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ORIGINAL ARTICLE

Potential diagnostic value of regional myocardial adrenergic imaging using ^{123}I-MIBG SPECT to identify patients with Lewy body diseases

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Abstract
Purpose The aim of this study was to determine the potential diagnostic value of regional myocardial adrenergic ^{123}I-metaiodobenzylguanidine (MIBG) single photon emission computed tomography (SPECT) imaging to identify patients with Lewy body diseases (LBD+).
Methods Sixty-four consecutive patients who underwent cardiac ^{123}I-MIBG SPECT to differentiate LBD+, including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), from patients without LBD (LBD−) were retrospectively reviewed. A neurologist expert in memory disorders determined the final clinical diagnosis by using international clinical diagnostic criteria. Planar [heart to mediastinum ratio (HMR)] and ^{123}I-MIBG SPECT[(innervation defect score (IDS)] using the 17-segment left ventricular model (five-point scale) were obtained 4 h after the injection of ^{123}I-MIBG on a low-energy high-resolution (LEHR) collimator. Receiver-operating characteristic (ROC) analysis was performed to determine the optimal HMR and IDS cut-off values to discriminate LBD+ from LBD−.
Results Of the 64 patients, 45 (70 %) were diagnosed LBD+ (DLB, n=27; PD, n=18) and 19 were diagnosed LBD− (5 other dementias, 14 other parkinsonisms). The HMR and IDS of LBD+ were significantly different from those of LBD− (1.30±0.21 vs 1.65±0.26, p<0.001; 39±28 vs 8±16, p=0.001). The optimal HMR and IDS cut-off values to discriminate LBD+ (n=45) from LBD− (n=19) were 1.47 and 6/68, providing a sensitivity and specificity of 82.2 and 84.2 % and 86.7 and 73.7 %, respectively.
Conclusion Regional myocardial adrenergic ^{123}I-MIBG imaging SPECT has a potential diagnostic value to identify LBD+.

Keywords ^{123}I-MIBG · SPECT · Lewy body diseases · Dementia with Lewy bodies · Parkinson's disease · Heart to mediastinum ratio

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Introduction

Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) are sometimes difficult to differentiate from other diagnoses, such as other types of dementia (OD) or other types of parkinsonism (OP) on the basis of clinical criteria. An early diagnosis of these disorders is critical for a suitable management of the patient and an appropriate assessment of the prognosis, especially if neuroprotective treatments are developed in the coming years. Lewy body diseases (LBD) has become a usual term for these two overlapping disorders which share common clinical and neuropathological features, characterized by a Lewy body deposition in the nervous system. Metaiodobenzylguanidine (MIBG) is a norepinephrine analogue that is taken up in the postganglionic adrenergic neurons. Cardiac ^{123}I-MIBG scintigraphy is a diagnostic modality to evaluate myocardial sympathetic innervation and noradrenergic postganglionic cardiac denervation which is a common feature in PD and DLB [1, 2]. Several studies have revealed

low cardiac ^{123}I-MIBG uptake in patients with PD and DLB in comparison with other types of neurological disorders, and cardiac ^{123}I-MIBG scintigraphy appears to be a useful technique to differentiate patients with LBD (LBD+) from patients without LBD (LBD−) [3, 4].

Planar imaging is the most frequently used method in myocardial ^{123}I-MIBG scintigraphy. The delayed heart to mediastinum ratio (HMR) is the most common semi-quantitative parameter used to assess the cardiac MIBG uptake in neurological indications. The HMR provides information regarding the uptake, storage and release of MIBG at nerve endings [5]. Nevertheless, there are some limitations to this technique such as the superposition of extracardiac structures and the lack of segmental analysis. Single photon emission computed tomography (SPECT) analysis may overcome some of these limitations. SPECT images can be achieved to obtain the regional ^{123}I-MIBG uptake of the left ventricle (LV) by calculating an innervation defect score (IDS) [5]. To date, no study comparing planar and SPECT ^{123}I-MIBG innervation imaging has been published in suspected LBD+. The aim of the study was to determine the potential diagnostic value of regional myocardial adrenergic imaging using ^{123}I-MIBG SPECT to identify patients with LBD.

Materials and methods

Patients

We retrospectively reviewed the data from 68 consecutive patients who underwent cardiac ^{123}I-MIBG scintigraphy for differential diagnosis between DLB and OD (n=34) or between PD and OP (n=34). Examinations were performed as part of the clinical routine at the Department of Nuclear Medicine of the University Hospital of Caen (France) between 2009 and 2013. Patients were recruited from the Departments of Neurology and Gerontology. Exclusion criteria were: history of heart failure, pregnancy, breastfeeding and drugs (mianserin, clomipramine) that could interfere with the cardiac ^{123}I-MIBG uptake [5, 6].

Cardiac ^{123}I-MIBG scintigraphy

The thyroid blockage was performed by an oral administration of Lugol's solution 30 min before the injection of ^{123}I-MIBG and 3 days after the examination. The dose of ^{123}I-MIBG was adapted to the patient's weight (<60 kg 148 MBq, 60–90 kg 222 MBq, >90 kg 296 MBq). Planar and SPECT ^{123}I-MIBG images were performed with the patient lying in the same supine position and with the arms of the patient elevated above the head. The energy window was centred to 20 % of the 159 keV ^{123}I photopeak for both planar and SPECT acquisitions. Anterior thoracic planar images were acquired for 10 min 4 h after the injection of ^{123}I-MIBG (AdreView®, General Electric Healthcare) and stored in a 128×128 matrix.

Thereafter, a SPECT study was performed for 20 min to assess the regional ^{123}I-MIBG uptake of the LV. We used a dual-head camera system (Symbia T2 True Point, Siemens Medical Solutions, Erlangen, Germany) with a low-energy high-resolution (LEHR) parallel-hole collimator. SPECT images were acquired by a single pass of 30 steps at 30 s per step, using a rotation of 180° starting at a 45° right anterior oblique projection and proceeding counterclockwise to the 45° left posterior oblique projection. Dual detectors were in a 90° configuration. The HMR was calculated from planar imaging after manually drawing regions of interest (ROI) over the entire heart and the upper mediastinum (7×7 pixels), according to the European Association of Nuclear Medicine (EANM) Cardiovascular Committee recommendations [5]. The mediastinum landmarks were the apex of the lungs and ROIs were drawn in the middle of the two apexes of the lungs. Reconstructions of the regional LV ^{123}I-MIBG uptake were performed using a filtered backprojection algorithm and recorded with a 64 × 64 matrix. Data were reconstructed into standard short axis, long vertical long axis and horizontal long axis of the heart.

The IDS was calculated by assessment of the segmental myocardial ^{123}I-MIBG uptake score using the 17-segment LV model [7]. Each myocardial segment of the LV was scored according to a five-point scale using visual evaluation: 0= normal tracer uptake, 1=mildly reduced tracer uptake, 2= moderately reduced tracer uptake, 3=severely reduced tracer uptake and 4=no tracer uptake. The IDS obtained from SPECT were calculated by the summation of segmental tracer uptake scores and ranged from 0/68 to 68/68. In the case of a global and severe decrease of the cardiac^{123}I-MIBG uptake, each LV segment was quoted as 4/4 leading to an IDS of 68/68. We did not consider the physiological decrease of the ^{123}I-MIBG uptake in the inferior part of the LV. Innervation defects were also evaluated according to 5 cardiac territories using the 17-segment LV model as follows: inferior (segments 4, 10 and 15), septal (segments 2, 3, 8, 9 and 14), apical (segment 17), lateral (segments 5, 6, 11, 12 and 16) and anterior walls (segments 1, 7 and 13). Two expert nuclear medicine physicians (DA, AM) reviewed all examinations without knowing the final diagnoses.

Data analysis

All patients were evaluated by a neurologist or a geriatrist expert in memory disorders. International clinical diagnostic criteria were used to determine final clinical diagnoses (UK Parkinson's Disease Brain Bank Criteria for PD [8], revised McKeith criteria for DLB [9], criteria from Gilman et al. in 2008 for multiple system atrophy (MSA) [10], National Institute of Neurological Disorders and Stroke (NINDS)-

Society for Progressive Supranuclear Palsy (SPSP) criteria for progressive supranuclear palsy (PSP) [11] and criteria proposed by Armstrong et al. in 2013 for corticobasal degeneration (CBD) [12]. Data were described as mean±SD. Continuous variables were compared between groups using the nonparametric Mann–Whitney test. Receiver-operating characteristic (ROC) curve analysis was performed to determine the optimal HMR and IDS cut-off values to differentiate LBD+ from LBD− using Youden's J statistic. Graphs and analyses were carried out using Prism (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

Sixty-eight consecutive patients underwent cardiac ^{123}I-MIBG scintigraphy after injection of 227±96 MBq of ^{123}I-MIBG for differential diagnosis between LBD+ and LBD−. The dosimetry was 3.63±1.54 mSv/patient according to publication 80 of the International Commission on Radiological Protection (ICRP) [13]. Four patients were excluded because of the use of drugs that could interfere with the cardiac ^{123}I-MIBG uptake. Of the 64 patients, 45 (70 %) were diagnosed LBD+ (DLB, n=27; PD, n=18) and 19 were diagnosed LBD− (OD, n=5; OP, n=14) (Table 1).

Cardiac ^{123}I-MIBG scintigraphy was performed in order to differentiate DLB from OD in 32 patients. Among these patients, 27 had a final diagnosis of DLB (male/female 12/15, mean age 76±7.5 years) and 5 had OD (male/female:1/4, mean age 82±5 years). OD were divided into AD (n=3), vascular dementia (VD) (n=1) and undetermined dementia (UP) (n=1).

Cardiac ^{123}I-MIBG scintigraphy was performed in order to differentiate PD from OP in 32 patients. Among these patients, 18 had a final diagnosis of PD (male/female 9/8, mean age 64±15 years) and 14 had OP (male/female 6/8, mean age 68±10 years). OP were divided into PSP (n=5), MSA (n=4), CBD (n=1), drug-induced parkinsonism (DIP, n=1), Perry syndrome (n=1) and undetermined parkinsonism (UP) (n=2). The mean follow-up time after the onset of the symptoms was 69 months.

Planar ^{123}I-MIBG analysis

The mean HMR in LBD+ was significantly lower than the mean HMR in LBD− (1.30±0.21 vs 1.65±0.26, p<0.001) (Fig. 1). The mean HMR in DLB was significantly lower than that in OD. The mean HMR in PD was significantly lower than that in OP (Table 1). Mean HMR were not significantly different between PD and DLB. The optimal HMR cut-off value to discriminate LBD+ (n=45) from LBD− (n=19) was 1.47 with 0.859 area under the ROC curve, providing a sensitivity, specificity, positive predictive value and negative predictive value of 82.2, 84.4, 92.5 and 66 %, respectively (Fig. 2). Planar analysis was truly positive in 37/45 (82 %) LBD+, including 22 DLB and 15 PD. This scintigraphic

Table 1 Results of planar and SPECT cardiac ^{123}I-MIBG imaging in LBD+ and LBD−

Final clinical diagnosis	Mean HMR	p value[a]	Mean IDS	p value[a]
PD (n=18)	1.32±0.19	p=0.001	37±27	p=0.013
Other types of parkinsonism (n=14)	1.60±0.25		7±18	
	PSP 1.59±0.21		PSP 36±27	
	MSA 1.44±0.22		MSA 17±34	
	UP 1.56±0.23		UP 11±7	
	CBD 1.60		CBD, DIP and Perry 0	
	DIP 2.10			
	Perry 1.91			
DLB (n=27)	1.29±0.22	p=0.028	42±29	p=0.022
Other types of dementia (n=5)	1.80±0.24		8±10	
	AD 1.94±0.20		AD 7±1	
	VD 1.55		VD 0	
	UD 1.64		UD 18	

HMR delayed heart to mediastinum ratio, *IDS* innervation defect score, *AD* Alzheimer's disease, *CBD* corticobasal degeneration, *DIP* drug-induced parkinsonism, *DLB* dementia with Lewy bodies, *LBD+* patient with Lewy body diseases, *LBD−* patient without Lewy body diseases, *MSA* multiple system atrophy, *PD* Parkinson's disease, *PSP* progressive supranuclear palsy, *UD* undetermined dementia, *UP* undetermined parkinsonism, *VD* vascular dementia

[a] Comparison between LBD+ (PD or DLB) and LBD− (other types of parkinsonism or other types of dementia). HMR and IDS were not significantly different between PD and DLB

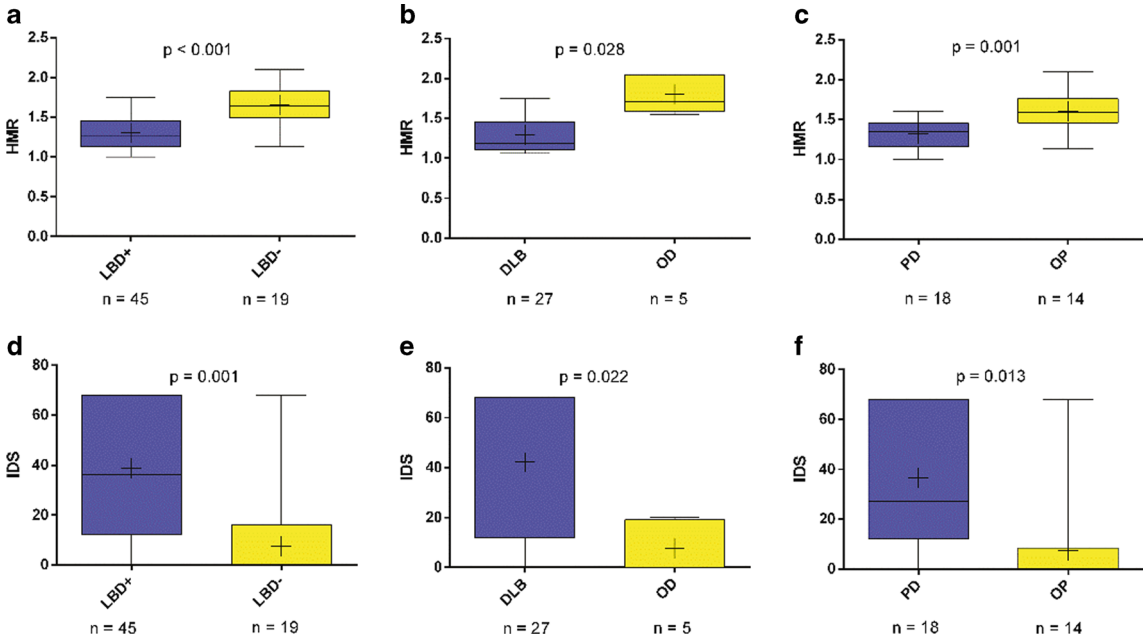

Fig. 1 Comparison between planar and SPECT cardiac ^{123}I-MIBG imaging for the detection of LBD. **a** HMR of LBD+ and LBD−, **b** HMR of DLB and OD, **c** HMR of PD and OP, **d** IDS of LBD+ and LBD−, **e** IDS of DLB and OD, **f** IDS of PD and OP. Data are presented as box plots with medians represented by the *crosses* with the 75th percentiles at the top and the 25th percentiles at the bottom of the boxes. Ranges are depicted as *whiskers*. The asymmetric distribution was due to one patient with a MSA showing an IDS of 68/68. *DLB* dementia with Lewy bodies, *HMR* delayed heart to mediastinum ratio, *LBD+* patients with Lewy body diseases, *IDS* innervation defect score, *LBD−* patients without Lewy body diseases, *OD* other types of dementia, *OP* other types of parkinsonism, *PD* Parkinson's disease

method was falsely negative in 8/45 (18 %) LBD+, including 5 DLB and 3 PD. Planar analysis was truly negative in 16/19 LBD− (84 %), including 4 PSP, 3 MSA, 3 AD, 1 CBD, 1 VD, 1 UP, 1 undetermined dementia (UD) and 1 Perry syndrome. This scintigraphic method was falsely positive in 3/19 (16 %) LBD−, including 1 MSA, 1 PSP and 1 UP.

^{123}I-MIBG SPECT analysis

The mean IDS in LBD+ was significantly higher than the mean IDS in LBD− (39±28 vs 8±16, p=0.001) (Fig. 1). The asymmetric distribution was due to one patient with a MSA showing an IDS of 68/68. The mean IDS in DLB was significantly higher than that in OD (Table 1). The mean IDS in PD was significantly higher than that in OP (Table 1). Mean IDS were not significantly different between PD and DLB.

The optimal IDS cut-off value to discriminate LBD+ (n=45) from LBD− (n=19) was 6/68 with 0.836 area under the ROC curve providing a sensitivity, specificity, positive predictive value and negative predictive value of 86.7, 73.7, 88.6 and 70 %, respectively (Fig. 2). Areas under the ROC curves were not significantly different between planar and SPECT analyses (p=0.76). We calculated the relative risk (RR) of having LBD according to imaging results. The RR (95 % confidence interval) was 2.77 (1.5–4.9), 2.95 (1.5–5.8) and 3.7 (1.5–8.8), respectively, with positive findings on planar

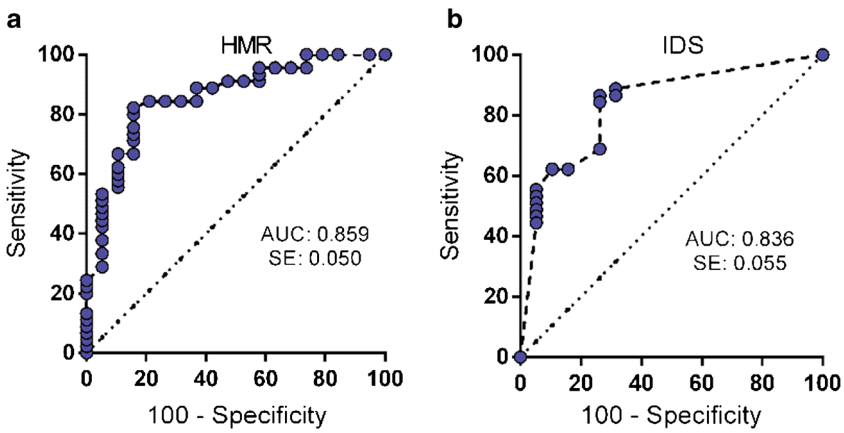

Fig. 2 ROC curves for the differential diagnosis between LBD+ and LBD− using planar imaging (**a**, HMR) or SPECT imaging (**b**, IDS). *AUC* area under the curve, *HMR* delayed heart to mediastinum ratio, *IDS* innervation defect score *LBD+* patients with a Lewy body diseases, *LBD−* patients without Lewy body diseases, *SE* standard error

imaging, SPECT or the combination of planar and SPECT, without significant differences between the three techniques (all p=NS).

SPECT analysis was truly positive in 39/45 (87 %) LBD+, including 23 DLB and 16 PD. This scintigraphic method was falsely negative in 6/45 (13 %) LBD+, including 3 DLB and 3 PD. SPECT analysis was truly negative in 14/19 (74 %) LBD −, including 4 PSP, 3 MSA, 2 AD, 1 CBD, 1 DIP, 1 VD, 1 Perry syndrome and 1 UP. This scintigraphic method was falsely positive in 5/19 (26 %) LBD−, including 1 MSA, 1 PSP, 1 AD, 1 UP and 1 UD.

Patients with a global cardiac sympathetic denervation

Of the 64 patients, 22 (34 %) (14 DLB, 7 PD and 1 MSA) had a global cardiac sympathetic denervation with a mean IDS of 68/68. In this group of patients, the mean HMR was 1.14±0.08. Figure 3a is an example of a patient with a severe cardiac sympathetic denervation evaluated with ^{123}I-MIBG (HMR=1.09, IDS=68/68).

Patients with a preserved cardiac sympathetic innervation

Of the 64 patients, 18 (28 %) (4 PSP, 3 MSA, 3 DLB, 2 PD, 2 AD, 1 VD, 1 CBD, 1 DIP and 1 Perry syndrome) had a preserved cardiac sympathetic denervation. In this group of patients, the mean HMR was 1.65±0.20.

Patients with a regional myocardial sympathetic denervation

Of the 64 patients, 24 (38 %) exhibited a regional myocardial sympathetic denervation with an IDS different from 0/68 or 68/68 (Table 2). They had a mean HMR of 1.47±0.22 and a mean IDS of 19±11. This group was mainly composed of LBD+ (19/24 patients, 79 %) with 10 DLB and 9 PD. The five remaining patients were composed of two UP, one AD, one UD and one PSP. Among the ten DLB, the inferior wall

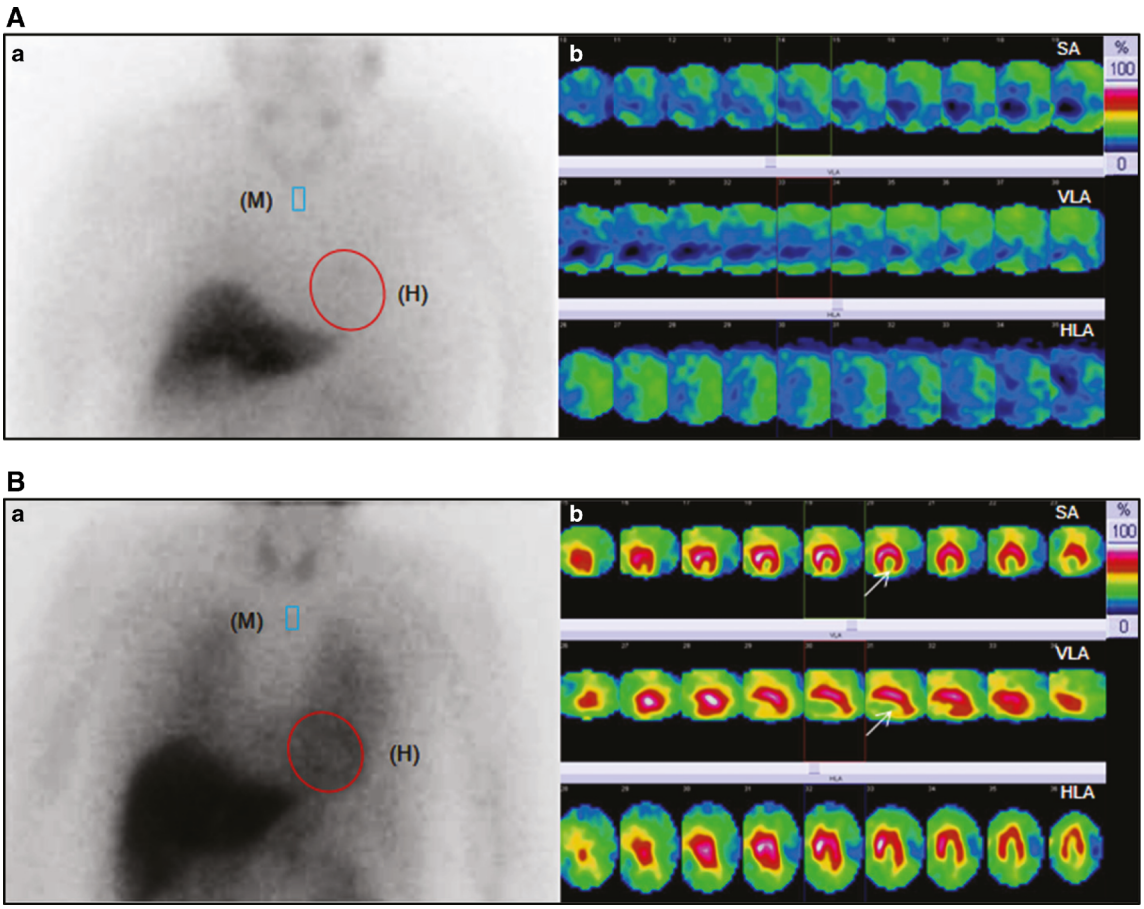

Fig. 3 **a** A 68-year-old patient referred for a parkinsonian syndrome with visual hallucinations and cognitive disorders.*a* Planar ^{123}I-MIBG anterior view of the thorax showed a drastic decrease of the HMR (1.09). *b* ^{123}I-MIBG SPECT showed a complete myocardial denervation with an IDS of 68/68. The final clinical diagnosis was dementia with Lewy bodies. *HMR* delayed heart to mediastinum ratio, *IDS* innervation defect score, *SA* short axis, *VLA* vertical long axis, *HLA* horizontal long axis, *(H)* heart, *(M)* mediastinum **b** An 82-year-old patient referred for a parkinsonian syndrome. *a* Planar ^{123}I-MIBG anterior view of the thorax showed an HMR=1.68. *b* ^{123}I-MIBG SPECT showed a regional myocardial denervation in the entire inferior wall (*white arrows*) with an IDS of 12/68. The final diagnosis was PD. *HMR* delayed heart to mediastinum ratio, *IDS* innervation defect score, *HLA* horizontal long axis, *SA* short axis, *VLA* vertical long axis, *(H)* heart, *(M)* mediastinum

Table 2 Cardiac ^{123}I-MIBG imaging features of patients with a regional myocardial sympathetic denervation (IDS different from 0/68 and 68/68)

Final clinical diagnosis	LBD+	PD	DLB	LBD−
n=24	19	9	10	5
HMR	1.43±0.18	1.41±0.14	1.44±0.21	1.62±0.29
IDS	19±12	20±9	19±14	15±5
Regional pattern of denervation				
Inferior	14/19 (73 %)	6/9 (66 %)	8/10 (80 %)	4/5 (80 %)
Apical	10/19 (52 %)	5/9 (55 %)	5/10 (50 %)	2/5 (40 %)
Lateral	7/19 (37 %)	3/9 (33 %)	4/10 (40 %)	2/5 (40 %)
Septal	7/19 (37 %)	4/9 (44 %)	3/10 (30 %)	1/5 (20 %)
Anterior	3/19 (16 %)	3/9 (33 %)	0/10	0/5

HMR delayed heart to mediastinum ratio, *IDS* innervation defect score, *DLB* dementia with Lewy bodies, *LBD+* patients with Lewy body diseases, *LBD−* patients without Lewy body diseases, *PD* Parkinson's disease

was the most frequently impaired cardiac territory followed by the apical, the lateral, the septal, and the anterior walls. In the nine PD, the inferior wall was also the most frequently affected myocardial territory followed by the apical, the septal, the lateral, and the anterior walls.

Importantly, 6/24 patients (25 %) with a regional myocardial sympathetic denervation were LBD+ (3 DLB and 3 PD) with a preserved mean HMR of 1.64±0.1 and a mean IDS of 12±6. The inferior and the apical walls (three of six patients for each territory, 50 %) were the most frequently affected myocardial territory followed by the septal (two of six patients, 33 %) and the lateral walls (two of six patients, 33 %). Figure 3b is an example of an LBD+ patient with an HMR >1.47 and an increased IDS.

An additional statistical analysis was performed after excluding the data obtained in patients with a DIP and Perry syndrome that may be responsible for a bias due to remarkably high HMR and low IDS. This analysis demonstrated that the HMR in LBD+ was significantly lower than in LBD− (1.30±0.21 vs 1.61±0.24, $p<0.0001$) and the IDS in LBD+ was significantly higher than in LBD− (39±28 vs 8±17, $p<0.0001$). The HMR in PD was significantly lower than in OP (1.32±0.19 vs 1.54±0.20, $p=0.0038$) and the IDS in PD was significantly higher than in OP (37±27 vs 9±20, $p=0.0011$).

Discussion

Clinical discrimination of LBD+ from LBD− can be challenging, especially in the early stage of the disease. Our study evaluated the potential diagnostic value of regional myocardial adrenergic imaging using ^{123}I-MIBG SPECT to identify patients with LBD.

Planar ^{123}I-MIBG analysis

In our study, myocardial ^{123}I-MIBG planar scintigraphy appears to be a useful tool to differentiate LBD+ from LBD− with significantly lower HMR in LBD+ compared to LBD−. This was in agreement with the meta-analysis of King et al. which showed that patients with Lewy body-related disorders composed of PD, DLB and rapid eye movement behaviour disorder had significantly lower mean HMR than did AD, PSP or MSA [3]. We observed a normal HMR in patients with AD, DIP, VD and Perry syndrome which was consistent with the literature [14–17].

The mean HMR in DLB was lower than the mean HMR in PD, without a statistically significant difference. This was in keeping with the review of Spiegel which indicated that myocardial MIBG uptake is slightly more reduced in DLB than in PD [4]. He also noticed that MIBG scintigraphy cannot differentiate between both diseases due to the broad overlap between DLB and PD. Suzuki et al. also compared sympathetic myocardial innervation between DLB and PD and reported a lower ^{123}I-MIBG uptake in DLB than in PD [18]. According to the authors, this result could reflect a greater postganglionic cardiac sympathetic denervation in DLB and a more important Lewy body deposition in sympathetic ganglia in DLB compared to PD.

In our study, the optimal HMR was 1.47 which led to a sensitivity and specificity of 82.2 and 84.2 %, respectively. The recent meta-analysis of King et al. suggested that cardiac planar ^{123}I-MIBG scintigraphy had a high diagnostic performance to differentiate LBD+ from LBD− with overall sensitivity of 94 % and specificity of 91 %. King et al. found a higher cut-off value (1.77) compared to our study [3]. Technical issues including collimation and sensitivity of SPECT systems may explain the discrepancies noted between our findings and some previous results [19]. Our HMR

threshold is similar to previous findings when using a LEHR collimator [20], but lower than previously reported when using different types of collimators [3]. In a multicentre phantom study, Nakajima et al. recently demonstrated that acquisition parameters and posttreatment should be harmonized over nuclear medicine departments in order to obtain a homogenous HMR over a wide range of equipment [21].

^{123}I-MIBG SPECT analysis

In our study, IDS of LBD+ were significantly higher than IDS of LBD−. The optimal IDS cut-off value to discriminate LBD+ from LBD− was 6/68 which led to a sensitivity and specificity of 86.7 and 73.7 %, respectively.

The value of cardiac ^{123}I-MIBG SPECT remained limited in both the group of patients with preserved cardiac innervation and in the group of patients with global cardiac denervation. In the group of the 24 patients showing a regional cardiac sympathetic denervation with an IDS different from 0/68 or 68/68, we found some discrepancies between planar and SPECT results. Indeed, six LBD+ showed an impairment of regional myocardial sympathetic innervation on SPECT images without severe global myocardial innervation (HMR= 1.64±0.1) on planar images as depicted in Fig. 3b. Even if it was quite difficult to define the heart axis and perform optimal reconstruction due to the absence of cardiac ^{123}I-MIBG uptake, the total defect score was always 68/68 in patients with severe LBD.

This result suggested that cardiac ^{123}I-MIBG SPECT may have a potential diagnostic value for identification of suspected LBD+. This was in keeping with the study of Courbon et al. who suggested that a regional MIBG uptake alteration might precede global uptake reduction assessed by the HMR and could be the earliest event and precede the decrease in the HMR [22]. Myocardial ^{123}I-MIBG SPECT analysis seems to detect more LBD+ than planar imaging (sensitivity 86.7 vs 82.2 %), whereas planar imaging could exclude LBD+ better than ^{123}I-MIBG SPECT (specificity 84.2 vs 73.7 %). These two methods of myocardial ^{123}I-MIBG uptake analysis appear complementary to identify LBD+.

Myocardial ^{123}I-MIBG SPECT showed that the inferior wall was the most frequently affected myocardial territory in LBD+ with a regional sympathetic cardiac denervation due to a Lewy body deposition. Two other mechanisms may explain this phenomenon [22]. The first mechanism is a physiological variation in sympathetic innervation. Indeed, previous studies demonstrated that the anterior wall of the LV has a predominantly sympathetic innervation and the inferior wall a predominantly parasympathetic innervation [23]. The second one is photon attenuation by the diaphragm.

In patients with preserved cardiac innervation with an IDS of 0, the mean HMR was 1.65 which may be lower than anticipated. The normal value in our institution is 2.3±0.30 [24]. However, this normal value was assessed in younger patients (age=42±10 years) compared to the present study (age=71.6±11.9 years). Estorch et al. demonstrated that ^{123}I-MIBG uptake is related to age, showing a decrease in the HMR with aging [25]. Especially in patients over 60 years of age, they reported a mean HMR of 1.56±0.16, which is in accordance with our present findings.

False-negative and false-positive results

We observed 8 false-negative (HMR>1.47) results by using planar analysis, including 5 DLB and 3 PD, and 6 false-negative (<6/68) results by using SPECT analysis, including 3 DLB and 3 PD. Treglia et al. considered these results as either the presence of an early stage disorder, a tremor-dominant phenotype or a genetically determined PD [26]. SPECT analysis provided information about relative heterogeneity of cardiac ^{123}I-MIBG, and tracer uptake in the different segments was based on the relative scale where the best innervation region was set to maximum, which may explain false-negative results of this modality [5].

On the other hand, we found 3 false-positive (HMR<1.47) results by using planar MIBG scintigraphy, including 1 MSA, 1 PSP and 1 UP, and 5 false-positive (<6/68) results by using SPECT analysis, including the same 3 false-positive patients of the planar analysis and 2 other patients (1 UD and 1 AD). According to Treglia et al., these results may be age-related and not only Lewy body disease-related postganglionic sympathetic degeneration, because myocardial MIBG uptake has a significant age-related decrease [26].

In agreement with the previous studies, most patients with PSP or MSA showed an HMR>1.47 [1, 27]. However, 1 MSA showed a reduced HMR (<1.47) with an IDS>6/68. This reduced cardiac uptake has already been described in this disorder [26]. Indeed, it is important to note that some MSA have postmortem evidence of postganglionic cardiac sympathetic denervation, such as that found in LBD+ [28]. We also found 1 PSP with a reduced HMR (<1.47) and an increased IDS (>6/68). Yoshita et al. also observed a reduced myocardial ^{123}I-MIBG uptake in 3/14 patients with a PSP [29]. Our AD had a normal HMR (2.05) but also a significant regional defect of LV innervation particularly in the inferior wall. These results can be explained by an AD coupled to an early stage of DLB. Indeed, several studies have reported varying degrees of change in the sympathetic nervous system in AD [30].

In our study, four patients receiving drugs that could interfere (two patients on clomipramine and two patients on mianserin) with the cardiac ^{123}I-MIBG uptake were excluded. They were three patients with DLB (HMR=1.2, 1.33 and 1.1 and all IDS=68/68) and one with PD (HMR=1.06 and IDS= 68/68). We considered that the exclusion of these patients did

not hamper the extrapolation of the data to clinical practice because they would have presented a severe decrease of the HMR even in the case of using these types of drugs.

Limitations

The main limitations of our study were the small size of the population, the retrospective design and the absence of pathological confirmation of diagnoses. However, all 64 consecutive patients were seen in a University Hospital where all files were reviewed by a movement disorder specialist and final diagnoses were made according to international diagnostic criteria.

Although it has been found that medium-energy collimators provide better quantitative accuracy with a higher HMR, we used low-energy collimators in our department. Further prospective studies in a large number of subjects suspected of LBD will be necessary to generate the use of cardiac SPECT innervation imaging as a commonly used tool.

Finally, it is not yet possible to extrapolate the present results to individual data insofar as our ^{123}I-MIBG cut-off values require a prospective validation in a separate patient group with suspected LBD to fulfil the standards of clinical research.

Conclusion

Regional myocardial adrenergic imaging using ^{123}I-MIBG SPECT analysis seems to detect more LBD+ than planar imaging, whereas planar imaging could exclude LBD+ better than ^{123}I-MIBG SPECT. These two methods of myocardial ^{123}I-MIBG uptake appear complementary to identify patients with LBD.

Conflicts of interest None.

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Compliance with ethical standards For this type of study formal consent is not required.

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