image domains with a Z-score value >2 based on GLB). (ANT, anterior; INF, inferior; LT.LAT, left laterl; LT.MED, Left medial; Post, Posterior; RT.LAT, right lateral; RT.MED, right medial; and SUP, Superior).

Figure 3. A dementia with Lewy bodies (DLB) case that was positive on metaiodobenzylguanidine scintigraphy and negative on brain perfusion single-photon emission CT (SPECT) imaging: a 75-year-old male MMSE 20 probable DLB case. Only fluctuating cognition was evident among the core features. Early heart-to-mediastinum ratio was 1.5 in ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) myocardial scintigraphy, and no occipital lobe hypoperfusion was apparent with ¹²³I-IMP brain perfusion SPECT. In a three-dimensional stereotactic surface projection (3D-SSP) image based on the global lobe brain (GLB), no statistically significant hypoperfusion in the occipital lobe is recognized on images with a Z-score value >2. (a) An ¹²³I-MIBG planar image (an anterior view), (b) an ¹²³I-IMP SPECT image (a section including the frontal lobe, basal ganglia, thalamus and occipital lobe) and (c) 3D-SSP images (enlarged 3D-SSP image domains with a Z-score value >2 based on GLB). (ANT, anterior; INF, inferior; LT.LAT, left laterl; LT.MED, Left medial; Post, Posterior; RT.LAT, right lateral; RT.MED, right medial; and SUP, Superior).

The brain perfusion SPECT is inferior to other indexes for the diagnosis of DLB. However, this imaging technique is effective in determining other degenerative diseases such as the Alzheimer type or vascular dementias, and thus, it can be regarded as an essential parameter in the overall evaluations of dementia cases.

As for the correlation of early H/M ratio on ¹²³I-MIBG myocardial scintigraphy and brain perfusion imaging, the severity scores of the occipital lobe, praecuneus and posterior cingulate had *R*-value coefficients of -0.173 , -0.09 and -0.256 , respectively. But, it was only the posterior cingulate ($p = 0.015$) that displayed a significant correlation, albeit a low one. The H/M ratio on the ¹²³I-MIBG myocardial scintigraphy is regarded as a high index for sensitivity, but because correlation with the degree of hypoperfusion is said to be small on the brain perfusion SPECT imaging, it is treated as a low index of sensitivity. The opinions presented in past reports may prove helpful, but the differential diagnostic ability of brain perfusion SPECT imaging alone can be considered to be low.

¹²³I-MIBG myocardial scintigraphy usefulness decreases against not only DLB but also PD. Therefore, when the accumulation decreases on ¹²³I-MIBG myocardial scintigraphy and an abnormal finding is seen by brain perfusion SPECT scanning, the onset of DLB can be suspected more than the presence of PD. From this perspective, combining brain perfusion SPECT and ¹²³I-MIBG myocardial scintigraphy would seem a more useful approach.

Probable DLB cases are shown in Figures 2 and 3. All three core features are positive in Figure 2 and on brain perfusion SPECT, the hypoperfusion of the occipital lobe and the low uptake on the ¹²³I-MIBG myocardial scintigraphy present a typical example. In contrast in Figure 3, only the core feature of fluctuating cognition appears as positive, while the hypoperfusion of the occipital lobe is not evident in brain perfusion SPECT, but is offered as an example of low-uptake ¹²³I-MIBG myocardial scintigraphy. Our results demonstrated MIBG scintigraphy to be a sharp inspection tool and thus it can be put to effective use in the differential diagnosis of DLB.

Our study has some limitations. First, owing to the absence of histological confirmation data, some patients may have been

misdiagnosed. Second, the AUC for the early H/M ratio in our study was lower than that in previously reported studies for differentiating probable DLB from other dementias. This is probably because our subjects included patients in the very early stages of DLB.²⁸ Third, ¹²³I-FP-CIT-SPECT was not included in the evaluation index. In 2006, ¹²³I-FP-CIT-SPECT was reported to provide features suggestive of DLB⁵ and according to Treglia et al,²⁹ ¹²³I-MIBG myocardial scintigraphy and ¹²³I-FP-CIT-SPECT were of similarly a high diagnostic accuracy. This study would be more complete if the suggestive features of ¹²³I-FP-CIT-SPECT and the supportive features of brain perfusion SPECT had been performed and they had included a comparison with ¹²³I-MIBG myocardial scintigraphy. However, on commencing this study, ¹²³I-FP-CIT-SPECT was not included in the assessment procedure owing to the fact that the cost of performing it would not be covered by the National Health Insurance system adopted in Japan. These issues remain to be clarified further in the future studies.

CONCLUSION

Our study focused on whether ¹²³I-MIBG myocardial scintigraphy and brain perfusion SPECT provided useful information for the diagnosis of DLB and whether this information is comparable with the diagnostic value of dominant symptoms. The results showed that for the diagnosis of DLB, ¹²³I-MIBG myocardial scintigraphic findings were of the same high diagnostic value as the accepted core features. ¹²³I-MIBG myocardial scintigraphy performed at the initial clinical examination can facilitate the early identification or exclusion of DLB and the early H/M ratio may be a diagnostic biomarker for DLB. An accurate diagnosis of dementia should not be based solely on recorded patient complaints or interviews, as the patient claims are subjective and often inconsistent. In contrast, imaging studies yield objective information. More than that, nuclear imaging techniques provide sensitive qualitative and quantitative detection of a radiotracer and can assess functional activity. In the next guidelines to be issued for the diagnosis of DLB, we expect the ¹²³I-MIBG myocardial scintigraphy findings to be upgraded to the level of suggestive or core features.

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