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Clinical Short Communication

MIBG myocardial scintigraphy in progressive supranuclear palsy

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ABSTRACT

Background and objectives: Meta-iodobenzylguanidine (MIBG) myocardial scintigraphy is an effective tool for distinguishing Parkinson's disease (PD) from other diseases accompanied by parkinsonism. Unlike other Parkinsonian diseases, in PD, MIBG accumulation in the heart tends to decrease. However, previous studies have reported that a decrease in MIBG accumulation also occurs in progressive supranuclear palsy (PSP). Thus, we analyzed the relationship between the degree of MIBG accumulation decrease, clinical symptoms, and brainstem atrophy in PSP.

Methods: We retrospectively collected data from patients who underwent MIBG myocardial scintigraphy and compared MIBG indices (heart to mediastinum [H/M] ratio, washout rate) between subjects with PSP and other diseases including PD. In addition, we evaluated the relationship between clinical characteristics, MIBG accumulation, and brainstem atrophy in patients with PSP.

Results: Patients with PSP had a significantly lower early H/M ratio compared with multiple system atrophy with predominant parkinsonism (MSA-P) patients, and a control group. In PSP patients there was a correlation between the decrease in delay H/M ratio, atrophy of the pons, and clinical severity as evaluated by Hoehn and Yahr score.

Conclusion: Unlike in PD, PSP patients exhibited a mild decrease in MIBG accumulation in MIBG myocardial scintigraphy, which may be related to brainstem atrophy.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by resting tremor, muscular rigidity, akinesia or bradykinesia, postural instability, and is caused by the degeneration of dopaminergic neurons in the substantia nigra compacta [1]. Degeneration of nigral dopamine neurons is pathologically unique because of the formation and accumulation of Lewy bodies that include aggregated α-synuclein [2]. The characteristic motor symptoms of PD are referred to as parkinsonism. However, PD is not the only disease that involves symptoms of parkinsonism. The major non-PD disorders involving parkinsonism are collectively referred to as parkinsonian syndromes (PS). These include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), drug-induced PS, and vascular PS [1]. A major difference between PD and other PS is the response to dopaminergic therapy. In other PS dopaminergic replacement therapy is often less effective than in PD. The clinical course of the disease is also different between PD and other PS. Thus, correct diagnosis of PD and other PS is important for devising an appropriate treatment strategy.

Meta-iodobenzylguanidine (MIBG) myocardial scintigraphy is an effective tool for distinguishing PD from other PS [3–7]. MIBG is a physiological analogue of noradrenaline (NA) and shares uptake and storage mechanisms with NA in sympathetic nerve endings [8]. [^{123}I]-MIBG myocardial scintigraphy is used to evaluate cardiac sympathetic activity dysfunction in heart disease [9]. In PD Lewy bodies are mainly

Abbreviations: CBS, corticobasal syndrome; H/M, heart to mediastinum; MCP, middle cerebellar peduncle; MIBG, Meta-iodobenzylguanidine; MRPI, Magnetic Resonance Parkinsonism Index; MSA, multiple system atrophy; NA, noradrenaline; PD, Parkinson's disease; P/M, midsagittal area of pons to midsagittal area of midbrain; PS, parkinsonian syndromes; PSP, progressive supranuclear palsy; ROI, region of interest; SCP, superior cerebellar peduncle; WR, washout rate

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observed in the brainstem and mesencephalon, but recent studies have revealed that Lewy bodies are widely observed in the olfactory bulb, cerebral cortex, basal ganglia, spinal cord, and peripheral autonomic nervous system [10–12]. Lewy bodies are also observed in cardiac sympathetic nerves [13],which disappear from the distal axons due to the accumulation of α-synuclein [14–16]. Degeneration of the cardiac sympathetic nerve in PD may occur simultaneously or even before that of the central nervous system [17]. Thus, many PD cases show a decrease in cardiac MIBG accumulation in MIBG myocardial scintigraphy at an early stage of disease [18,19]. In PS without Lewy body accumulation (i.e., not PD or Lewy body dementia), the decrease in MIBG accumulation seen by MIBG myocardial scintigraphy is not generally observed [3,4,7,19,20]. Thus, MIBG myocardial scintigraphy is an effective tool for diagnosing PD from other PS. However, a mild decrease in MIBG accumulation by MIBG myocardial scintigraphy is also observed in some patients with PSP [3,4,6,7]. The clinical significance of MIBG accumulation decrease in PD and PSP may be different. In the current study we sought to elucidate MIBG accumulation decrease using MIBG myocardial scintigraphy in patients with PSP and analyze its relationship with clinical symptoms and brainstem atrophy.

2. Materials and methods

This study was approved by the Ethics Committees of Kurume University School of Medicine. For this retrospective study we selected patients who had undergone MIBG myocardial scintigraphy for differential diagnosis of PD in the Department of Neurology at Kurume University Hospital between October 2010 and March 2012. Patients with diabetes mellitus, ischemic heart disease, and those who were taking oral medications such as droxidopa and monoamine oxidase-B inhibitors that affected MIBG myocardial scintigraphy results were excluded. We used the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria for diagnosis of PD [21], and the National Institute of Neurological Disorders and Stroke and Society for PSP (NINDS-SPSP) criteria for the diagnosis of PSP [22]. We used widely accepted criteria for the diagnosis of MSA, reported in 2008 [23], and used the Cambridge criteria for the diagnosis of CBS [24]. Essential tremor was diagnosed using the widely accepted criteria reported in 1998 by Deuschl et al. [25]. Regarding other PS diseases we comprehensively diagnosed patients based on genetic testing, clinical manifestations and course, neuroradiology images, and exclusion of differential diagnosis.

MIBG myocardial scintigraphy was performed using a dual head γ camera. Evaluation of cardiac accumulation of MIBG was performed at 30 min (the early phase) and 3 h (the delay phase) respectively, after intravenous injection of 111 MBq of [^{123}I]-MIBG at rest. The heart to mediastinum (H/M) ratio was calculated by dividing the count density of the mediastina region of interest (ROI) from that of the left ventricular ROI, according to the standard method used at our institution. Cardiac MIBG washout rate (WR) was calculated as the percentage change in activity from the count density of the early phase to that of the delay phase within the left ventricular ROI. The chi-square test was used to evaluate differences among categorical variables, and the Kruskal-Wallis test was used to evaluate differences among continuous variables.

The difference in calculated values of H/M ratio between PSP, PD, MSA, CBS, and other diseases was investigated using Welch's two sample *t*-test, and the differential results were compared between the early phase (the early H/M ratio), the delay phase (the delay H/M ratio), and WR. The severity of PSP was evaluated using the Hoehn and Yahr score, which is the standard evaluation method used for rating PD severity. In addition, local brain atrophy in PSP patients was evaluated using the Magnetic Resonance Parkinsonism Index (MRPI), which has been reported as an effective tool for accurately diagnosing PD from PSP at a relatively early stage [26,27]. The midbrain area, pons area, middle cerebellar peduncle (MCP) width, and superior cerebellar peduncle (SCP) width were measured according to a previously reported method [26,27]. Briefly, the midbrain area, pons area, MCP width and SCP width were measured using mid-sagittal T1-weighted MR images. First, we drew a line connecting the superior pontine notch and the inferior edge of the quadrigeminal plate. The midbrain area was measured by tracing around the midbrain tegmentum above the line. We then drew a line through the inferior pontine notch parallel to the first line. The pons area was traced and measured along the edges of anterior and posterior of the pons located between two lines. For the measurement of bilateral MCP width we chose the slice with the most clearly depicted MCP between the pons and the cerebellum in the parasagittal view. The distance between the superior and inferior boundaries of the MCP was measured as the MCP width. Mean MCP width was calculated by averaging the values from both sides. The coronal image slices with the inferior colliculi and SCPs were separated and used as the starting view for SCP measurement. SCP width was measured as the largest linear distance between the medial and lateral border of the SCP in two consecutive sections and the mean value obtained from two consecutive slices was calculated. Furthermore, mean SCP width was calculated by averaging the values from both sides. MRPI was calculated by multiplying the ratio of the midsagittal area of the pons to the midsagittal area of the midbrain (P/M) by the ratio of the MCP width to the SCP width (i.e., MRPI = [P/M] × [MCP/SCP]). The relevance of Hoehn and Yahr score to the age of onset, disease duration, early H/M ratio, delay H/M ratio, WR, midbrain area, pons area, P/M ratio, MCP width, SCP width, and MRPI were investigated using Pearson's correlation coefficients. Results were considered statistically significant at a p-value < 0.05.

3. Results

Fifty-nine patients were recruited as subjects. Of these 59 patients, six had PSP, 22 had PD, two had MSA with predominant cerebellar ataxia (MSA-C), three had MSA with predominant parkinsonism (MSA-P), six had CBS, and 20 had other diseases. Of the 20 patients with other diseases, four had vascular PS, two had drug-induced PS, one had Segawa syndrome, two had cortical cerebellar atrophy, three had hereditary spastic paraplegia (SPG 4) [28], one had Gerstmann-Sträussler-Scheinker syndrome, one had hereditary neuropathy [29], three had essential tremor, one had idiopathic normal pressure hydrocephalus, and two had somatoform disorders. Age, sex, age at onset, disease duration, diagnosis, early H/M ratio, delay H/M ratio, and WR in each disease group are shown in Table 1.

Clinical characteristics, MIBG indices and quantitative MR parameters in PSP cases are shown in Tables 2 and 3. In all six cases with PSP patients exhibited hummingbird sign, reflecting atrophy of the midbrain in mid-sagittal MR imaging (data not shown). Brain perfusion single-photon emission computed tomography was performed in three cases (cases 2, 4, and 5; data not shown). All three cases showed bilateral hypoperfusion of the frontal region. Moreover, all six cases showed poor responsiveness to L-dopa (300 to 600 mg/day). Early H/M ratio, delay H/M ratio, and WR are also shown in Fig. 1A, B, and C, respectively, where the average and standard deviation of each value in each case are evaluated for PSP, PD, MSA-C, MSA-P, CBS, and other diseases. The early H/M ratio in PSP was significantly lower than in MSA-P as well as other diseases, and the early H/M ratio of PD was significantly lower than in all other groups except PSP and MSA-C. Additionally, the early H/M ratio in CBS was significantly lower than in MSA-P. There was no significant difference in delay H/M ratio between PSP patients and the other groups. The delay H/M ratio in PD patients was significantly lower than in MSA-P, CBS, and other diseases. The WR in PSP and PD were significantly higher than in CBS and other diseases. The relevance of the severity of PSP (evaluated by Hoehn and Yahr score) with age at onset, disease duration, early H/M ratio, delay H/M ratio, WR, midbrain area, pons area, P/M ratio, MCP width, SCP width, and MRPI is shown in Table 4, where Pearson's correlation coefficients

Table 1
Clinical characteristics and MIBG indices in each disease group.

Diagnosis	Number	Age at examination (years)	Sex (M:F)	Age at onset (years)	Disease duration (years)	Early H/M ratio	Delay H/M ratio	Washout rate (%)
PSP	6	74.1	2:4	70.1	4.0	1.9	1.9	60.6
PD	22	70.7	7:15	67.1	3.7	1.6	1.4	61.5
MSA-C	2	68.0	0:2	66.0	2.0	2.4	2.4	41.3
MSA-P	3	61.0	0:3	58.3	2.6	2.9	3.0	27.9
CBS	6	72.0	2:4	68.0	4.0	2.2	2.2	38.7
Others	20	55.8	7:13	49.7	6.3	2.4	2.6	29.0
p-value	1.8×10^{-7}	4.6×10^{-7}	0.784	0.038	0.926	4.6×10^{-7}	1.01×10^{-6}	6.29×10^{-7}

Abbreviations: F, female; M, male; PSP, progressive supranuclear palsy; PD, Parkinson's disease; MSA, multiple system atrophy; CBS, corticobasal syndrome. Others include vascular parkinsonism (four cases), drug-induced parkinsonism (two cases), Segawa syndrome (one case), cortical cerebellar atrophy (two cases), hereditary spastic paraplegia (three cases), Gerstmann-Sträussler-Scheinker syndrome (one case), hereditary neuropathy (one case), essential tremor (three cases), idiopathic normal pressure hydrocephalus (one case), and somatoform disorders (two cases).

Table 2
Clinical characteristics and MIBG indices in PSP cases.

Case No.	Sex	Onset age	Diagnosed age	Disease duration (years)	Hoehn-Yahr score	Early H/M ratio	Delay H/M ratio	Washout rate (%)
1	F	80	82	2	3	2.88	2.75	43.85
2	F	60	72	12	4	1.87	1.40	74.68
3	F	60	64	4	5	1.38	1.20	68.28
4	F	72	73	1	3	2.1	1.76	58
5	M	76	77	1	2	2.34	3.41	38.12
6	M	73	77	4	4	1.35	1.09	81.12

Abbreviations: H/M, heart to mediastinum; F, female; M, male.

Table 3
Quantitative MR parameters in PSP cases.

Case no.	Midbrain area (mm^2)	Pons area (mm^2)	P/M raito	MCP width (mm)	SCP width (mm)	MRPI
1	95	488	0.19	9.40	3	14.41
2	77	438	0.18	8.60	4	15.05
3	84	435	0.19	8.55	5	21.60
4	75	448	0.17	8.80	3	21.90
5	71	596	0.12	10.00	2	14.60
6	69	426	0.16	7.40	4	14.74

Abbreviations: P/M, midsagittal area of pons to midsagittal area of midbrain; MCP, middle cerebellar peduncle; SCP, superior cerebellar peduncle; MRPI, magnetic resonance parkinsonism index.

and the corresponding *p*-values were calculated in each case. The results revealed that the delay H/M ratio was significantly inversely correlated with the pons area.

4. Discussion

MIBG myocardial scintigraphy is a useful tool for distinguishing PD from other PS, and many previous studies have compared the results of MIBG myocardial scintigraphy between PD and other PS [3,5–7,19,20]. In most previous studies patients with PD were found to exhibit a significantly decreased H/M ratio compared with control subjects, but other PS such as PSP, MSA, and CBS were not significantly different [3,7,19,20]. In addition, many PD cases were reported to show a trend toward declining H/M ratio over time [4,19]. A decrease in MIBG accumulation observed by MIBG myocardial scintigraphy is thought to reflect the denervation of cardiac sympathetic nerves [14,15]. In pathological examination denervation of cardiac sympathetic nerves was observed in most cases with PD, but was not observed in any cases with PSP and CBS, or in most cases with MSA [14–16,30]. The current results revealed a decrease in early H/M ratio in PSP compared with MSA-P and other diseases, and an increase in WR compared with CBS and other diseases. In the delay H/M ratio PSP showed a decreasing trend in comparison with diseases other than PD; however, this trend was not statistically significant. Since H/M ratio and WR are affected by aging and disease duration [6,18], differences in age and disease duration should be taken into account. Unfortunately, we were not able to calculate the influence of aging and disease duration on H/M ratio and WR.

In previous reports that evaluated the decrease of MIBG accumulation in MIBG myocardial scintigraphy of PS including PSP, PSP patients showed a significant decline in H/M ratio compared with control

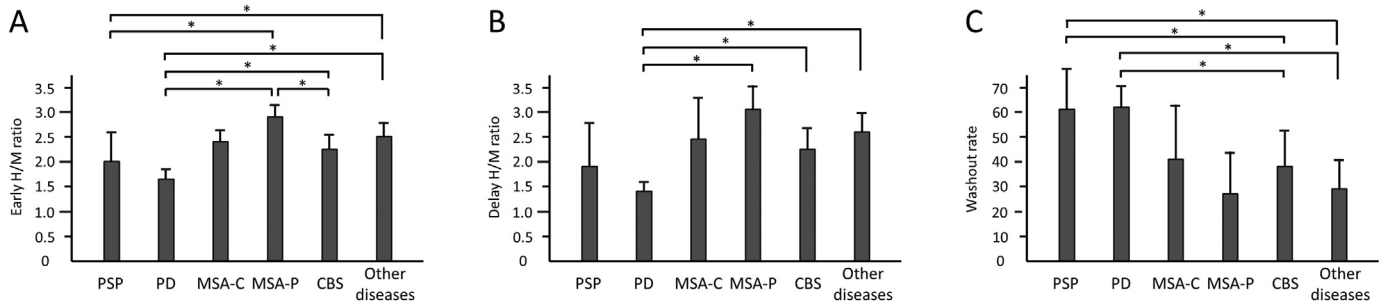

Fig. 1. Early (A) and delay (B) heart to mediastinum (H/M) ratio and washout rate (C) in PSP, PD, MSA-C, MSA-P, CBS, and other disease groups ("others"). (A) PSP was significantly lower than MSA-P and others. (B) There was no significant difference between PSP and others. (C) PSP was significantly higher than CBS and others. *$p < 0.05$, unpaired *t*-test.

Table 4
Pearson's correlation coefficients and corresponding *p*-values between PSP severity (evaluated by Hoehn and Yahr score) and clinical characteristics, MIBG indices, and quantitative MR parameters in PSP cases.

	Age at onset	Disease duration (years)	Early H/M ratio	Delay H/M ratio	Washout rate (%)	Midbrain area (mm^2)	Pons area (mm^2)	P/M raito	MCP width (mm)	SCP width (mm)	MRPI
Correlation coefficient	−0.76	0.51	−0.75	−0.88	0.8	0.15	−0.82	0.69	−0.71	−0.77	0.38
P-value	0.076	0.306	0.084	0.021	0.054	0.779	0.046	0.132	0.114	0.072	0.459

Abbreviations: H/M, heart to mediastinum; P/M, midsagittal area of pons to midsagittal area of midbrain; MCP, middle cerebellar peduncle; SCP, superior cerebellar peduncle; MRPI, magnetic resonance parkinsonism index.

subjects [3,4], and some showed a decrease in delay H/M ratio [6,7]. Unlike in PD, pathological examination of the cardiac muscle in patients with PSP revealed no denervation of the sympathetic nerve [14,30]. Thus, it is likely that factors other than the denervation of the cardiac sympathetic nerve caused the decrease in myocardial MIBG accumulation in PSP. One of the key features of PSP is marked atrophy of the midbrain tegmentum. Based on this feature, the MRPI, derived from the midbrain and pons areas, MCP width, and SCP width, is used for distinguishing between PSP and other degenerative diseases [26,27]. The relationships between PSP severity, evaluated by Hoehn and Yahr score, and age at onset, disease duration, early H/M ratio, delay H/M ratio, and WR, were analyzed in this study. Furthermore, the relationships between PSP severity, evaluated by Hoehn and Yahr score, and the midbrain area, pons area, P/M ratio, MCP width, SCP width, and MRPI were also analyzed. A significant correlation was found between PSP severity and delay H/M ratio, and between PSP severity and pons area. In a comparison of PSP and PD using MRPI, the PSP group had a significantly smaller area for both the midbrain and pons [27]. The center of the sympathetic nerve activity of the cardiovascular system is mainly located on the rostral ventrolateral medulla (RVLM) of the brainstem [31]. In addition, the dorsomedial periaqueductal gray of the midbrain and the A5 noradrenaline nerve on the ventral side of the pons indirectly regulate the sympathetic nervous activity of the cardiovascular system [32,33]. Therefore, atrophy in brainstem regions such as in the midbrain and pons could result in the central autonomic dysfunction that is observed in PSP. According to a study evaluating autonomic function in PSP, MSA, idiopathic PD (iPD), and healthy subjects, autonomic dysfunction is observed in not only MSA and iPD, but also in PSP, and these three groups could not be distinguished by a cardiovascular autonomic function test [34]. In PSP it is thus plausible that central autonomic dysfunction associated with brainstem atrophy, including of the pons and medulla oblongata, might be reflected as an MIBG accumulation decrease in MIBG myocardial scintigraphy. Unfortunately, we were unable to exclude the possibility that a decrease in MIBG accumulation is related to midbrain atrophy for three reasons: 1) atrophy of midbrain is more pronounced in PSP than MSA [27] which exhibited no decrease in MIBG accumulation; 2) atrophy of the pons is more severe in MSA [27] compared with PSP; 3) a significant relationship was not detectable because the midbrain had atrophied in early disease-stage in PSP.

In conclusion, the current results revealed that PSP is associated with a mild decrease of MIBG accumulation in the heart. Decreased MIBG accumulation in PD is thought to reflect the denervation of cardiac sympathetic nerves. However, the current findings suggest that the phenomenon may reflect an impairment in central autonomic function derived from brainstem atrophy.

Compliance with ethical standards

This study was reviewed and approved by the Ethics Committees of Kurume University School of Medicine.

Conflict of interest

The authors declare that they have no conflict of interest.

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