^{123}I-metaiodobenzylguanidine myocardial scintigraphy in Parkinson's disease

S Orimo, E Ozawa, S Nakade, T Sugimoto, H Mizusawa

Abstract

***Objectives*—^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy is clinically used to estimate local myocardial sympathetic nerve damage in some forms of heart disease, autonomic nerve disturbance in diabetic neuropathy, and disturbance of the autonomic nervous system in neurodegenerative disease. In the present study, examinations were performed to clarify (1) the proportion of cardiac sympathetic nerve disturbance in Parkinson's disease, (2) the usefulness of ^{123}I-MIBG myocardial scintigraphy to detect sympathetic nerve disturbances compared with autonomic function tests, (3) cardiac function in patients who have a decreased MIBG uptake in ^{123}I-MIBG myocardial scintigraphy, (4) the usefulness of ^{123}I-MIBG myocardial scintigraphy to differentiate Parkinson's disease from the other neurological diseases mimicking it.**

***Methods*—^{123}I-MIBG myocardial scintigraphy was performed, together with autonomic function tests and cardiac examinations in 46 patients with Parkinson's disease and 25 patients with vascular parkinsonism, essential tremor, or multiple system atrophy.**

***Results*—In an anterior image study, the average count per pixel in heart to mediastinum (H/M) ratio decreased in 80% of the patients with Parkinson's disease in the early phase and 84% in the late phase. The mean H/M ratio in Parkinson's disease was significantly lower than that in controls and the other diseases. The H/M ratio tended to decrease with the disease progression. In almost half of the patients in Hoehn and Yahr stage I, the H/M ratio was already decreased. The sympathetic skin response in upper and lower limbs, head up tilt test, and coefficient of variation of R-R interval were abnormal in 17%, 31%, 30%, and 17% of the patients, respectively. All the patients with abnormal autonomic functions were in Hoehn and Yahr stage III, IV, or V. Echocardiography showed normal left ventricular function. Twenty four hour Holter electrocardiography detected no serious arrhythmias except for one patient with non-sustained ventricular tachycardia.**

***Conclusion*—^{123}I-MIBG myocardial scintigraphy might detect early disturbances of the sympathetic nervous system in Parkinson's disease and might give useful diagnostic information to differentiate vascular parkinsonism, essential tremor, and multiple system atrophy from Parkinson's disease.**

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Department of Neurology
S Orimo
E Ozawa

Department of Radiology
S Nakade

Kanto Central Hospital, 6- 25–1 Kami-Yoga, Setagaya-ku, Tokyo 158, Japan
T Sugimoto

Department of Neurology, Tokyo Medical and Dental University, 1–5–45, Yushima, Bunkyo-ku, Tokyo 113, Japan
H Mizusawa

Correspondence to:
Dr S Orimo, Department of Neurology, Kanto Central Hospital, 6- 25–1 Kami-Yoga, Setagaya-ku, Tokyo 158, Japan. Telephone 0081 3 3429 1171; fax 0081 3 3429 1236.

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Patients with idiopathic Parkinson's disease may have several symptoms of autonomic dysfunction including constipation, anhidrosis, sialorrhoea, seborrhoea, postural hypotension, and urinary disturbances. The cause of autonomic dysfunction in Parkinson's disease may be due to the pathological changes in the centres of autonomic regulation. Lewy bodies, sometimes associated with neuronal loss, can be found in the sympathetic as well as the parasympathetic nervous system—namely, in the hypothalamus,[1] the dorsal vagal motor nucleus,[2] the Edinger-Westphal nucleus,[3] the intermediolateral spinal column,[4] and the sympathetic ganglia.[5] Clinically various autonomic function tests have been carried out in patients with Parkinson's disease. However the prevalence and severity of autonomic dysfunction vary, depending on the researchers. Magalhães *et al* reported that constipation, orthostatic hypotension, and bladder dysfunction were found in about one third of the patients with pathologically verified disease.[6] On the contrary, van Dijk *et al* reported that no evidence of autonomic dysfunction was found in unmedicated patients and that mild autonomic dysfunctions were found in advanced or medicated patients.[7] Now autonomic dysfunction in Parkinson's disease is considered not to be rare, and may become apparent with progression of the disease or medication.[8]

Metaiodobenzylguanidine (MIBG) is a physiological analogue of noradrenaline (norepinephrine)[9] and is actively transported into noradrenaline granules of sympathetic nerve terminals by the noradrenaline transporter. ^{123}I-MIBG myocardial scintigraphy can be performed very safely[10] and is clinically used to estimate local myocardial sympathetic nerve damage in some heart diseases,[11–17] autonomic nerve disturbance in diabetic neuropathy,[18] disturbance of the autonomic nervous system in neurodegenerative diseases,[19–25] pure autonomic failure,[26] and familial amyloidotic polyneuropathy.[27]

In the present study, we performed ^{123}I-MIBG myocardial scintigraphy together with autonomic function tests and cardiac examinations in patients with Parkinson's disease, vascular parkinsonism, essential tremor, and

multiple system atrophy to clarify (1) the proportion of cardiac sympathetic nerve disturbance in Parkinson's disease, (2) the usefulness of ^{123}I-MIBG myocardial scintigraphy to detect sympathetic nerve disturbance compared with autonomic function tests in Parkinson's disease, (3) cardiac functions in the patients with Parkinson's disease who have a decreased MIBG uptake in ^{123}I-MIBG myocardial scintigraphy, (4) the usefulness of ^{123}I-MIBG myocardial scintigraphy to differentiate Parkinson's disease from the other neurological diseases that mimic Parkinson's disease.

Material and methods

PATIENTS

We examined 46 patients with definite Parkinson's disease according to the criteria of the United Kingdom Brain Bank.[28] We evaluated clinical severity using Hoehn and Yahr stage and the rating scale by described by Webster.[29] Patients with the other neurological diseases —13 patients with vascular parkinsonism, five patients with essential tremor, and seven patients with multiple system atrophy according to the criteria described eleswhere[30] and 10 age matched disease controls (for example, patients with headache, dizziness, or vertigo) were also examined. All the patients and disease controls had neither diabetes mellitus nor heart diseases, including ischaemic heart disease, cardiomyopathy, hypertensive heart disease, and congestive heart disease. Also, they were not receiving drugs that may have interfered with MIBG uptake by sympathetic nerve terminals, such as tricyclic antidepressant drugs, reserpine, and clonidine. If a patient showed detectable defects by thallium scintigraphy, the patient was excluded from the evaluation. The ethics committee of the Kanto Central Hospital approved these procedures. Informed consent was obtained from all the patients before enrolment.

METHODS

^{123}I-MIBG myocardial scintigraphy

^{123}I-MIBG myocardial scintigraphy was performed simultaneously with ^{201}thallium chloride (TlCl) myocardial scintigraphy. After being in the supine position for 20 minutes, 111mBq ^{123}I-MIBG (Daiichi Radioisotope Laboratories Co, Tokyo, Japan) and the same amount of ^{201}Tl (as chloride; Daiichi Radioisotope Laboratories Co, Tokyo, Japan) were injected intravenously. A single photon emission computed tomography (SPECT) and a planar image of the chest were obtained using a double headed gamma camera (PRISM-2000, Shimadzu Co, Japan) after 20 minutes (early phase) and 3 hours (late phase). Photopeak energy was centred at 159 keV (^{123}I-MIBG) and 70 keV (^{201}Tl) with a 10% window. For the anterior planar image, the data acquisition matrix was 512×512, and a present time of 5 minutes was used for image acquisition. Relative organ uptake of ^{123}I-MIBG was determined by setting the region of interest (ROI) on the anterior view.[31] Regions of interest in the heart were drawn where myocardial uptake of ^{201}Tl was seen on the same view. A circular ROI was also set on the upper mediastinum. Using average counts per pixel in heart (H) and mediastinum (M), the ratio H/M was calculated. Background subtraction was not performed from any ROI count. The normal value of the H/M ratio in this hospital, obtained in 10 healthy volunteers (seven men and three women, mean age 58.8 (SD 13.6) (range 38–73) years) is 2.26 (0.16) (1.94–2.58) (early phase) and 2.30 (SD 0.22) (range 1.86–2.74) (late phase).

Head up tilt test

A head up tilt test was performed using a tilt table. After being in the supine position for 10 minutes, each patient was lifted in the head up position, at least 60°, using a tilt table. When a reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg occurred within 3 minutes after the upright position, the patient was diagnosed as having orthostatic hypotension.[30]

Sympathetic skin response

The sympathetic skin response was performed according to the method described by Yokota *et al*.[32] Briefly, standard EMG disc electrodes were covered with conducting paste and attached to the palm as well as to the sole bilaterally. The skin temperature in all patients was kept above 31°C. Recordings were made on Neuropac Four (Nihon Kohden Co, Japan). Stimuli consisting of single square pulses of 200 ms duration, 20 mA intensity, were applied to the supraorbital nerves bilaterally on the forehead. More than 5 stimuli were administered at irregular intervals. Peak to peak amplitude of each response was measured. The following responses were considered to be abnormal as described previously[33]; (1) absence of response, (2) absence of response at one site when responses at the other sites were continuously recorded. When the amplitude of the responses was <1000 μV for the palm or <300 μV for the sole, we considered it as alow response.

Coefficient of variation in R-R interval ($CV_{R\text{-}R}$)

Electrocardiography was recorded by Cardiofax A (Nihon Kohden Co, Japan). After being in the supine position for 10 minutes, the ECG of each patient was recorded for 3 minutes. The $CV_{R\text{-}R}$ was calculated as 1 SD of R-R interval/mean value of R-R interval) ×100 (%). The age matched normal value in this hospital, obtained from 20 healthy volunteers (10 men and 10 women, mean age 66.8 (SD11.6) (range 42–84) years of age) is 2.84 (SD 0.92) (range 1.00–4.67)%.

Cardiac examinations

Echocardiography was recorded at rest to evaluate left ventricular function and valvular diseases. Twenty four hour Holter ECG was also recorded.

STATISTICAL ANALYSIS

The results are expressed as means (SD). Differences of the variances and averages were tested by Student's *t* test and one way analysis

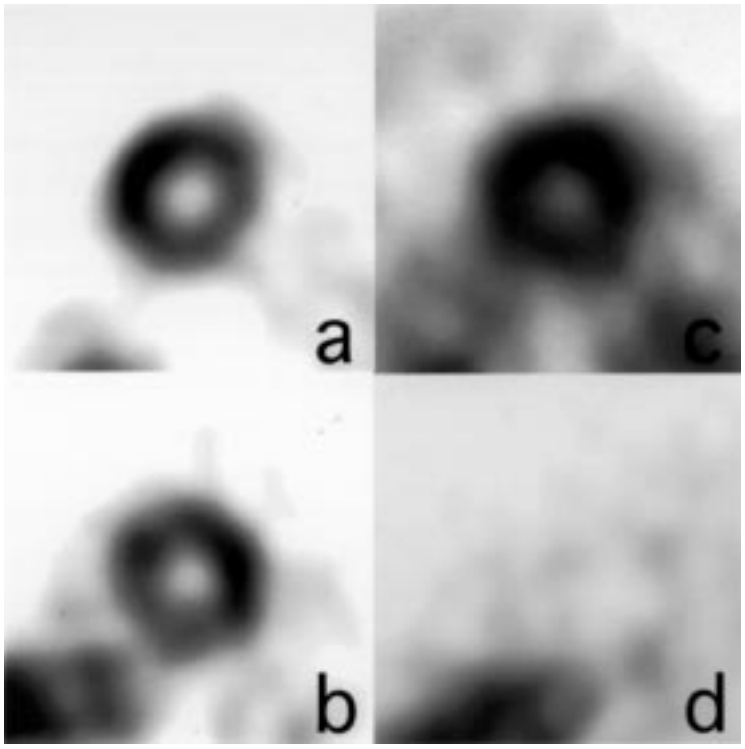

Figure 1 Short axis views of SPECT of [201]TlCl and [123]I-MIBG myocardial scintigraphy in a healthy control (a, b) and a 57 year old woman with Parkinson's disease (Hoehn and Yahr stage I) (c, d).

of variance (ANOVA). Correlations between the two groups were assessed by Pearson's correlation test. p Values <0.05 was considered to indicate statistical significance.

Results

[201]TL MYOCARDIAL SCINTIGRAPHY

One patient with Parkinson's disease and two patients with vascular parkinsonism disclosed an abnormal defect of the inferior or apex wall in the early phase. The rest of the patients examined were within normal limits.

CLINICAL CHARACTERISTICS

We excluded one patient with Parkinson's disease and two patients with vascular parkinsonism with abnormal Tl scintigraphy and evaluated 45 patients with Parkinson's disease (17 men and 28 women, mean age 68.8 (SD 10.2) (range 41–84) years). The mean duration of illness was 4.3 (3.9) (0.25–19) years and Hoehn and Yahr stage was I in eight patients, II in three, III in 21, IV in nine, and V in four. Twenty five patients were given antiparkinsonian drugs at the time of examination: 432 (138)(200–600) mg levodopa/carbidopa in 14 patients, 467 (103) (400–600) mg levodopa in six, 4.5 (0.9) (4–6) mg trihexyphenidyl in 15, 115 (24)(100–150) mg amantadine in 13, 435 (339) (50–1000) μg pergolide in 13, 5.0 (3.5)(2.5–7.5) mg bromocriptine in two, and 500 (245) (200–800) mg l-threo-DOPS in five. The patients with other neurological diseases were as follows. Eleven patients had vascular parkinsonism (nine men and two women, mean age 72.8 (6.2) (62–83) years). Mean duration of illness was 2.8 (3.0) (0.25–5) years. Two patients were given 100 mg amantadine.

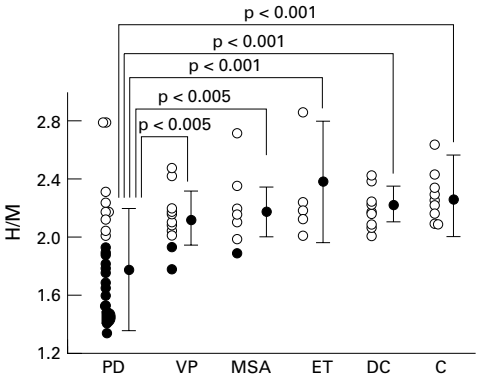

Figure 2 The comparison of the H/M ratio (early phase) among diseases and controls. Open and closed circles show normal and abnormal H/M ratios, respectively. PD=Parkinson's disease, VP=vascular parkinsonism, MSA=multiple system atrophy, ET=essential tremor, DC=disease controls, C=healthy controls.

Five patients had essential tremor (one man and four women, average age 68.4 (9.9) (52–77) years. Mean duration of illness was 9.4 (6.8) (3–20) years. Seven patients had multiple system atrophy (five men and two women, mean age 54.3 (7.0) (42–58) years). Mean duration of illness was 1.9 (1.8) (0.5–4.4) years. Two patients were given 300 mg levodopa/carbidopa.

[123]I-MIBG MYOCARDIAL SCINTIGRAPHY

In all the patients on whom [123]I-MIBG myocardial scintigraphy was performed, no adverse reactions were found. Figure 1 shows short axis views of SPECT of [201]Tl and [123]I-MIBG myocardial scintigraphy in a healthy control and a 57 year old woman with Parkinson's disease (Hoehn and Yahr stage I). The myocardial uptake of both Tl (a) and MIBG (b) is normal in a healthy control. Although the myocardial uptake of Tl is normal (c), no uptake of MIBG (d) is seen in a patient with Parkinson's disease.

In the patients with Parkinson's disease, the H/M ratio decreased in 36 patients (80%) in the early phase and in 38 patients (84%) in the late phase. The mean H/M ratio in the early and late phase was 1.71 (0.36) and 1.53 (0.36) in patients with Parkinson's disease, 2.26 (0.16), 2.30 (0.22) in normal controls, and 2.20 (0.16) and 2.16 (0.22) in disease controls. The H/M ratio in the early/late phases was significantly less than in normal ($p<0.001$/$p<0.001$) and disease controls ($p<0.001$/$p<0.001$)(fig 2). The H/M ratio in the early and late phase tended to decrease with the progression of Hoehn and Yahr stage and the H/M ratio in the early/late stage in Hoehn and Yahr stage I was significantly high compared with stages III, IV, and V. In the early stage of Parkinson's disease (Hoehn and Yahr stages I and II), the H/M ratio had already decreased in six patients (55%) in the early phase and eight patients (73%) in the late phase (fig 3). The H/M ratio in the early/late phase was correlated with the Parkinson's disease rating scale ($p<0.05$, $r=-0.37$/$p<0.05$, $r=-0.35$). The duration of illness was correlated with the H/M ratio in the early phase ($p<0.05$, $r=-0.31$) but not with that in the late phase ($p=0.0509$).

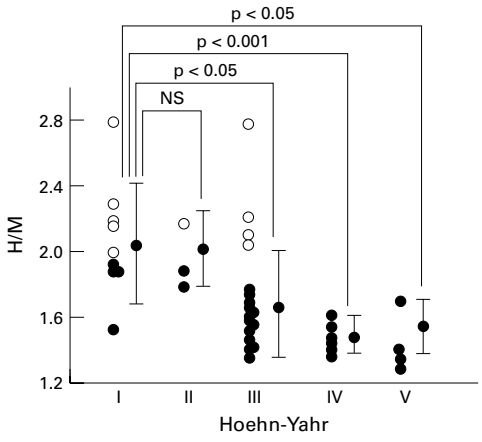

Figure 3 Relation between the H/M ratio (early phase) and Hoehn and Yahr stage. Open and closed circles show normal and abnormal H/M ratios, respectively.

The mean H/M ratio in the early/late phase of the patients treated with antiparkinsonian drugs (1.56 (0.19)/1.39 (0.19)) was significantly less ($p<0.005/p<0.005$) than that in the patients not treated with antiparkinsonian drugs (1.88 (0.44)/1.69 (0.43)). But the mean Hoehn and Yahr stage (3.54 (0.98)) in the first was significantly advanced ($p<0.01$) compared with the second (2.29 (1.00)). Therefore we analysed stage II, III, and IV treated with (19 patients) or without antiparkinsonian drugs (14 patients) to adjust the Hoehn and Yahr stage between the two groups. There was no statistical difference in Hoehn and Yahr stage, Parkinson's disease rating scale, and the H/M ratio (early/late) between the patients with and without antiparkinsonian drugs.

AUTONOMIC FUNCTION TESTS

A head up tilt test was performed on 43 patients. Thirteen patients (30%) had orthostatic hypotension. All the patients with orthostatic hypotension were in Hoehn and Yahr stage III, IV, and V. Three out of 13 patients had no medication. Levodopa/carbidopa or levodopa were given in seven patients. We compared the H/M ratio and clinical characteristics of the 13 patients with orthostatic hypotension with 30 patients without orthostatic hypotension. Hoehn and Yahr stage and Parkinson's disease rating scale were significantly higher in the patients with orthostatic hypotension and the mean H/M ratio of early/late phase in the patients with orthostatic hypotension (1.51 (0.13)/1.33 (0.12)) were significantly ($p<0.05/p<0.05$) lower compared with those in the patients without orthostatic hypotension (1.80 (0.39)/1.61 (0.39)).

Sympathetic skin response was performed in 36 patients. This was abnormal in the upper and lower limbs in six (17%) and 11 (31%) patients and there was a low response in four (11%) and one (3%), respectively. We compared 12 patients with abnormal or low sympathetic skin response with 24 patients with normal response, for H/M ratio and clinical characteristics. Age, duration of illness, and Hoehn and Yahr stage were significantly higher in patients with abnormal or low response. However the mean H/M ratio of early/late phase was not different between the two groups.

A $CV_{R\text{-}R}$ was obtained in 39 patients. Three patients were excluded because of atrial fibrillation (two patients) and frequent premature atrial contraction (one patient). The $CV_{R\text{-}R}$ was abnormal in four out of 36 patients (17%).

All the patients with abnormal autonomic functions were in Hoehn and Yahr stage III, IV, or V.

CARDIAC EXAMINATIONS

Echocardiography (36 patients) showed normal left ventricular function in all the patients examined. Mild or very mild valvular abnormalities were seen in nine patients. Twenty four hour Holter ECG detected non-sustained (eight beats) ventricular tachycardia in one patient. This patient was an 82 year old woman (Hoehn and Yahr stage III). The early phase of the H/M ratio (1.37) was the third lowest and the late phase of the H/M ratio (1.17) was the lowest of all. No serious arrythmias were detected in the remaining patients and ST changes were not seen in any patients examined.

OTHER NEUROLOGICAL DISEASES

The mean H/M ratios (early/late) of the patients with vascular parkinsonism, essential tremor, and multiple system atrophy were 2.11 (0.25)/1.95 (0.28), 2.31 (0.33)/2.37 (0.42), and 2.15 (0.30)/2.16 (0.36), respectively and were not significantly different compared with normal and disease controls. The mean H/M ratio (early/late) of the patients with Parkinson's disease was significantly lower than for the patients with vascular parkinsonism ($p<0.005/p<0.005$), essential tremor ($p<0.001/ p<0.0001$), and multiple system atrophy ($p<0.005/p<0.0001$) (fig 2). The H/M ratios (early/late) of two patients of multiple system atrophy with orthostatic hypotension were 1.82/1.49 and 1.94/2.06, respectively.

Discussion

Hakusui *et al* first reported a decreased myocardial MIBG uptake in patients with Parkinson's disease by ^{123}I-MIBG myocardial scintigraphy.[19] After that several investigators reported that myocardial MIBG uptake often decreased in patients with Parkinson's disease.[21–25] However, the clinical relevance of this, as shown by ^{123}I-MIBG myocardial scintigraphy, remains to be elucidated. In the present study, we performed examinations to clarify (1) the proportion of cardiac sympathetic nerve disturbance in Parkinson's disease, (2) usefulness of ^{123}I-MIBG myocardial scintigraphy to detect sympathetic nerve disturbance compared with autonomic function tests in Parkinson's disease, (3) cardiac functions in the patients with Parkinson's disease who have a decreased MIBG uptake in ^{123}I-MIBG myocardial scintigraphy, (4) the usefulness of ^{123}I-MIBG myocardial scintigraphy to differentiate Parkinson's disease from the other neurological diseases mimicking Parkinson's disease.

Firstly, we discuss the safety of ^{123}I-MIBG myocardial scintigraphy. It was reported to be safe as follows: in 981 patients studied with ^{123}I-MIBG myocardial scintigraphy, there were no severe adverse reactions, except complains of burning on the injection site of the agent, nausea, palpitations, and feeling ill from four patients (0.4%).[10] And in all the patients in whom ^{123}I-MIBG myocardial scintigraphy was performed, no adverse reactions were found. Therefore we infer that it can be performed very safely compared with the autonomic function tests such as the head up tilt test, sympathetic skin response, and CVR-R.

In the present study, cardiac sympathetic nerve disturbances were detected in 84% of the patients with Parkinson's disease. The severity of the disturbances was correlated with the progression of the disease and the duration of illness. The decrease in MIBG uptake in the early phase was considered to be attributable to denervation of the postganglionic cardiac sympathetic nerve due to diabetic neuropathy[18] or various heart diseases including myocardial infarction,[11 12] cardiomyopathy,[13] hypertensive heart disease,[16] and congestive heart disease,[17] disturbance of the sympathetic nerve in the CNS,[15] disturbance of the noradrenaline transporter, and several drugs already mentioned. The decrease in MIBG uptake in the late phase was due to increased MIBG wash out from the myocardium in addition to the causes in the early phase. In the present study, no patients were receiving drugs that may have interfered with MIBG uptake by sympathetic nerve terminals. Antiparkinsonian drugs in clinical use also had no effects on the MIBG uptake according to the present study and other reports.[22 24] Although the disturbance of the noradrenaline transporter has been reported in heart diseases including ischaemic heart disease,[12] left ventricular hypertrophy,[14] and congestive heart disease,[16] and diabetic neuropathy,[18] all the patients had no evidence of them. Therefore, we infer that the decreased myocardial uptake is due to disturbances of sympathetic nerves including the postganglionic cardiac sympathetic nerves or the sympathetic nerves in the CNS. Recently Goldstein *et al* presented a new clinical pathophysiological classification of dysautonomias using myocardial 6-[^{18}F] fluorodopamine PET (6-[^{18}F]-F-DA on PET) and cardiac noradrenaline spill over.[34] In the patients with Parkinson's disease with autonomic failure, both decreased cardiac concentration of 6-[18F]-F-DA on PET and cardiac noradrenaline spill over were shown to be similar to those in patients with pure autonomic failure, indicating the loss of myocardial sympathetic nerve terminals. This peripheral lesion which is responsible for autonomic failure in Parkinson's disease is similar to that in a previous report.[35]

We detected cardiac sympathetic nerve disturbances in 84% of the patients with Parkinson's disease and even in the early stage (Hoehn and Yahr stages I and II), the H/M ratio was already decreased in 73% of the patients. On the contrary, only 29%, 42% (abnormal and low response), and 11% of the patients showed abnormality in the head up tilt test, sympathetic skin response, and CVR-R, respectively. None of the patients in Hoehn and Yahr stages I and II showed abnormal autonomic functions. In previous reports, orthostatic hypotension was found in various proportions of the patients with Parkinson's disease, depending on the accuracy of the diagnosis for Parkinson's disease, disease severity, antiparkinsonian drugs, and criteria for orthostatic hypotension. Magalhães *et al* reported that orthostatic hypotension was found in about one third of the patients with pathologically verified Parkinson's disease,[6] Hirashima *et al* reported that 36.1% of the patients with Parkinson's disease showed abnormal sympathetic skin response, and 12% showed a low response,[33] and Braune *et al* reported that 48% of the patients showed an abnormal sympathetic skin response compared with age matched controls.[36] These data are consistent with the present study. Kuroiwa *et al* reported that 19% of patients studied with Parkinson's disease had abnormal CVR-R at rest,[37] which is similar to the present study. With the previous reports and the present study taken together, ^{123}I-MIBG myocardial scintigraphy is one of the most useful methods of detecting autonomic nerve disturbances in patients with Parkinson's disease.

We also performed cardiac examinations. One patient exhibited non-sustained ventricular tachycardia on 24 hour Holter ECG. Because the H/M ratio of this patient was very low, serious arrhythmias might occur in a patient with extremely decreased myocardial MIBG uptake. But even such patients might not have serious arrhythmias because these were not found in the rest of the patients. Moreover, left ventricular function was normal in all the patients examined by echocardiography. However left ventricular function under exercise or pharmacological stress remains to be elucidated.

It is occasionally difficult to differentiate vascular parkinsonism from Parkinson's disease especially when the disease is associated with multiple brain infarctions. Also, it is not always easy to differentiate essential tremor, multiple system atrophy, and progressive supranuclear palsy from Parkinson's disease especially in the early stage. Recently Yoshita reported that the mean value of H/M ratio in patients with Parkinson's disease was significantly lower than that in those with striatonigral degeneration and progressive supranuclear palsy, and that ^{123}I-MIBG myocardial scintigraphy might be helpful in differentiating between these three diseases, especially in the early stage.[25] In the present study, the mean ages of patients with vascular parkinsonism and essential tremor were matched with that of Parkinson's disease and the mean value of the H/M ratio in the patients with Parkinson's disease was significantly lower than that in those with vascular parkinsonism or essential tremor. Therefore ^{123}I-MIBG myocardial scintigraphy might give us useful diagnostic information to aid in differentiation between vascular parkinsonism or essential tremor and Parkinson's

disease. For multiple system atrophy, the H/M ratio of the patients with orthostatic hypotension showed a slight decrease or lower limit. The rest of the patients had no orthostatic hypotension and had normal MIBG uptake. Although the mean age of patients with multiple system atrophy was not matched with that of Parkinson's disease and there were only a few cases, scintigraphy may give useful diagnostic information to differentiate Parkinson's disease from multiple system atrophy without orthostatic hypotension, as reported by Yoshita *et al.*[22]

In conclusion, we infer that ^{123}I-MIBG myocardial scintigraphy can be performed very safely and that it might detect early disturbances of the sympathetic nervous system in Parkinson's disease and also that it might give us useful diagnostic information to differentiate vascular parkinsonism, essential tremor, and multiple system atrophy from Parkinson's disease.

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