Value of MIBG in the Differential Diagnosis of Neurodegenerative Disorders

19

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Contents

Abstract

^{123}I-*Meta*iodobenzylguanidine (MIBG) has a history of 30 years as a marker of myocardial sympathetic activity and has been used for assessment of various cardiac diseases. Reduced cardiac MIBG uptake in myocardial scintigraphy has been reported in patients with Parkinson's disease (PD), dementia with Lewy bodies (DLB), pure autonomic failure (PAF), rapid eye movement sleep behavior disorder (RBD), and familial PD linked to *SNCA* duplication. In 2005, the Dementia with Lewy Bodies Consortium considered ^{123}I-MIBG myocardial scintigraphy a "supportive" diagnostic tool. Recently, reliable and clear evidence for the usefulness of ^{123}I-MIBG scintigraphy in the diagnosis of Lewy body disorders has been accumulated, and it has become increasingly popular, whereas reduction of cardiac MIBG accumulation was reported in some cases of atypical

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R. A. J. O. Dierckx et al. (eds.), *PET and SPECT in Neurology*,
https://doi.org/10.1007/978-3-030-53168-3_19

parkinsonian syndromes such as progressive supranuclear palsy and multiple system atrophy. In ^{123}I-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropan (FP-CIT) SPECT-supplemented MIBG scintigraphy of PD and DLB, FP-CIT binding in basal ganglia is closely related to cardiac MIBG uptake. Based on the high diagnostic specificity in our multicenter study with standardized techniques, weighting of ^{123}I-MIBG myocardial scintigraphy was upgraded in the revised criteria for the clinical diagnosis of DLB.

Abbreviations

^{123}I-IMP	*N*-Isopropyl-*p*-[^{123}I]-iodoamphetamine
AD	Alzheimer's-type dementia
CBD	Corticobasal degeneration
DLB	Dementia with Lewy bodies
DOPS	Dihydroxyphenylserine
ECD	Ethyl cysteinate dimer
FDG	Fluorodeoxyglucose
FP-CIT	*N*-ω-Fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropan
HMPAO	Hexamethyl-propylene-amine-oxine
LBD	Lewy body disease
MAO	Monoamine oxidase
MIBG	*Meta*iodobenzylguanidine
PAF	Pure autonomic failure
PD	Parkinson's disease
PSP	Progressive supranuclear palsy

19.1 Introduction

*Meta*iodobenzylguanidine (MIBG) is a physiologic analog of norepinephrine, used to determine the location, integrity, and function of postganglionic noradrenergic neurons. ^{123}I-MIBG cardiac scintigraphy is a noninvasive tool for estimating local myocardial sympathetic nerve damage in various myocardial and neurological diseases (Glowniak et al. 1989; Merlet et al. 1992; Yoshita 1998). Noradrenergic postganglionic sympathetic denervation is a common feature of Parkinson's disease (PD) and related Lewy body disorders. Patients with PD can exhibit reduced cardiac ^{123}I-MIBG accumulation without other evidence of autonomic failure, whereas those with dementia with Lewy bodies (DLB) can have reduced cardiac ^{123}I-MIBG uptake without evidence of parkinsonism (Yoshita et al. 1998, 2006). In this chapter, usefulness of ^{123}I-MIBG myocardial scintigraphy is reviewed with special emphasis on diagnostic issues in neurodegenerative disorders.

19.2 Evaluation of Cardiac Sympathetic Nerve Activity

After subjects have been in a supine position for 20 min, 111 MBq ^{123}I-MIBG is injected intravenously. The energy discrimination is centered on 159 keV with a 20% window. Early and delayed planar images are obtained at 20–30 min and 3–4 h, respectively. Acquisition conditions and normal values are reported elsewhere (Nakajima et al. 1990). A single-photon emission computed tomography (SPECT) scan is also obtained in both early and delayed imaging. Anterior planar imaging is required for the quantification of the heart-to-mediastinum (H/M) ratio.

Relative organ uptake is determined by setting the region of interest (ROI) on the anterior view. A polygonal ROI is manually drawn over the whole heart, including the left ventricular cavity, and a rectangular ROI is set on the mediastinum (Fig. 19.1). The H/M ratio is calculated by dividing the count density of the ventricular ROI by that of the mediastinum ROI. The washout rate (WR) is calculated as follows: $WR = 100 \times (Ec - Dc)/Ec$, where Ec is the early cardiac count density and Dc is the decay-corrected delayed cardiac count density. Recently, a method for standardization of H/M ratios was developed to avoid the influence of different acquisition conditions (Nakajima et al. 2012).

Though several medications can interfere with MIBG uptake, among anti-Parkinson drugs, particularly L-threo-DOPS and MAO-B inhibitors may reduce the cardiac MIBG uptake (Solanki et al. 1992) (Table 19.1). For reliable results, the use of these drugs should be avoided.

It is well-known that various type of cardiac diseases and diabetes mellitus exhibited low MIBG uptake. In those cases, distribution pattern of MIBG accumulation may help the differential diagnosis. Three-dimensional evaluation using SPECT and echocardiographic assessment for cardiac wall motion is recommended to confirm the cause of MIBG uptake reduction (Nakajima et al. 2008).

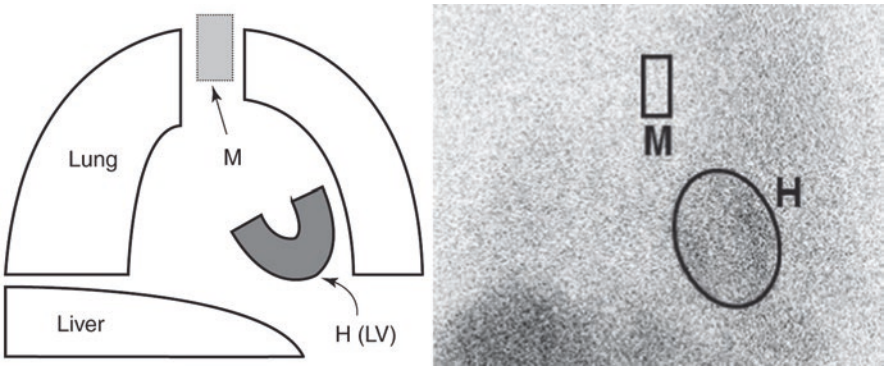

Fig. 19.1 Example of mediastinal and cardiac region of interest (ROI) on anterior planar image. The left ventricular ROI was drawn including the ventricular cavity (H), and a rectangular ROI was set on the middle mediastinum (M)

Table 19.1 Drugs interacting with MIBG

Antidepressants
Amitriptyline, amoxapine, clomipramine, desipramine, imipramine, trazodone, mianserin, etc.
α- and β-blocker
Labetalol, phenoxybenzamine, etc.
Sympathomimetics and sympatholytics
L-Threo-DOPS, norepinephrine, dobutamine, dopamine, phenylephrine, phenylpropanolamine, salbutamol, selegiline, brimonidine, etc.
Antipsychotics
Chlorpromazine, trazodone, haloperidol, droperidol, clozapine, quetiapine, risperidone, etc.
CNS stimulants
Cocaine, caffeine, amphetamine, etc.
Calcium channel blocker
Diltiazem, isradipine, nicardipine, nifedipine, nimodipine, verapamil, etc.

19.3 Pathology in Lewy Body Disease

Pathological assessment of Lewy body disease (LBD) reveals aggregates of α-synuclein, referred to as Lewy bodies, found in neurons and glia. Their presence is required for the pathological diagnosis of LBD. Lewy bodies are present not only in the brain stem but also in the limbic system and neocortex in relation to their phenotypes. In addition to central nervous system involvement, variable amounts of Lewy body burden are found in the peripheral nervous system and autonomic nervous system (Wakabayashi and Takahashi 1997). A postmortem study reported cardiac plexus was more heavily involved than the sympathetic ganglia in a patient with PD (Mitsui et al. 2006). On the other hand, other movement disorders and dementia syndromes, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), essential tremor, frontotemporal dementia, and Alzheimer's-type dementia (AD), generally found no sympathetic ganglionic changes. Accordingly, Lewy body disease is not specific to the brain but instead is a generalized neuronal disorder.

19.4 *Meta*iodobenzylguanidine Imaging in Lewy Body Disease

PD, DLB, and pure autonomic failure (PAF) are recognized as LBD. Among all neurological diseases, they are characterized by a significant reduction in MIBG uptake. Recently, a markedly reduced cardiac MIBG uptake was also reported in idiopathic rapid eye movement sleep behavior disorder (RBD), consistent with the loss of sympathetic terminals and suggesting an association of RBD with Lewy body pathology (Miyamoto et al. 2006) (Fig. 19.2). It was revealed that cardiac MIBG uptake for early and delayed images was correlated with the proportion of residual cardiac sympathetic TH-positive nerve fibers at autopsy (Takahashi et al.

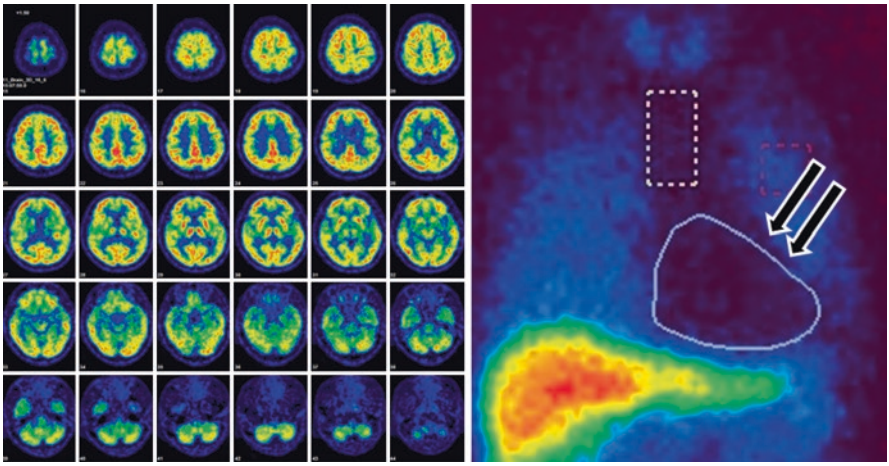

Fig. 19.2 Brain ^{18}F-FDG-PET and anterior planar MIBG image of patients with REM sleep behavior disorder. ^{18}F-FDG-PET shows normal brain metabolism, but no cardiac MIBG uptake (arrows)

Table 19.2 FP-CIT SPECT and MIBG scintigraphy in discrimination of DLB from AD

Tracer	Diagnostic significance (McKeith et al. 2017)	Subject	Method	Sensitivity/ specificity (%)
FP-CIT	Indicative biomarkers	Probable DLB vs. non DLB	Multicenter	77.7/90.4 (McKeith et al. 2007)
MIBG	Indicative biomarkers	Probable DLB vs. probable AD	Multicenter	69–77/89–97 (Yoshita et al. 2015; Komatsu et al. 2018)

FP-CIT N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropan, *MIBG meta*iodobenzylguanidine

2015). As ^{123}I-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropan (FP-CIT) SPECT successfully visualizes presynaptic dopaminergic degeneration of the nigrostriatal tract, the finding of reduced tracer uptake in basal ganglia is recognized as a "indicative biomarker" of DLB (Mckeith et al. 2017) (Table 19.2). A study aimed at differentiation of PD from atypical parkinsonian disorder revealed that ^{123}I-FP-CIT SPECT and MIBG scintigraphy have similar diagnostic accuracy (Südmeyer et al. 2011).

19.4.1 Parkinson's Disease

MIBG studies for PD began in 1994 (Hakusui et al. 1994; Yoshita et al. 1996; Iwasa et al. 1998). Their clinical value has become recognized by an increasing number of reports and experiences (Yoshita 1998; Braune et al. 1998; Orimo et al. 1999; Reinhardt et al. 2000; Druschky et al. 2000; Takatsu et al. 2000a, b; Taki et al.

2000). A characteristic feature of MIBG imaging in PD has been shown to be an impressively low uptake in the whole myocardium. The severely depressed cardiac MIBG uptake in PD seems to occur in a disease-specific manner among related movement disorders. Based on a meta-analysis of studies, the overall sensitivity and specificity for correct discrimination of patients with PD were both about 90% (Braune 2001; Orimo et al. 2012; Treglia et al. 2012).

Although the H/M ratio tends to decrease with disease progression, many PD patients in Hoehn and Yahr stage I have decreased cardiac MIBG uptake. The H/M ratio is not suitable as an index of the disease severity. Tremor-dominant patients with PD had higher MIBG uptake than those with postural instability and gait disorder, while reduced MIBG uptake was linked to greater bradykinesia, higher age at onset, and longer disease duration (Saiki et al. 2004; Spiegel et al. 2007).

Cardiac MIBG uptake is not correlated with dysautonomic clinical symptoms in patients with PD, though some cardiac autonomic tests showed a negative correlation of MIBG uptake and cardiac sympathetic denervation (Oka et al. 2011). The use of different methods for evaluation of cardiac MIBG uptake or early occurrence of sympathetic nerve fiber loss in LBD might explain such poor correlations (Iwanaga et al. 1999; Taki et al. 2004).

In genetically identified cases of PD, cardiac MIBG uptake findings are not consistent. MIBG or fluorodopamine uptake in the heart decreased in some patients with PARK1, PARK4, PARK6, PARK7, and PARK 8 mutations (Quattrone et al. 2008; Valldeoriola et al. 2011; Tijero et al. 2010). On the contrary, patients with PARK2 mutations showed no difference in H/M ratios as compared to controls (Orimo et al. 2005).

19.4.2 Dementia with Lewy Bodies

Antemortem diagnosis of DLB and differentiation of DLB from AD is important, because some patients with DLB may show an accelerated disease progression, life-threatening adverse reaction to antipsychotic medications, and a good response to anticholinesterase inhibitors. Clinical utility of MIBG scintigraphy in differentiating DLB from AD has been reported (Watanabe et al. 2001; Yoshita et al. 2001, 2006; Treglia and Gason 2012). Although the diagnosis of DLB may be confounded by the absence of parkinsonism, DLB patients without parkinsonism had a decreased MIBG accumulation in the heart as well as those with parkinsonism (Yoshita et al. 2006) (Fig. 19.3). The MIBG uptake reduction does not correlate with disease duration. To increase diagnostic weighting of MIBG in the criteria (McKeith et al. 2005), standardization of the MIBG techniques and multicenter study with standardized MIBG were performed. First, differences between collimators in institutions were standardized by using a calibration phantom (Nakajima et al. 2012, 2014). Setting of ROIs for heart and mediastinum was semi-automated by using “smart MIBG” (standardized method for automatic ROI setting in MIBG study) (Okuda et al. 2011). These methods made it possible to obtain standardized data of the H/M ratio from different institutions. Second, a prospective multicenter

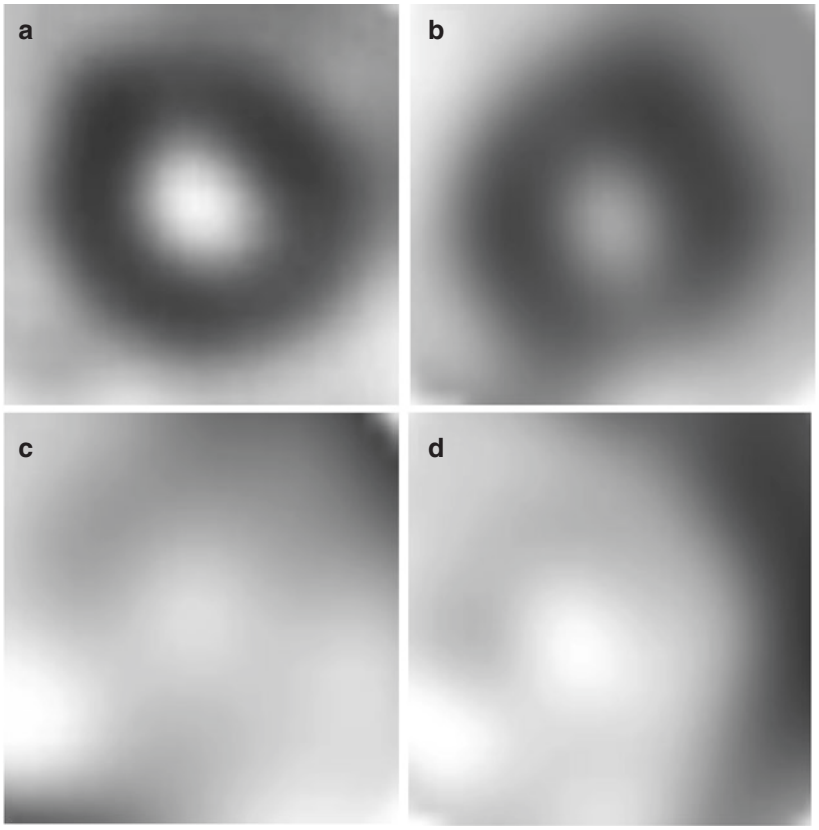

Fig. 19.3 Cardiac radioactivity in delayed short axis view after injection of ^{123}I-MIBG in a control subject, a patient with *AD*, a patient with DLB with parkinsonism, and a patient with DLB without parkinsonism. Both patients with DLB have undetectable myocardial ^{123}I-MIBG radioactivity. (**a**) Control, (**b**) AD, (**c**) DLB with parkinsonism, (**d**) DLB without parkinsonism

study for evaluation of cardiac sympathetic function for the diagnosis of DLB, involving ten institutions in Japan, was performed. Independent committees performed clinical and MIBG assessment. One hundred and thirty-three patients were registered, including probable DLB, possible DLB, and probable AD cases. This multicenter study to date found a sensitivity of 69% and specificity of 89% (Yoshita et al. 2015). The diagnostic accuracy of MIBG in this study improved when compared with clinical diagnosis 3 years after the scan (sensitivity 77%, specificity 97%) (Komatsu et al. 2018). Consensus guidelines for the clinical and pathologic diagnosis of DLB were published in 2017 (McKeith et al. 2017). In this guideline, clinical features and diagnostic biomarkers were clearly distinguished. Significant new evidence about previously reported aspects of DLB has been incorporated, with increased diagnostic weighting given to RBD and ^{123}I-MIBG myocardial scintigraphy.

Table 19.3 Discriminating DLB from AD using brain perfusion SPECT

Tracer	Subjects	Sensitivity/specificity (%)
^{99m}Tc-HMPAO	23 DLB (definite 4, probable 17, possible 2) vs. 50 AD (definite 2, probable 21, possible 27)	65/87 (Lobotesis et al. 2001)
^{123}I-IMP	19 probable DLB vs. 39 probable AD	74/82 (Hanyu et al. 2006)
^{99m}Tc-ECD	23 probable DLB vs. 23 probable AD	65/75 (Yoshita and Yamada 2003)

HMPAO hexamethyl-propylene-amine-oxine, *^{123}I-IMP* *N*-isopropyl-*p*-[^{123}I]-iodoamphetamine, *ECD* ethyl cysteinate dimer

Occipital hypoperfusion on brain perfusion SPECT is a "suggestive biomarker" of DLB as well as less severe medial temporal lobe atrophy on structural imaging (McKeith et al. 2017). When the MIBG study was compared with brain perfusion SPECT with ^{99m}Tc-ethylene cysteine dimer or ^{123}I-*N*-isopropyl-iodoamphetamine, the MIBG study seemed to be more accurate as a means of discriminating DLB from AD (Yoshita and Yamada 2003; Hanyu et al. 2006) (Table 19.3). Although brain perfusion SPECT failed to demonstrate significant hypoperfusion in the occipital region in some patients with DLB, a marked reduction of MIBG uptake was found in most of the patients with DLB.

19.4.3 Pure Autonomic Failure

PAF is a rare phenotype of Lewy body disease in which patients have prominent autonomic disturbance thought to be associated with a diffuse loss of sympathetic terminal innervations. PET with 6-^{18}F-flurodopamine as well as MIBG studies revealed a loss of cardiac tracer uptake, indicating cardiac denervation in PAF (Goldstein et al. 2000; Yoshida et al. 1997). ^{123}I-MIBG cardiac scintigraphy should be able to distinguish MSA and PAF (Hirayama et al. 1995; Kashihara et al. 2006).

19.5 Differential Diagnosis of Lewy Body Disease Using ^{123}I-MIBG Cardiac Scintigraphy

In general, a neurological differential diagnosis in the early stages between PD, MSA, PSP, and corticobasal degeneration (CBD) is important because of differences in prognosis and therapy among these diseases. In contrast with PD, central and preganglionic neurons are predominantly affected, while postganglionic neurons are usually spared in MSA. Therefore, cardiac MIBG uptake might not be impaired. In MSA, cardiac MIBG uptake is higher than that in PD, irrespective of the severity of autonomic dysfunction (Yoshita 1998; Braune et al. 1999; Orimo et al. 1999). Although 77–95% discrimination specificity between PD and MSA has been proposed (Braune 2001; Treglia et al. 2011), the Quality Standards Subcommittee of the American Academy of Neurology found insufficient evidence

Table 19.4 Demographic and clinical data

	PSP	CBD	PD	DLB	CN	*p* value
N (M/F)	19 (13/6)	7 (2/5)	19 (8/11)	11 (5/6)	13 (6/7)	NA
Duration (months)	29.4 ± 20.9	18.4 ± 12.5	67.4 ± 61.6	36.3 ± 24.6	NA	<0.01[a]
Age (years)	69.6 ± 6.7	65.6 ± 10.2	68.7 ± 5.9	75.1 ± 5.6	69.6 ± 6.7	<0.05[b]
HY stage	3.2 ± 0.4	2.9 ± 1.2	2.7 ± 1.3	2.6 ± 0.7	NA	0.33
MMSE	24.3 ± 4.9	24.3 ± 4.5	26.3 ± 1.7	20.8 ± 6.0	NA	0.078

Values are expressed as the mean ± SD
PSP progressive supranuclear palsy, *CBD* corticobasal degeneration, *PD* Parkinson's disease, *DLB* dementia with Lewy body, *CN* control, *HY stage* Hoehn and Yahr stage, *MMSE* Mini-Mental State Examination, *NA* not applicable
Post hoc comparison of significant group differences:
[a]PD vs. CBD
[b]DLB vs. CBD

to recommend MIBG cardiac imaging for differentiating PD from MSA (Suchowersky et al. 2006). A few cases of patient with MSA showed decreased cardiac MIBG uptake (Yoshita 1998, 2000). A small number of patients with MSA have postmortem evidence of postganglionic cardiac denervation which may account for the reported decreased cardiac MIBG uptake (Orimo et al. 2007). These cases of MSA may have involvement of both glial cytoplasmic inclusion in the brain and Lewy bodies in sympathetic ganglia.

PSP, classified as tauopathy, is a degenerative disorder causing supranuclear gaze palsy, bradykinesia, muscular rigidity with progressive axial dystonia, pseudobulbar palsy, and subcortical dementia. The H/M ratio of this disease entity is within normal range or slightly reduced (Yoshita 1998; Taki et al. 2000). However, we have noted a markedly low MIBG uptake in about 20% of patients with PSP (Yoshita et al. 2008) (Table 19.4, Figs. 19.4 and 19.5). These cases of PSP may have concomitant Lewy bodies (Mori et al. 2002).

CBD, also classified as tauopathy, shows asymmetric akinetic-rigid syndrome, cortical signs, and cognitive decline. MIBG imaging showed normal uptake which could be used to differentiate CBD from Lewy body diseases (Taki et al. 2000; Orimo et al. 2003; Kashihara et al. 2006; Yoshita et al. 2008), whereas autopsy-proven CBD cases which had decreased myocardial uptake of MIBG were reported. In one case, Lewy bodies, which were not seen in the central nervous system, were seen only in the sympathetic ganglia, and a severe loss of nerve fibers was apparent in the sympathetic nerve endings in the heart (Mori et al. 2012). In another case, there were no Lewy pathologies in both the central nervous system and the sympathetic ganglia (Yoshimura et al. 2018). There might be other mechanisms such as norepinephrine transporter dysfunction to reduce cardiac MIBG accumulation besides pathologically proven cardiac sympathetic damage (Yoshita 1998).

Nagayama et al. reported that nearly 70% of the patients without PD also had low uptake, and there were considerable overlaps in the H/M ratio (2005). Although reduced cardiac accumulation of MIBG represents a pathological change in the sympathetic nerve endings in the heart, the distribution of Lewy bodies cannot be

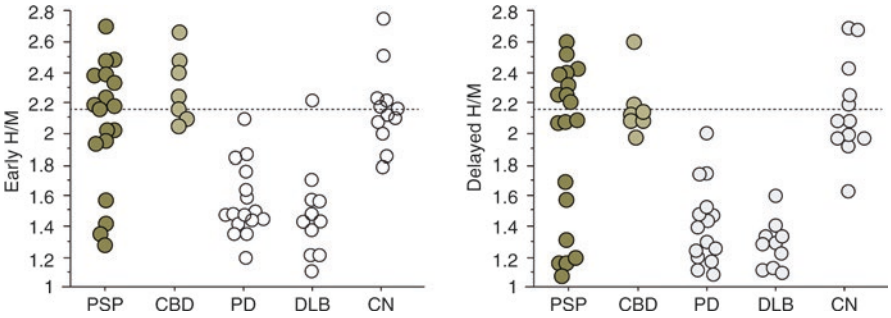

Fig. 19.4 Individual values for the H/M ratio in the study of LBD, PSP, and CBD. The dashed line indicates the mean value in the control (CN) group. Significantly reduced H/M ratios in both the early and the delayed images were observed in the Lewy body disease (LBD) group in comparison with progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and CN groups. Four of the early and five of the delayed images of the patients with PSP have a reduced H/M ratio

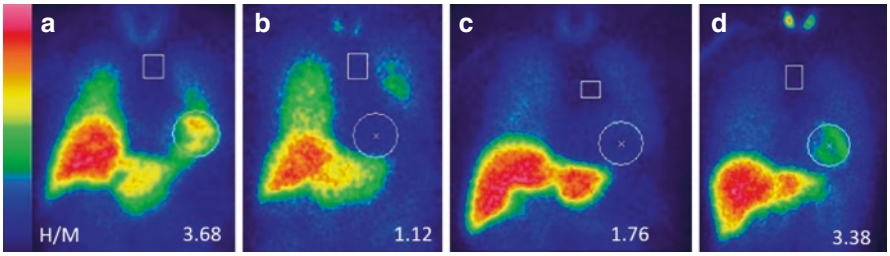

Fig. 19.5 smartMIBG (Okuda et al. 2011) view of delayed planar images in AD, PSP, and DLB patients. Patients with AD (**a**) and PSP (**d**) show significant cardiac accumulation. Patients with DLB (**b**) and another PSP (**c**) have no cardiac uptake and reduced H/M ratio

determined from this finding. Thus, MIBG cardiac scintigraphy should not be used alone to confirm a diagnosis of PD. With respect to this, combining other neuroimaging method such as brain MRI, ^{123}I-FP-CIT SPECT, or transcranial sonography measurement to MIBG scintigraphy may improve diagnostic accuracy of PD in comparison with MIBG scintigraphy alone (Kollensperger et al. 2007; Kajimoto et al. 2009; Rascol and Schelosky 2009; Südmeyer et al. 2011).

A few data show that ^{123}I-MIBG cardiac scintigraphy is useful to distinguish LBD from other movement disorder and dementia syndromes, such as essential tremor, drug-induced parkinsonism, vascular parkinsonism, and frontotemporal dementia (Orimo et al. 1999; Lee et al. 2007; Movellino et al. 2010).

19.6 Conclusion

In Lewy body disease, both central and peripheral autonomic nervous systems are involved. The myocardial MIBG defects reflect a pathological progression of the disease process involving extensive autonomic involvement. Considering all the

data together, severe myocardial MIBG uptake reduction seems to be a specific marker of Lewy body disease. If these ^{123}I-MIBG findings reflect cardiac Lewy body pathology and precede CNS involvement, ^{123}I-MIBG myocardial scintigraphy may have the potential to diagnose Lewy body disease in its preclinical stages, which could be useful in evaluating the impact of disease-modifying and preventive interventions.

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