Chapter 15
Findings of ^{123}I-MIBG Cardiac Scintigraphy: Parkinson's Disease and Related Disorders and Others (RBD, Cardiac Diseases, DM, etc.)

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Abstract A wide range of autonomic dysfunctions has been described in Parkinson's disease (PD). Since its description, myocardial iodine-123-*meta*-iodobenzylguanidine (^{123}I-MIBG) cardiac scintigraphy has attracted attention as a useful tool for the diagnosis of PD. There is a general agreement that the H/M ratio in ^{123}I-MIBG cardiac scintigraphy is significantly low in both early and delayed images of PD patients. Reduced cardiac MIBG uptake has been reported in not only patients with PD but also in dementia with Lewy bodies (DLB), rapid eye movement behavior disorder (RBD), and pure autonomic failure (PAF). In this regard, ^{123}I-MIBG cardiac scintigraphy can be useful for differentiating Lewy body disorders from other parkinsonian syndromes and dementias.

In this chapter ^{123}I-MIBG cardiac scintigraphy findings are described from various perspectives of PD, and we also review RBD, PAF, and other related disorders. Finally, we describe comorbidities associated with reduced cardiac MIBG uptake for careful interpretation.

Keywords ^{123}I-MIBG cardiac scintigraphy • Parkinson's disease • Lewy body disease • Parkinsonism

15.1 Parkinson's Disease

Parkinson's disease (PD) is the most common neurodegenerative parkinsonism characterized by degeneration of both dopaminergic and non-dopaminergic neurons with intracytoplasmic eosinophilic inclusions known as Lewy bodies. The cardinal clinical motor signs of PD are resting tremor, rigidity, and bradykinesia and response to dopaminergic drugs. Postural instability is specific to the advanced

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stage of PD. Other non-motor signs are frequently present, including autonomic dysfunction, cognitive and psychiatric changes, sensory symptoms, sleep disturbances, and hyposmia, although the frequency of these features varies from one patient to another.

15.1.1 ^{123}I-MIBG Cardiac Scintigraphy Findings in Parkinson's Disease

A wide range of autonomic dysfunctions has been described in PD such as orthostatic and postprandial hypotension, gastrointestinal dysfunction especially constipation, urinary disturbance, sexual dysfunction, and sweating abnormalities. Since its description, cardiac dysautonomia has attracted attention as a useful tool for the diagnosis of PD. Iodine-123-*meta*-iodobenzylguanidine (^{123}I-MIBG) cardiac scintigraphy is a useful diagnostic tool for cardiac dysautonomia. Reduced cardiac MIBG uptake is observed in 80–90 % of patients with PD, and most images show no accumulation of MIBG in the heart. Hakusui et al. [1] were the first to report reduced cardiac MIBG uptake in patients with PD. Since the first description, reduced cardiac MIBG uptake in patients with PD has become one of the main characteristics of PD, and many groups reported that the reduced uptake could be implemented in the differential diagnosis of PD from other atypical parkinsonisms.

The threshold value of the H/M ratio can be used for the differentiation of PD from other neurodegenerative parkinsonisms. In this regard, Shin et al. [2] reported that the threshold values of the early and delayed H/M ratios, which distinguished PD patients from the controls, were 1.57 (sensitivity, 95.0 %, specificity, 88.9 %) and 1.56 (sensitivity, 95.0 %, specificity, 100 %), respectively. There was no difference in the discrimination power of the early and delayed H/M ratios ($p = 0.188$, 95 % confidence interval [95 %CI] = −0.014 to 0.07). The same study found that the threshold values of the early and delayed H/M ratio that distinguished PD patients from MSA patients were 1.38 (sensitivity, 65.7 %; specificity, 95.7 %) and 1.36 (sensitivity, 80.0 %; specificity, 100 %), respectively. Furthermore, the delayed H/M ratio was significantly better than the early H/M ratio ($p = 0.068$, 95 % CI= −0.005 to 0.138).

However, Nagayama et al. [3] reported a lower specificity than other studies. In their study, patients showing one or more parkinsonian-like symptoms were enrolled. The sensitivity and specificity of ^{123}I-MIBG cardiac scintigraphy for the diagnosis of PD were 87.7 % and 37.4 %, respectively; these values were due to the fact that nearly half of their patients with senile dementia of Alzheimer type (SDAT) had low MIBG uptake. In their study, the patients with SDAT showed motor signs, and they could have had Lewy body disorder in addition to the Alzheimer pathology.

On the other hand, Orimo et al. [4] conducted meta-analysis study of 13 studies and reported that the pooled sensitivity and specificity of the early H/M ratio to

differentiate PD from other neurodegenerative parkinsonisms were 82.6 % and 89.2 %, respectively, and those of the delayed H/M ratio were 89.7 % and 82.6 %, respectively. When PD was limited to that of early stage (Hoehn and Yahr (H-Y) stage 1 or 2), the pooled sensitivity and specificity by the delayed H/M ratio were 94.1 % and 80.2 %, respectively.

Considered together, we conclude that ^{123}I-MIBG cardiac scintigraphy can be used with high sensitivity and specificity to differentiate PD from other neurodegenerative parkinsonisms using both early and delayed imaging phases, despite potential interinstitutional differences in the H/M ratio based on differences in collimators and scinticameras used at each institution. Standardization of the H/M ratio is continuously carried out in Japan and standard values will be presented in the near future. This standardization process is described in detail in Chap. 14.

Postmortem examination of the anterior walls of the left ventricles demonstrated markedly low density of nerve fibers immunoreactive to tyrosine hydroxylase (TH), a marker of sympathetic axons, in patients with PD, compared to those with multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and control subjects [5–8]. These results suggest postganglionic involvement in PD [5]. More details about the pathophysiological mechanism of the reduced cardiac MIBG uptake in PD are described in Chap. 18.

15.1.2 ^{123}I-MIBG Cardiac Scintigraphy and Clinical Features of PD

The correlation between ^{123}I-MIBG cardiac scintigraphy findings and age at disease onset, disease duration, different clinical phenotypes, disease severity, non-motor symptoms, and other tests are described below.

15.1.2.1 Age at Onset and Disease Duration

Age at onset correlates negatively with the H/M ratio [9–11]. Previous studies also reported that the H/M ratio correlated with disease duration [12], although others reported no such correlation [9, 13, 14].

15.1.2.2 Disease Severity

Several studies have demonstrated a significant negative correlation between cardiac MIBG uptake and H-Y stage [3, 9, 13]. One study of 34 patients with PD reported a significant correlation between early H/M ratio and the Unified Parkinson's Disease Rating Scale (UPDRS) score [10]. However, no correlation between the H/M ratio and disease severity in UPDRS III motor score was found in

patients with early PD H-Y stages I–III [15] and those with advanced stage. Another study showed no significant difference in the H/M ratio in 24 patients with PD H-Y stages III, IV, and V [12]. The same trend was noted also in another study of 40 patients with H-Y stage III or IV [14] with no significant correlation between the H/M ratio and disease severity in UPDRS III motor score.

15.1.2.3 Clinical Phenotype

PD patients can be classified according to the clinical phenotype into the tremor-dominant type (TDT), akinetic/rigid type (ART), mixed type (MT), and postural instability/gait difficulty (PIGD) dominant type. One study of 102 patients with PD reported that cardiac MIBG uptake was significantly higher in TDT patients than ART and MT patients [16], while another study of 34 patients showed higher uptake in TDT patients than PIGD [10]. In another study of 143 patients with PD, cardiac MIBG uptake correlated negatively with bradykinesia, but not with tremor, rigidity, or postural instability [11]. Another study of 102 patients with PD showed a significant correlation between cardiac MIBG uptake and severity of hypokinesia as well as rigidity, but not with severity of resting or postural tremor irrespective of H-Y stage [16]. In contrast, in another study of 53 patients with PD, cardiac MIBG uptake was significantly lower in TDT patients compared with ART patients [15]. The study concluded that the discrepant results were probably due to different disease duration. The same results were later confirmed in another study of 37 patients with PD [17].

Generally, the presence of bradykinesia and rigidity tends to correlate with reduced cardiac MIBG uptake compared with the tremor type. These results suggest that cardiac sympathetic degeneration correlates with hypokinetic rigidity symptoms in PD, but not with tremor. Admittedly, these results remain controversial mainly due to population heterogeneity. Nevertheless, ^{123}I-MIBG cardiac scintigraphy could be used to predict the rate of progress of rigidity and axial symptoms in UPDRS III motor score in the subsequent 3–8 years. Such prediction is not possible using other motor symptoms, such as resting tremor, postural tremor, and bradykinesia [18].

15.1.2.4 Non-motor Symptoms

Clinical Symptoms of Dysautonomia

The relation between cardiac MIBG uptake and symptoms of autonomic failure in PD remains poorly defined. Most clinical studies found that reduced cardiac MIBG uptake is independent of such symptoms, as represented by orthostatic hypotension (OH) [19, 20]. However, Orimo et al. [21] reported significantly lower cardiac MIBG uptake in PD patients with OH than those without it. Interestingly, they also reported no significant difference in cardiac MIBG uptake between patients with

and without constipation. Another study showed a significant difference in cardiac MIBG uptake between patients with and without bladder dysfunction [14]. These results indicate that not all dysautonomia-related clinical symptoms correlate with reduced cardiac MIBG uptake.

Hyposmia

The prodromal stage of PD occurs several years in advance of typical motor symptoms. Early diagnosis is important for early implementation of disease-modifying therapy. Several studies have indicated that hyposmia precedes the motor symptoms of PD [22, 23]. Furthermore, Jennings et al. [24] reported ^{123}I-FP-CIT ^{23}I-N-3-fluoropropyl-2beta-carbomethoxy-3beta-4-iodophenyl tropane (^{123}I-FP-CIT) single-photon emission computed tomography (SPECT) deficit in 11 % of 203 hyposmic subjects compared with 1 % of 100 normosmic subjects.

In their study of 23 non-demented patients with early-stage PD, Mizutani et al. [25] demonstrated that hyposmia correlates with cardiac MIBG uptake within 2 years from the onset of motor symptoms. The results also highlighted the potential utility of ^{123}I-MIBG cardiac scintigraphy in subjects with hyposmia and prodromal PD. Hyposmia and reduced MIBG uptake correlate well in the early stage of PD, suggesting that degenerations in olfactory nerves and cardiovascular sympathetic nerves represent similar processes. Therefore, it could be postulated that the prodromal stage of PD encompasses cardiovascular sympathetic nerve degeneration and reduced cardiac MIBG uptake.

Hallucination

Psychosis is a disabling non-motor complication of PD. Hallucination is one of the common psychotic symptoms in both demented and non-demented PD, occurring in approximately 40–50 % of PD patients [26, 27]. Uchiyama and colleagues [28] reported that in 97 patients with Lewy body disease (LBD) (90 patients with PD, seven with DLB), early and delayed H/M ratios independently correlated with hallucinations. In another study of 95 patients with PD [29], analysis of covariance, adjusted for the age of the patients as covariate, demonstrated that early and delayed H/M ratios were significantly lower in PD patients with hallucinations but no dementia, as well as PD patients with dementia, than in PD patients with no hallucinations or dementia. These findings indicate that reduced cardiac MIBG uptake may be associated with hallucination in PD patients.

15.1.3 Comparison with Other Tests

15.1.3.1 ^{123}I-FP-CIT SPECT

^{123}I-FP-CIT SPECT is helpful in the evaluation of patients with nigrostriatal dopaminergic deficit. Several studies have demonstrated that ^{123}I-FP-CIT SPECT is highly accurate in differentiating patients with neurodegenerative parkinsonisms from those with non-neurodegenerative parkinsonisms. In particular, ^{123}I-FP-CIT scanning offers help in the diagnosis of PD at early stages. However, only few studies have evaluated the relationship between ^{123}I-FP-CIT and cardiac MIBG uptake. In a study of 18 PD patients with early stage (limited only to H-Y stage I), Spiegel et al. [30] found a strong relationship between striatal binding on the impaired site and the H/M ratio of ^{123}I-MIBG cardiac scintigraphy. They concluded that the functional loss of nigrostriatal dopaminergic neurons is closely related to cardiac sympathetic dysfunction [30, 31]. In contrast to the above study, Chiaravalloti et al. [17] reported no relationships between ^{123}I-FP-CIT SPECT and early and delayed images of ^{123}I-MIBG cardiac scintigraphy in 37 patients with PD (H-Y stage I, $n = 15$; stage IV, $n = 8$; stage II, $n = 7$; stage III, $n = 7$). They also reported no significant relationship between subtypes TDT and ART of the single PD phenotype. The results suggest that the rate of sympathetic neurodegeneration is not related to the rate of nigrostriatal degeneration and vice versa.

A possible explanation of these discrepancies can be based on the different rates of disease severity and differences in PD phenotypes. Differences in PD phenotypes do not seem to explain the results of Chiaravalloti et al. [17]. In fact, the weak correlation between early cardiac MIBG uptake and ^{123}I-FP-CIT uptake in ART in the ipsilateral striatum is hampered by the medium-size effect on their statistical analysis. Further research is needed to determine the relationship between sympathetic and dopaminergic system in PD.

Only a few studies have compared the use of ^{123}I-FP-CIT SPECT and ^{123}I-MIBG cardiac scintigraphy. These two techniques were compared in 68 patients with suspected LBD [32]. The overall sensitivity, specificity, accuracy, and positive and negative predictive values for ^{123}I-MIBG cardiac scintigraphy were 83 %, 79 %, 82 %, 86 %, and 76 %, respectively, and 93 %, 41 %, 73 %, 71 %, and 80 %, respectively, for ^{123}I-FP-CIT SPECT. While these values were significantly different between the two methods in patients without LBD, they were not in patients with LBD. ^{123}I-FP-CIT SPECT has a high sensitivity in the diagnosis of LBD, while ^{123}I-MIBG cardiac scintigraphy may have a complementary role in the differential diagnosis of PD and other parkinsonisms [32].

15.1.3.2 Brain Perfusion SPECT

Hypoperfusion of the occipital lobe is one of the characteristics of PD [33, 34]. Nagamachi et al. [35] compared absolute regional cerebral blood flow (rCBF) values of ^{99m}Tc-HMPAO between 49 patients with PD and 28 patients with other neurodegenerative parkinsonisms. In the correlation analysis, reduced rCBF of occipital lobe correlated positively with reduced H/M ratio. With regard to the diagnostic ability, neither specificity nor accuracy improved by adding occipital lobe hypoperfusion to reduced cardiac MIBG uptake findings. However, the sensitivity improved by accounting for occipital hypoperfusion compared with reduced cardiac MIBG uptake findings alone. Adding analysis of occipital lobe rCBF to ^{123}I-MIBG cardiac scintigraphy is recommended.

15.1.3.3 Transcranial Sonography (TCS) of the Substantia Nigra (SN)

Becker et al. [36] first described SN hyperechogenicity as a typical sign for PD in 1995. About the pathophysiology of SN hyperechogenicity, Berg et al. [37] reported in a rat experimental model that iron may be the cause of the increased echogenicity of the SN. The same group also performed postmortem studies in 20 patients without extrapyramidal disorders during lifetime and showed that the echogenicity of the SN correlated with its iron content [38]. Another group also reported positive correlation between SN hyperechogenicity and iron and ferritin levels and negative correlation with neuromelanin content in postmortem brains from normal subjects [39]. In this regard, Berg et al. [40] also reported that SN echogenicity in 33 brains correlated with microglia activation, after correction for iron and neuromelanin content.

With regard to the correlation between SN hyperechogenicity and reduced cardiac MIBG uptake, Kajimoto et al.[41] reported that in 30 patients with PD whose midbrain was adequately displayed by TCS (46.2 % of the study group), no significant correlation was found between the area of SN echogenicity and the early H/M ratio. However, when the cutoff values were set at mean + 1 SD for TCS and mean − 2 SD for ^{123}I-MIBG cardiac scintigraphy, 29 patients (97 %) were identified as abnormal by the combination of TCS and ^{123}I-MIBG cardiac scintigraphy. Behnke et al. [42] analyzed the relation between the findings of TCS and ^{123}I-MIBG cardiac scintigraphy in 42 patients with PD. They demonstrated no correlation between the extent of SN hyperechogenicity (which was contralateral to the clinically more affected body side) and reduced cardiac MIBG uptake. The sensitivity of TCS in the diagnosis of PD was 79 %, compared with 81 % for ^{123}I-MIBG cardiac scintigraphy. On the other hand, the sensitivity of the combination of both was 95 %. Based on the above two studies, it seems that the combination of TCS of SN and ^{123}I-MIBG cardiac scintigraphy could improve the diagnosis of PD.

15.1.3.4 Microneurography

Shindo et al. [43] recorded muscle sympathetic nerve activity (MSNA) from the peroneal nerve in 14 patients with PD. No significant correlation was found between MSNA and H/M ratio and washout ratio of ^{123}I-MIBG cardiac scintigraphy.

15.1.3.5 Pupillary Sympathetic and Parasympathetic Sensitivity

Pupillary postganglionic autonomic dysfunction (pupillary sensitivity) is tested by assessing changes in pupil diameter using eye drops of parasympathomimetic [0.05 % pilocarpine hydrochloride (PL)] and sympathomimetic agents [0.02 % dipivefrine hydrochloride (DPE)]. Hori et al. [44] reported that in 40 patients with PD, pupillary supersensitivity to PL and DPE was found to be significantly greater in PD patients than in control subjects. Pupillary sensitivity to PL and DPE did not correlate with delayed H/M ratio. On the other hand, Yamashita et al. [45] reported in 40 patients with PD a weak and inverse correlation between delayed H/M ratio and pupillary sympathetic sensitivity to DPE. Further studies are required to explore this issue.

15.1.3.6 Apparent Diffusion Coefficient (ADC)

Kollensperger et al. [46] measured the apparent diffusion coefficient (ADC) in the putamina to differentiate PD from MSA parkinsonism (MSA-P). The sensitivity and specificity of ADC were higher than ^{123}I-MIBG cardiac scintigraphy. Their data suggest that ADC is superior to ^{123}I-MIBG cardiac scintigraphy in the differential diagnosis of PD versus MSA-P. However, the number of subjects in their study (nine with PD and nine with MSA-P) was small and more than half of the patients with MSA-P showed reduced cardiac MIBG uptake. Further studies are required to determine the diagnostic value of ADC.

15.1.4 Prodromal PD and Incidental Lewy Body Disease (iLBD)

15.1.4.1 Prodromal PD or DLB

The prodromal stage of PD is somewhat mentioned in non-motor features of this chapter. Again, detecting biomarkers of neurodegeneration that precede the apparent clinical symptoms of PD is important for early implementation of disease-modifying therapy. Braak et al. [47] proposed that prodromal pathological changes in PD first appear in the dorsal motor nuclei of the glossopharyngeal and vagal

nerves and the anterior olfactory nucleus. Autonomic failure (constipation and postural hypotension), depression/anxiety, rapid eye movement behavior disorder (RBD), hyposmia, and mild memory disorder are known to be the prodromal symptoms of PD or DLB

Sakakibara et al. [48] studied 254 patients with memory complaints and found reduced cardiac MIBG uptake in 13 of 44 amnestic MCI cases (30 %). None of the 13 patients had the core clinical features of DLB. They also reported that among 1600 outpatients, only five had constipation and reduced cardiac MIBG uptake without apparent motor disorders, indicating LBD, nor apparent neurologic diseases other than LBD. Some patients also showed RBD, hallucinations, occipital hypoperfusion by SPECT, and other prodromal biomarkers. These studies suggest that reduced cardiac MIBG uptake can be a biomarker for Lewy body pathology in patients with amnestic MCI and constipation. Other prodromal biomarkers are discussed elsewhere in this chapter.

15.1.4.2 Incidental Lewy Body Disease

Incidental Lewy body disease (iLBD) [49, 50] is a term used to describe the presence of Lewy bodies at routine postmortem examination in individuals free of any clinical signs of PD or dementia in life. Orimo et al. [51] compared cardiac tissues and paravertebral sympathetic ganglia of patients with iLBD and PD and demonstrated earlier accumulation of α-synuclein aggregates in the distal axons of the cardiac sympathetic nervous system compared with neuronal somata or neurites in the paravertebral sympathetic ganglia, a finding that heralds centripetal degeneration of the cardiac sympathetic nerve in LBD, such as iLBD and PD. These results suggest that the reduced cardiac MIBG uptake in iLBD subjects represents degeneration of the cardiac sympathetic nerves that might predate the damage of striatal presynaptic dopaminergic terminals.

At present, ^{123}I-MIBG cardiac scintigraphy is not recommended for patients free of parkinsonism or dementia, because it is mainly used to differentiate LBD from other parkinsonisms or dementia. No postmortem studies have directly investigated the relationship between the findings of antemortem ^{123}I-MIBG cardiac scintigraphy and cardiac sympathetic denervation in cases of iLBD. Reduced cardiac MIBG uptake was reported in an autopsy case of MSA with Lewy bodies in neurons of the dorsal vagal nucleus, locus coeruleus, and the basal nucleus of Meynert [52]. Reduced cardiac MIBG uptake was also reported in an autopsy case of CBD with Lewy bodies in the sympathetic ganglia [53]. Although these were not ideal iLBD cases, the presence of reduced cardiac MIBG uptake could be considered to represent incidental Lewy body pathology during the lifetime.

15.1.5 ^{123}I-MIBG Cardiac Scintigraphy Findings in Familial PD

To date, 22 familial PD mutations have been identified. It seems that cardiac MIBG uptake varies according to the type of mutations.

15.1.5.1 Autosomal-Dominant Forms of PD: PARK1, PARK4, and PARK8

Point mutations in the gene for *α-synuclein*, non-A4 component of amyloid precursor (*SNCA*), duplications and triplications of the entire gene, and mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene cause autosomal-dominant forms of PD.

PARK1

The point mutation E46K in *SNCA* gene (PARK1) [54] causes an aggressive form of PD with relatively early onset. Most cases have been identified in families with multiple affected individuals. Patients with E46K substitution in the *SNCA* gene both with and without autonomic symptoms showed complete lack of cardiac MIBG uptake in life and showed a complete absence of TH-immunoreactive nerve fibers in the cardiac tissues on postmortem examination [55] and normal ^{123}I-FP-CIT SPECT in a subject with asymptomatic carrier [56].

PARK4

***SNCA* Gene Duplication and Triplication and Iowa Kindred** *SNCA* gene duplication and triplication causes typical late-onset PD (PARK4) [57]. Incomplete penetrance of *SNCA* gene duplication may result in a negative family history. The H/M ratio of ^{123}I-MIBG cardiac scintigraphy is reported to be less than that of the normal control [58]. Orimo et al. [59] used immunohistochemistry to examine cardiac tissues from three patients with PD linked to *SNCA* duplication. They found severe degeneration of the cardiac sympathetic nerve and sparse α-synuclein aggregates in the epicardial nerve fascicles of all three patients, a finding similar to idiopathic PD. In addition, scattered swollen phosphorylated neurofilament-immunoreactive axons were especially found in two of three patients, suggesting possible impairment of axonal flow. These results suggest that cardiac sympathetic denervation is closely related to the presence of Lewy bodies in not only sporadic Lewy body disorders but also in familial PD with duplication of *SNCA* and that it is associated with reduced cardiac MIBG uptake [59].

SNCA gene triplication causes parkinsonism in a well-characterized family called the "Iowa kindred" [60]. The results of cardiac PET scanning using the sympathoneural imaging agent, 6-[^{18}F]fluorodopamine, in affected members of this kindred showed a clear loss of cardiac sympathetic innervation [61].

PARK8

Mutations in the *LRRK2* gene are a common cause of dominant PD (PARK8) [62, 63]. To date, six mutations are known to be pathogenic (N1437H, R1441C, R1441G, Y1699C, G2019S, and I2020T). Overall, *LRRK2* mutations account for 5–15 % of dominant familial PD cases [64] and 1–3 % of sporadic PD cases [65]. Clinically, *LRRK2*-associated PD is indistinguishable from sporadic typical PD. A proportion of *LRRK2* patients with G2019S and R1441G mutations present with lower cardiac MIBG uptake compared with the control and relatively higher uptake than PD patients, while the remaining of the patients with these mutations showed normal cardiac MIBG uptake [66, 67].

I2020T mutation is described to have a single-founder effect in Japanese patients. One patient with the mutation had normal cardiac MIBG uptake, while the remaining two patients had reduced cardiac MIBG uptake [68]. These results highlight the heterogeneity of this disease.

15.1.5.2 Autosomal-Recessive Forms of PD: PARK2, PARK6, and PARK7

PARK2

Homozygous or compound heterozygous mutations in *parkin* gene are the most common familial PD (PARK2) [69]. Up to half of familial PD cases with a disease onset under the age of 45 and a recessive form of inheritance are caused by *parkin* mutations. Similarly, *parkin* mutations underlie about 15 % of sporadic PD cases with disease onset before the age of 45. The clinical course of patients with *parkin* mutations is overall benign. Motor fluctuations and levodopa-induced dyskinesia are frequent, whereas marked cognitive or autonomic disturbances are rare. Except for one patient, the reported cases of *parkin* mutations had normal cardiac MIBG uptake [67, 70–72]. In one study, postmortem examination showed preservation of TH-immunoreactive nerve fibers in the epicardial nerve fascicle [71]. These results suggest that PARK2 is a distinct disease entity from PD.

PARK6 and PARK7

Homozygous or compound heterozygous mutations in *PINK1*(PARK6) [73] and homozygous or compound heterozygous mutations in *DJ-1* genes (PARK7) [74]

Table 15.1 Summary of cardiac MIBG uptake in familial PD

Locus	Inheritance	Gene	Cardiac MIBG uptake	Lewy bodies
PARK1	AD	SNCA mutation	Reduced	+
PARK2	AR	Parkin	Normal	−
PARK4	AD	SNCA multiplication	Reduced	+
PARK6	AR	PINK1	Reduced or normal	+
PARK7	AR	DJ-1	Reduced or normal	Not published
PARK8	AD	LRRK2	Reduced or normal	+ or −

Cardiac MIBG uptake results may vary due to the relatively small number of subjects
AD autosomal dominant, *AR* autosomal recessive

are less common, accounting for only 1–8 % and 1–2 % of early-onset and sporadic cases, respectively [75–77]. The phenotype associated with *PINK1* and *DJ-1* mutations is basically indistinguishable from that associated with mutation in *parkin*. One previous study reported preservation of cardiac MIGB uptake in one of two patients with *DJ-1* mutations and in one of two brothers with *PINK1* mutations [67] (Table 15.1).

15.2 Gaucher Disease (GD)

Mutations in the gene encoding the lysosomal enzyme glucocerebrosidase are associated with GD, the most common autosomal-recessive lysosomal storage disease. It is now clear that a subset of patients with GD develop parkinsonism. Postmortem brain tissue examination of patients with GD associated with parkinsonism has consistently shown classic PD pathology. Itokawa et al. [78] reported a patient with type I GD who had near-normal cardiac MIBG uptake, with partially defective cardiac MIBG uptake considered to be due to old myocardial infarction confirmed on Tc-99 m SPECT. On the other hand, Lebouvier et al. [79] reported a case with type I GD and abnormal cardiac MIBG uptake, with reduced early and delayed H/M ratios. Another study that sequenced the entire coding exons and exon/intron boundaries reported that 27 of 144 families (18.8 %) of index patients with Japanese familial PD were heterozygous for known GD mutations and presented with reduced cardiac MIBG uptake [80].

15.3 ^{123}I-MIBG Cardiac Scintigraphy Findings in Other Lewy Body Diseases

Cardiac sympathetic denervation has been reported to develop in patients with other Lewy body diseases, such as DLB and pure autonomic failure (PAF). In this regard, ^{123}I-MIBG cardiac scintigraphy can be useful for differentiating Lewy body

diseases from other parkinsonian syndromes and dementias. Furthermore, RBD is observed in α-synucleinopathy, especially in relation to Lewy body disease.

For this reason, we discuss PAF and RBD in this chapter, while DLB is described in Chap. 16.

15.3.1 Pure Autonomic Failure

PAF is considered a rare clinical manifestation of Lewy body diseases and is characterized by autonomic failure without any sign of parkinsonism. Previous studies reported reduced cardiac MIBG uptake in patients with PAF [81, 82].

15.3.2 Rapid Eye Movement (REM) Sleep Behavior Disorder (RBD)

RBD is characterized by dream-enactment behavior resulting from muscle activity during REM sleep. The development of RBD may be one of the first manifestations of α-synucleinopathy including PD, DLB, and MSA. While the exact mechanism of RBD is still unclear, it is speculated that disturbances in regions of the brainstem that control REM sleep play a pathological role. A few studies reported significantly reduced cardiac MIBG uptake in patients with idiopathic RBD similar to PD with and without RBD [83, 84]. The results suggest that most of RBD indicate Lewy body diseases. Furthermore, Koyama et al. [85] reported the presence of hyposmia, impaired facial expression recognition, and reduced cardiac MIBG uptake in one RBD patient free of parkinsonism. Impaired facial expression recognition may reflect the dysfunction of the amygdala. In RBD patients, neurodegeneration may occur more diffusively than the brainstem alone.

15.4 ^{123}I-MIBG Cardiac Scintigraphy Findings in Other Neurodegenerative Parkinsonism and Related Disorders

The clinical feature of atypical neurodegenerative parkinsonism, such as MSA, PSP, and CBD, resembles those of PD, especially in the early stages. Despite the presence of clinical consensus criteria for PD and other parkinsonisms, accurate diagnosis of these disorders remains a challenge for neurologists. ^{123}I-MIBG cardiac scintigraphy is a useful imaging tool for differentiating PD from other parkinsonisms.

15.4.1 Neurodegenerative Parkinsonism

15.4.1.1 Multiple System Atrophy

MSA is a late-onset neurodegenerative disease characterized by progressive autonomic failure, parkinsonism, and cerebellar and pyramidal tract symptoms. Neurodegeneration and the formation of glial cytoplasmic inclusions immunostained with α-synuclein are the hallmark of the disease. ^{123}I-MIBG cardiac scintigraphy is significantly higher in MSA than PD or within the normal range [86]. However, cardiac MIBG uptake is not necessarily preserved in patients with MSA, and approximately 30 % of patients with MSA have reduced cardiac MIBG uptake, and these levels do not correlate with disease duration or severity [87]. The mean value of the H/M ratio in striatonigral degeneration (SND), a subtype of MSA, with OH is lower than SND without OH [86].

It is known that central or preganglionic lesions, such as those in the cardiovascular autonomic center of the ventrolateral medulla or intermediolateral cell column of the spinal cord, contribute to the dysautonomia of MSA. Cohen et al. [88] hypothesized that in MSA, preganglionic lesions cause dysfunction of the postganglionic sympathetic fibers through the transsynaptic effects. Postmortem examination of a MSA patient with a slightly reduced cardiac MIBG uptake demonstrated no obvious neuronal loss in the peripheral sympathetic ganglia. Furthermore, TH-immunoreactive epicardial nerve fibers in the anterior wall of the left ventricle of the heart were preserved in patients with MSA [5]. Based on the above findings, it was proposed that postganglionic sympathetic nerves are not involved in MSA; rather, the central and preganglionic lesions account for the slightly reduced cardiac MIBG uptake in MSA [5]. The same group also reported mild or moderate decrease in the number of TH-immunoreactive epicardial nerve fibers of six of 15 patients with MSA, of whom four showed a decrease in TH immunoreactivity in the neuronal somata in the sympathetic ganglia. These pathological changes supported the hypothesis that preganglionic lesions cause dysfunction of the postganglionic sympathetic fibers through the transsynaptic effects in MSA.

15.4.1.2 Progressive Supranuclear Palsy

PSP is characterized by parkinsonisms, gaze palsy, pseudobulbar palsy, dysarthria, axial rigidity, frontal lobe dysfunction, and dementia and thus partially resembles PD. However, the clinical spectrum of PSP is known to be wider than originally described. The typical pathology is abnormal tau deposition that affects neurons and glial cells represented by tufted astrocytes. The mean value of the H/M ratio in patients with PSP is significantly higher than in PD, but the majority of patients have normal to slightly reduced cardiac MIBG uptake compared with normal control subjects [3, 83, 86, 89, 90]. Orimo et al. [6] reported that

TH-immunoreactive epicardial nerve fibers were well preserved in five pathologically confirmed patients with PSP.

15.4.1.3 Corticobasal Degeneration

CBD is characterized by asymmetric symptoms including rigidity and tremor, thus partially resembling PD. However, some patients with CBD present with clinical symptoms that do not resemble those of PD, such as dystonia, myoclonus, apraxia, cortical sensory deficits, and alien limb phenomena. In addition, some suffer from various cognitive and language deficits. CBD is pathologically characterized by abnormal tau deposition in neurons and glial cells, including astrocytic plaques. Only a few studies examined ^{123}I-MIBG cardiac scintigraphy in patients with CBD. The H/M ratio of CBD is not different from that of normal control subjects [8, 89, 90].

Another case report of postmortem histopathological examination of a CBD patient demonstrated well-preserved TH-immunoreactive epicardial nerve fibers, similar to the control subjects [8].

15.4.2 ^{123}I-MIBG Cardiac Scintigraphy Findings in Other Related Disorders

15.4.2.1 Vascular Parkinsonism

Orimo et al. [21] examined ^{123}I-MIBG cardiac scintigraphy in 11 patients with vascular parkinsonism and found it was not significantly different from normal and disease control subjects. Furthermore, the mean H/M ratio of the PD patients was significantly lower than patients with vascular parkinsonism. The same findings were confirmed in six patients [12] and 19 patients [91] with vascular parkinsonism.

15.4.2.2 Essential Tremor (ET)

ET is characterized by postural tremor affecting the hands, head, and other parts of the body. By definition, patients with ET should not have other clinical signs of parkinsonism. In some cases, it is difficult to differentiate ET from PD, especially in the early stages of the disease.

Orimo et al. [21] indicated that cardiac MIBG uptake measured in five patients with ET was comparable to that in normal and disease control subjects. Another group [92] also examined ^{123}I-MIBG cardiac scintigraphy in 20 patients with ET and reported significantly higher mean H/M ratio in patients with ET than in TDT or early PD [rated at H-Y of I and II with recent diagnosis (symptom duration 2 years)]. However, the mean H/M ratio of the ET group was not significantly

different from that of the control group. In the same study [92], the H/M ratio was higher in patients with ET than two standard deviations above the range of the ratio in patients with early PD or TDT. Another study of 16 patients with rest and postural tremor (mixed tremor), together with mild extrapyramidal features and abnormal striatal ^{123}I-FP-CIT SPECT, reported reduced cardiac MIBG uptake in delayed images in half of the patients [93]. The results suggest that the combined use of both ^{123}I-FP-CIT SPECT and ^{123}I-MIBG cardiac scintigraphy in patients with mixed tremors and extrapyramidal features can help distinguish patients with ET from those with PD and parkinsonism.

15.4.2.3 Drug-Induced Parkinsonism

Drug-induced parkinsonism (DIP) is a heterogeneous clinical syndrome, but almost all patients with DIP have normal cardiac MIBG uptake. All patients show improvement or complete resolution of parkinsonism after withdrawal of the offending drug. However, some DIP patients with significantly reduced cardiac MIBG uptake develop persistent and worsening parkinsonism or PD after discontinuation of the offending drug. ^{123}I-MIBG cardiac scintigraphy may be a useful tool for detecting DIP unrelated to PD and to identify DIP patients with subclinical PD [94–96] (Fig. 15.1).

15.4.2.4 Others

Spinocerebellar Ataxia Type 2

SCA2 is an autosomal-dominant neurodegenerative disorder associated with expanded CAG trinucleotide repeat in the *ATXN2* gene. It is clinically characterized by gait and limb ataxia, dysarthria, supranuclear ophthalmoplegia, peripheral neuropathy, sleep disorders, postural tremor, chorea, myoclonus, parkinsonism, pyramidal signs, and dementia. Most cases exhibit the cerebellar phenotype, though few present with parkinsonism as the predominant phenotype instead of cerebellar ataxia. The levodopa-responsive parkinsonism is considered a rare clinical presentation in SCA2.

Koyano et al. [97] found reduced cardiac MIBG uptake in SCA2 parkinsonian phenotype with homozygous SCA2 expansion (36/38). Another group [98] reported the postmortem findings of a SCA2 patient with parkinsonian phenotype and reduced cardiac MIBG uptake. They found atrophy of the olivopontocerebellar system and substantia nigra. Both findings were compatible with SCA2. In addition, they also found Lewy body pathology in the SN, the locus coeruleus, dorsal motor nuclei of vagus, and cardiac sympathetic nerves. De Rosa et al. [99] performed ^{123}I-MIBG cardiac scintigraphy in nine patients with SCA2 free of parkinsonism. The early and delayed H/M ratios were significantly lower in patients with SCA2 than the control subjects, though less marked than in PD patients. Another study reported

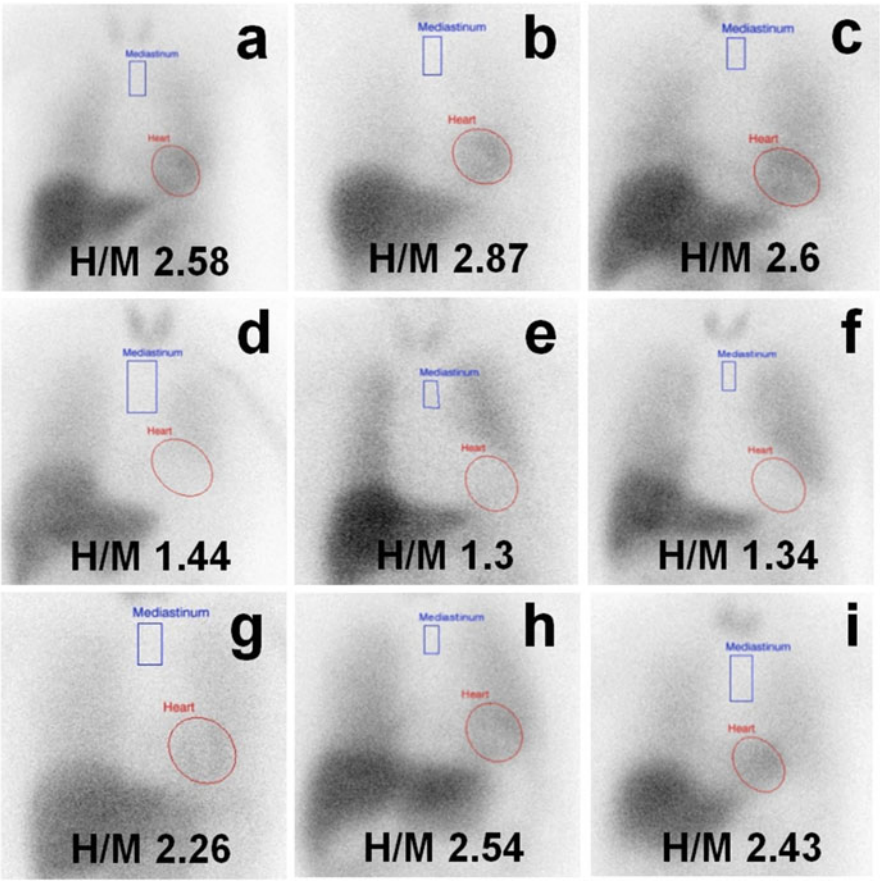

Fig. 15.1 ^{123}I-MIBG cardiac scintigraphy in representative cases of Parkinson's disease and related disorders. Cardiac MIBG uptake is lower than normal control in patients with Lewy body diseases such as PD, DLB, and PAF, but not in patients with other related disorders. (**a**) control, (**b**) vascular parkinsonism, (**c**) essential tremor, (**d**) Parkinson's disease, (**e**) dementia with Lewy bodies, (**f**) pure autonomic failure, (**g**) multiple system atrophy-parkinsonism type, (**h**) progressive supra nuclear palsy, (**i**) corticobasal degeneration

the results of postmortem examination of a Japanese SCA2 patient with parkinsonism [100]. In addition to the classic SCA2 neuropathological changes, Lewy bodies and Lewy neurites were identified in brainstem nuclei. Furthermore, genetic analysis demonstrated the presence of shorter abnormal expansion of CAG repeats (less than 39). In comparison, the authors did not find Lewy body pathology in two SCA2 cases free of parkinsonism. The study provided neuropathological evidence for a correlation between Lewy body pathology and parkinsonism of SCA2.

Since ^{123}I-MIBG cardiac scintigraphy demonstrated impairment of cardiac sympathetic function in SCA2, with and without parkinsonism, Lewy body pathology does not seem to explain all the findings of ^{123}I-MIBG cardiac scintigraphy.

Machado-Joseph Disease (MJD)

MJD or SCA3 is an autosomal-dominant neurodegenerative disorder associated with expanded CAG trinucleotide repeat in ATXN3 gene. It is characterized by ataxia, ophthalmoplegia, peripheral neuropathy, pyramidal dysfunction, and movement disorders. Only a few MJD patients develop parkinsonism. Although MJD is a relatively rare disease, it is the most frequent spinocerebellar ataxia with a worldwide distribution.

In a study of 19 patients with MJD who underwent ^{123}I-MIBG cardiac scintigraphy, the delayed H/M ratio was significantly lower in the patients than the control subjects, whereas the early H/M ratio was comparable between the two groups [101]. Six of the 19 patients showed abnormal sympathetic skin responses (SSR). The delayed H/M ratio was significantly lower in the latter group than in patients with normal SSR. These results suggest the presence of cardiac sympathetic dysfunction in MJD, as detected by ^{123}I-MIBG cardiac scintigraphy, which appears to correlate with sudomotor sympathetic dysfunction.

15.5 ^{123}I-MIBG Cardiac Scintigraphy Findings in Comorbidities

Finally, we describe the comorbidities associated with reduced cardiac MIBG uptake for careful interpretation of ^{123}I-MIBG cardiac scintigraphy findings.

15.5.1 Congestive Heart Failure (CHF), Cardiomyopathy, and Ischemic Heart Disease

Kline et al. [102] were the first investigators to use ^{123}I-MIBG cardiac scintigraphy and explore its utility in quantitative measurement of myocardial catecholamine content. Activation of the sympathetic nervous system is one of the main pathophysiological abnormalities associated with heart failure. The H/M ratio correlates significantly with myocardial noradrenaline concentration and with left ventricular ejection fraction in patients with idiopathic dilated cardiomyopathy [103]. Reduced cardiac MIBG uptake and high washout, especially reduced delayed H/M ratio, have been described in CHF [104], and the extent of such reduction correlated with the severity of CHF and response of treatment, prognosis, and mortality.

The failing heart requires sympathetic stimulation to increase cardiac performance, but paradoxically shows depletion of noradrenaline [105]. Recent studies have suggested that it is due to decreased noradrenaline reuptake [104, 106] and synthesis [107]. In this regard, Kanazawa et al. [108] demonstrated neurotransmitter switching from predominantly catecholaminergic to cholinergic or cholinergic

transdifferentiation of the cardiac sympathetic nervous system in patients with CHF, as an adaptive response. These results may explain the reduced cardiac MIBG uptake in patients with CHF.

With regard to ischemic heart disease, cardiac MIBG washout is globally increased after myocardial infarction within 14 days of early reperfusion therapy, even in patients with preserved left ventricular function [109]. Podio et al. [110] reported no changes in cardiac MIBG uptake from 1 week after infarction to after 30 months of follow-up. Enhanced washout may reflect increased sympathetic nerve tone and represent increased catecholamine turnover or impaired reuptake in the subacute phase of myocardial infarction [109].

15.5.2 Diabetes Mellitus (DM)

Evaluation of cardiac MIBG uptake in patients with DM began in 1988. The first report of use of ^{123}I-MIBG cardiac scintigraphy was in patients with diabetic autonomic neuropathy with sudden cardiac death presumably due to QTc interval prolongation [111], though the usefulness of imaging of the sympathetic nervous system in DM is unclear [112]. One study that followed 144 patients with DM and no other cardiac disease for 7 years after ^{123}I-MIBG cardiac scintigraphy showed that reduced cardiac MIBG uptake was associated with increased risk of cardiac mortality [113]. Coronary arterial and arteriolar narrowing is common in patients with diabetic autonomic neuropathy; therefore, reduced cardiac MIBG uptake may reflect a combination of denervation and decreased delivery of the trace to the sympathetic nerves due to coronary hypoperfusion [114]. However, reduced cardiac MIBG uptake can also occur in patients with DM without any evidence of coronary heart disease or autonomic neuropathy [115]. In addition, enhanced washout rate is independently associated with the incidence of major adverse cardiac and cerebrovascular events in type 2 diabetic patients free of structural heart disease [116].

Experimental studies in a rat model of DM showed a high cardiac MIBG washout rate, but unlike patients with heart failure. This was not due to systemic sympathetic hyperactivity. Rather, it was likely due to dysfunction of the reuptake and/or pooling mechanism since the plasma and myocardial noradrenaline concentrations in diabetic rats were significantly lower than those in nondiabetic rats [117].

Cardiac MIBG uptake is comparatively preserved in diabetic patients without heart failure [118] or even improved when blood sugar level is under control [119]. Thus, the presence of DM alone does not always cause reduced cardiac MIBG uptake. Recently Slaets et al. [120] described no significant difference in H/M ratio among DLB patients with DM, arterial hypertension, hyperlipidemia, ischemic heart disease, heart failure, and pharmacological treatment and those without clinically observable conditions. Furthermore, Otsuka et al. [121] examined differences in H/M ratio in patients with Alzheimer disease (AD) or amnestic MCI (aMCI) with or without DM. In their study, ^{123}I-MIBG cardiac scintigraphy

was performed in both the AD or aMCI without DM (AD/DM(−), $n = 248$) and AD or aMCI with DM (AD/DM(+), $n = 46$) and in age-matched control subjects (C, $n = 28$). The early/delayed H/M ratios in AD/DM(−), AD/DM(+), and C were $2.39 \pm 0.38/2.37 \pm 0.44$, $2.37 \pm 0.3/2.31 \pm 0.34$, and $2.43 \pm 0.24/2.44 \pm 0.26$, respectively, with no significant difference among the three groups. Five of 46 patients of the (AD/DM(+)) group showed slightly low H/M ratios but none of these patients showed no accumulation of MIBG in the planar image as typically seen in PD patients. These results suggest that DM does not always have a significant effect on cardiac MIBG uptake, particularly DM without diabetic autonomic neuropathy. Further studies are needed to confirm the cardiac MIBG uptake in DM patients with or without autonomic neuropathy.

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