

# Comparison of MRI and $^{123}\text{I}$ -FP-CIT SPECT for the evaluation of MSA-P clinical severity

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**Abstract.** The aim of the present study was to compare the efficacy of magnetic resonance imaging (MRI) and  $^{123}\text{I}$ -labeled 2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)-N-(3-fluoropropyl)nortropane single photon emission computed tomography ( $^{123}\text{I}$ -FP-CIT SPECT) for determining the clinical severity of patients with multiple system atrophy with Parkinsonism (MSA-P). MRI and  $^{123}\text{I}$ -FP-CIT SPECT images from 17 patients with MSA-P as diagnosed using the Unified MSA Rating Scale part IV (UMSARS IV) score were compared. Brain MRI scans were available for all 17 patients and  $^{123}\text{I}$ -FP-CIT SPECT images were available for 12 patients. Putaminal atrophy (PA), hyperintense putaminal rim (HPR), hyperintense pons (hot cross bun sign, HCB), atrophy of the cerebellar vermis and hemisphere (cerebellar atrophy, CA) and other abnormalities were evaluated in the MRI scans. Distribution of striatal uptake (SU) and the specific binding ratio (SBR) on each side of the bilateral striatum were evaluated using  $^{123}\text{I}$ -FP-CIT SPECT images. No significant associations were observed between HPR, HCB, CA and UMSARS IV score. However, the frequency of PA increased significantly with higher UMSARS IV score ( $P<0.05$ ). No significant association was observed between UMSARS IV score and SBR. The results of the present study suggest that PA, which is known to be a diagnostic indicator for MSA-P, may be used to determine the clinical severity of MSA-P with greater efficacy

than other MRI findings, including HPR, HCB and CA and  $^{123}\text{I}$ -FP-CIT SPECT results.

## Introduction

Magnetic resonance imaging (MRI) provides precise anatomical, volumetric and qualitative information, making it a reliable method for distinguishing between multiple system atrophy with Parkinsonism (MSA-P) and other Parkinsonism symptoms (1-3). Atrophy of the putamen, middle cerebellar peduncle, pons and/or cerebellum may be observed in the MRI scans of patients with MSA-P according MSA criteria (4). In addition, hyperintense putaminal rim (HPR) and hyperintense pons (hot cross bun sign, HCB) are often present in patients with MSA-P (1,5).

Previous studies have reported that  $^{123}\text{I}$ -labeled 2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography ( $^{123}\text{I}$ -FP-CIT SPECT) is useful for evaluating striatal dopamine transporter deficiency, which can cause Parkinsonism as well as MSA-P (6,7). Reduced striatal uptake (SU) is typically observed in the posterior putamen of patients with MSA-P and is similar to observations in other nigrostriatal degenerative diseases, including idiopathic Parkinson's disease (8,9). Dopaminergic neurologic deficiency may be quantified using the specific binding ratio (SBR), which uses the region-of-interest approach derived from the total count in the striatum (10).

The prognoses of patients with MSA, including those with MSA-P, is poor; mortality has been reported to occur within 2-21 years (median, 9.5 years) of the first appearance of symptoms (11,12). Increasing our understanding of disease progression is essential for predicting patient prognoses and developing effective treatment strategies for the future. However, patients with MSA-P present with various symptoms, including Parkinsonism, cerebellar symptoms and autonomic symptoms (4), which makes diagnosis clinically challenging. The International Cooperative Ataxia Rating Scale was previously used to assess cerebellar syndrome, while the Unified

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Parkinson's Disease Rating Scale was used to evaluate Parkinsonism; however, these scales evaluate only a subset of clinical manifestations (13,14). In 2004, the Unified Multiple System Atrophy Rating Scale (UMSARS) was proposed as a novel clinical severity scale for MSA - UMSARS is now widely used to evaluate the severity of MSA (15). UMSARS comprises four parts: I, historical review; II, motor examination scale; III, autonomic examination; and IV, global disability scale. Of these parts, part IV is considered to be associated with clinical severity (15).

A literature review was performed by our group and, to the best of our knowledge, no previous studies have used MRI and  $^{123}\text{I}$ -FP-CIT SPECT to evaluate the severity of MSA-P. Furthermore, although it has been reported that the severity of Parkinsonism is correlated with imaging results (16), few studies have focused on the correlation between global disability and image findings. In the present study, the efficacy of MRI and  $^{123}\text{I}$ -FP-CIT SPECT for detecting imaging features that indicate the clinical severity of MSA-P based on UMSARS IV score were compared.

## Materials and methods

**Ethics statement.** The present study was approved by the Ethical Review Board of Kochi Medical School (Nankoku, Japan). Due to the retrospective nature of the present study, written informed consent was waived.

**Patients.** A total of 17 patients (6 men, 11 women; mean age, 70 years; range, 54-74 years; mean disease duration, 36 months; range, 4-96 months) were diagnosed with MSA-P by a neurologist at the Department of Neurology at Kochi Medical School between October 2010 and March 2017 (4). Brain MRI was performed for all patients and  $^{123}\text{I}$ -FP-CIT SPECT was performed for 12 patients. All patients had been treated using levodopa (100-600 mg/day depending on disease severity and drug efficacy) for 1 to 22 months prior to imaging examinations. The interval between MRI and  $^{123}\text{I}$ -FP-CIT SPECT imaging was <6 months, during which time the clinical severity did not change in any of the patients.

**Imaging protocol.** Brain MRI was performed using a 1.5-T system (Signa HDx; GE Healthcare, Chicago, IL, USA) using an 8-channel coil. Images were recorded in the transverse plane using T1-weighted spin echo [repetition time (TR), 400-600 msec; echo time (TE), 300 msec; flip angle (FA), 90°; matrix, 320x224; number of excitations (NEX), 1], T2-weighted fast spin echo (TR, 3,000-4,000 msec; TE, 120 msec; FA, 90°; matrix, 384x256; NEX, 2) and fluid-attenuated inversion recovery (TR, 10,000 msec; TE, 142 msec; FA, 90°; matrix, 256x192; NEX, 1). The slice thickness was 5 mm (gap, 5 mm) and the field of view was 24 cm. All  $^{123}\text{I}$ -FP-CIT SPECT data were acquired using a SPECT CT system (Symbia T2 TruePoint SPECT CT; Siemens AG, Munich, Germany) equipped with a low-energy, high-resolution collimator. Attenuation correction used low-dose CT (17) and scatter correction was performed using the triple energy window method (18). SPECT images were obtained 3 h following injection of  $^{123}\text{I}$ -FP-CIT (167 MBq; Nihon Medi-Physics Co., Ltd., Tokyo, Japan).

**Assessment of the patients' severity.** Clinical severity (score 1-5) was assessed by an experienced neurologist based on UMSARS part IV (15).

**Image analysis.** All images were retrospectively evaluated by two diagnostic radiologists who were blinded to the clinical data. The following features were assessed: i) Putaminal atrophy [posterolateral linearization of the putaminal margin (19); PA]; ii) Hyperintense putaminal rim (HPR) on T2-weighted imaging (T2WI); iii) Hyperintense pons (hot cross bun sign, HCB) on T2WI; iv) Atrophy of the cerebellar vermis and hemisphere (cerebellar atrophy, CA); and v) other brain abnormalities on T1WI, T2WI or fluid-attenuated inversion recovery with reference to anatomical landmarks, including the internal and external capsules. The distribution of SU on  $^{123}\text{I}$ -FP-CIT SPECT images was visually assessed. SU was quantified using SBR with DaTView software (version 6.1; AZE, Ltd., Tokyo, Japan). Bilateral SBRs (for the right and left striatum) were individually divided into higher side (SBR higher) and lower side (SBR lower) groups with DaTView, regardless of their right or left positioning.

**Statistical analysis.** PA, HPR, HCB, CA and SBR were compared according to sex and age using the Mann-Whitney U test, Cochran-Armitage test and Fisher's exact test.  $^{123}\text{I}$ -FP-CIT SPECT findings and SBR were compared with UMSARS IV using the Cochran-Armitage and Jonckheere-Terpstra tests. SBR results are expressed as the mean (range). All statistical analyses were performed using Easy R (version 2.7.11; Saitama Medical Center, Jichi Medical University, Saitama, Japan.), a graphical user interface for R (version 3.3.3; The R Foundation, Vienna, Austria) (20).  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

**Patient characteristics and UMSARS IV scores.** The distribution of UMSARS IV scores was as follows: Score 1, 1 patient; score 2, 6 patients; score 3, 8 patients; score 4, 2 patients. Patient characteristics and the results of MRI and  $^{123}\text{I}$ -FP-CIT SPECT scans are summarized in Table I. The results of MRI and  $^{123}\text{I}$ -FP-CIT SPECT were not significantly associated with age or sex.

**MRI results.** Of the 17 patients enrolled in the present study, 12 were demonstrated to have at least one of PA, HPR, HCB or CA based on MRI results. PA was observed in 9/12 patients, including in 3 with HPR. HCB was observed in 1/12 and CA was evident in 9/12 patients. PA and HPR were identified asymmetrically in each patient, whereas HCB and CA were symmetrical (Fig. 1). A total of 9 patients were demonstrated to have symmetrical lacunar infarcts in the putamen. No other significant changes, including trauma or brain tumors, were identified from MRI results.

**$^{123}\text{I}$ -FP-CIT SPECT results.** For  $^{123}\text{I}$ -FP-CIT SPECT, asymmetric reduction of SU in the posterior putamen was observed in all 12 patients (Fig. 2). SBR higher had a range of 1.98-6.27 and SBR lower had a range of 1.56-4.71 (Table I).

Table I. Patient characteristics, MRI and <sup>123</sup>I-FP-CIT SPECT finding results.

Patient	Age (years)	Sex	DD (months)	MRI						<sup>123</sup> I-FP-CIT	
				PA	HPR	HCB	CA	LI	UMSARS IV	SBR (lower)	SBR (higher)
1	84	M	60	-	-	-	-	+	1	3.71	3.93
2	68	F	11	+	-	-	+	+	2	3.7	4.79
3	67	F	84	-	-	-	+	+	2	2.06	3.26
4	81	M	60	+	-	-	+	-	2	1.56	1.98
5	64	M	7	-	-	-	-	-	2	N/A	N/A
6	54	F	4	-	-	-	-	+	2	N/A	N/A
7	84	M	12	-	-	-	-	-	2	N/A	N/A
8	64	F	30	-	-	-	+	+	3	4.71	6.27
9	58	M	25	+	+	-	+	+	3	4.11	5.00
10	66	F	18	+	-	-	-	-	3	3.01	3.19
11	59	F	36	+	-	-	+	-	3	2.83	5.10
12	79	F	60	-	-	-	-	-	3	2.25	3.01
13	78	F	96	+	+	-	-	+	3	1.63	2.46
14	75	F	35	+	-	-	-	+	3	N/A	N/A
15	77	F	21	-	-	-	+	-	3	N/A	N/A
16	71	F	15	+	+	-	+	+	4	3.07	4.99
17	62	M	36	+	-	+	+	-	4	1.63	2.24

MRI, magnetic resonance imaging; <sup>123</sup>I-FP-CIT SPECT, <sup>123</sup>I-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography; M, male; F, female; DD, duration of disease; PA, putamenal atrophy; HPR, hyperintense putamenal rim; HCB, hot cross bun sign; CA, cerebellar atrophy; LI, lacunar infarction; SBR, specific binding ratios; UMSARS IV, Unified Multiple System Atrophy Rating Scale part IV; +, positive, -, negative; N/A, not available.

Table II. Relationship between MRI findings and UMSARS IV score.

UMSARS IV score (n)	MRI			
	PA (r) <sup>a</sup>	HPR (x)	HCB (y)	CA (z)
1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
2 (6)	2 (33)	0 (0)	0 (0)	3 (50)
3 (8)	5 (63)	2 (25)	0 (0)	4 (50)
4 (2)	2 (100)	1 (50)	1 (50)	2 (100)

Data were expressed as number (frequency). PA, putaminal atrophy; HPR, hyperintense putaminal rim; HCB, hot cross bun sign; CA, cerebellar atrophy; UMSARS IV, Unified Multiple System Atrophy Rating Scale part IV. r, PA/n x100; x, HPR/n x100; y, HCB/n x100; z, CA/n x100. <sup>a</sup>Increasing with increasing UMSARS IV score,  $P < 0.05$ .

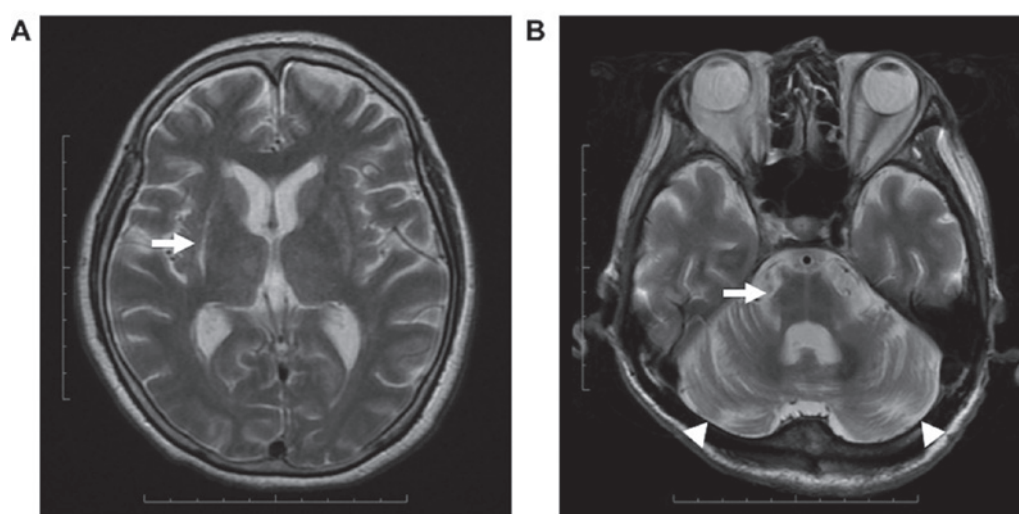


Figure 1. Representative brain MRI scans of multiple system atrophy with Parkinsonism. (A) Brain MRI of patient 16. Right putaminal atrophy and hyperintense putaminal rim were apparent on T2-weighted imaging. The arrow indicates right putaminal atrophy and a hyperintense putaminal rim. (B) Brain MRI of patient 17. Hot cross bun sign and bilateral cerebellar atrophy were evident on T2-weighted imaging. One division of the scale bar represents 10 mm. The arrow indicates hot cross bun sign, and arrowheads indicate bilateral cerebellar atrophy.

**Association between imaging results and UMSARS IV scores.** The frequency of PA increased significantly with increased UMSARS IV score ( $P < 0.05$ ); however, no significant associations were identified between UMSARS IV scores and HPR, HCB or CA (Table II). Furthermore, the results of the present study did not identify a significant association between UMSARS IV scores and SBR (Fig. 3).

## Discussion

To the best of our knowledge, the present study is the first report to evaluate whether MRI or  $^{123}\text{I}$ -FP-CIT SPECT is more effective for determining clinical severity in patients with MSA-P. The results of MRI revealed characteristic MSA-P features in 12 out of 17 patients. Among these, PA was observed in 9 patients. PA frequency increased significantly with increasing UMSARS IV score. For  $^{123}\text{I}$ -FP-CIT SPECT, reduced SU in the posterior putamen was observed in all patients; however, no significant association was observed between SBR and UMSARS IV score.

The results of the present study revealed a significant association between PA (as identified using MRI) and the clinical

severity (based on UMSARS IV) of patients with MSA-P. It has been reported that PA is associated with posterolateral-predominant neurologic deficiencies and gliosis (21). Neurologic deficiencies of the putamen cause serious defects in the dopamine transport synapse route, as well as a deficiency of nigral cells, which leads to Parkinsonism (19,21,22). It has previously been reported that the severity of Parkinsonism is correlated with PA and abnormal diffusivity (16,23). The severity of MSA-P may be associated with Parkinsonism, cerebellar symptoms and autonomic symptoms. However, no significant association was identified between CA appearing equivalent to PA and clinical severity. Based on the results of the present study, CA does not appear to significantly affect the severity of MSA-P and, as such, it has been hypothesized that Parkinsonism may be a factor that affects clinical severity.

The results of  $^{123}\text{I}$ -FP-CIT SPECT revealed reduced SU in the posterior putamen in all 12 patients, which supports previous reports (8,9). However, no significant association was identified between SBR and clinical severity. Degeneration in the striatum, including the putamen, is reportedly associated

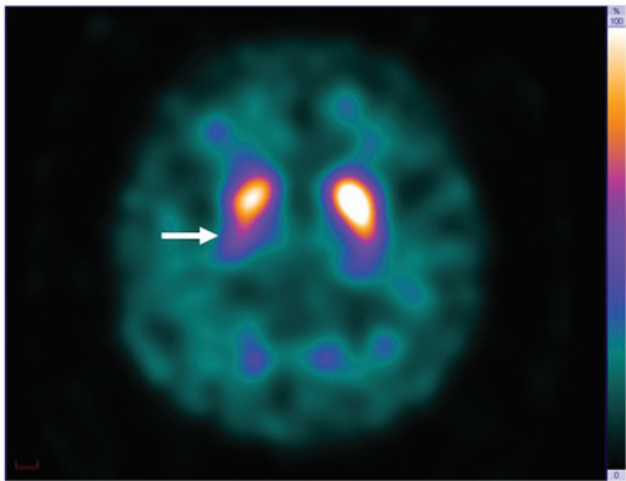


Figure 2. Brain  $^{123}\text{I}$ -labeled 2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)-N-(3-fluoro propyl) nortropane single photon emission computed tomography image of patient 9. Reduced striatal uptake is evident, predominantly in the posterior putamen (arrow).

with functional reductions in pre- and postsynaptic dopamine transport in patients with MSA-P (24). However, the results of  $^{123}\text{I}$ -FP-CIT SPECT demonstrate a reduction in presynaptic function only (8). It is therefore unlikely that the clinical severity of patients with MSA-P can be accurately assessed using  $^{123}\text{I}$ -FP-CIT SPECT alone. Reduced postsynaptic function may be correlated with PA; it has previously been reported that reductions in D2 receptors, as measured by raclopride positron emission tomography, are correlated with the clinical severity of MSA-P (25). Based on the present study and previous reports, it appears that presynaptic and postsynaptic functions both affect the clinical severity of patients with MSA-P. As such, evaluation of PA using MRI is essential for assessing the clinical severity of MSA-P.

The present study is not without limitations. Had a volume measurement tool been used as part of the MRI assessment in the present study, an exact, quantitative value for PA could have been obtained. Quantitative PA evaluation has been reported to correlate with the severity of Parkinsonism (16). Furthermore, the degree of pathological modification of the putamen has been reported to be associated with response to levodopa (21). Quantitative evaluation of PA may therefore be associated with the combined pre- and postsynaptic functions. Consequently, if the pre- and postsynaptic functions in PA (quantified using MRI) and the reduced presynaptic function (quantified using  $^{123}\text{I}$ -FP-CIT SPECT) can be compared, the results may reveal the overall degree of pre- and postsynaptic function reduction in individual patients with MSA-P. In addition, the effects of levodopa may be better predicted.

The present study was retrospective and the sample size was relatively small. However, this was unavoidable as MSA-P is a rare condition (26). The present study also utilizes a 1.5-T system, which is not optimal, as 3-T systems have been reported to be better for detecting HCB and HPR (27). Furthermore, no proton density-weighted imaging (PDWI) was used in conjunction with MRI in the present study. PDWI has been demonstrated to be useful in detecting HCB (28). At present, 3-T systems and PDWI are not included in the standard imaging protocol at Kochi Medical School. Future

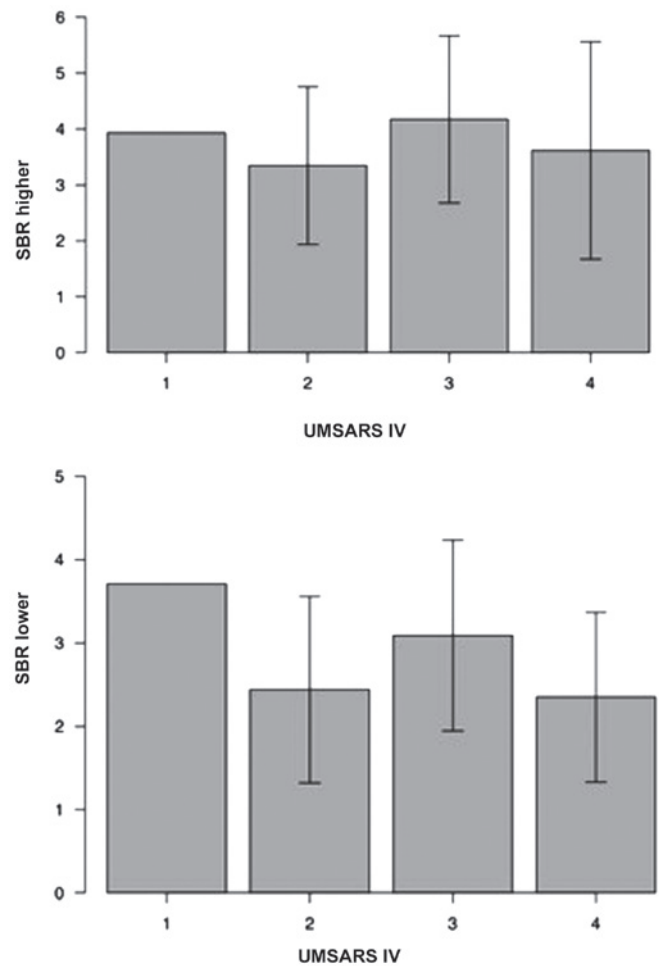


Figure 3. Relationship between SBR and UMSARS IV score. No association was observed between SBR and UMSARS IV score in the SBR higher or SBR lower groups. SBR, specific binding ratios; UMSARS IV, Unified Multiple System Atrophy Rating Scale part IV.

studies should aim to utilize a 3-T system and PDWI in order to better identify HPR and HCB in patients with MSA-P.

In conclusion, the use of  $^{123}\text{I}$ -FP-CIT SPECT does not appear to be more effective than MRI for evaluating the clinical severity of patients with MSA-P. Evaluating the presynaptic and postsynaptic dopamine function is essential in order to accurately assess the severity of MSA-P. As  $^{123}\text{I}$ -FP-CIT SPECT is only able to assess presynaptic function, this type of imaging alone is insufficient. However, PA, as identified using MRI, is significantly associated with clinical severity in patients with MSA-P. The results of the present study suggest that PA values obtained using MRI are the most useful parameter for evaluating the clinical severity of patients with MSA-P.

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## Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

## Authors' contributions

MN and YM designed the study and wrote the initial draft of the manuscript. HN contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors contributed to data collection and interpretation. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by Ethical Review Board of Kochi Medical School (Kochi, Japan). Due to the retrospective nature of the present study, written informed consent was waived. A statement explaining that individuals who did not want to participate in the study could request to opt-out was posted on the bulletin board at Kochi Medical School.

## Consent for publication

Not applicable.

## Competing interests

The authors declare no competing interests.

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