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Distinct clinical features of predominant pre-synaptic and trans-synaptic nigrostriatal dysfunction in multiple system atrophy

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ABSTRACT

Background: The severity of parkinsonism and response to levodopa vary in patients with multiple system atrophy (MSA) because of the heterogeneity of nigrostriatal neuropathology.
Objective: To investigate the difference in clinical features between MSA patients with predominantly pre-synaptic nigrostriatal dysfunction and those with trans-synaptic nigrostriatal dysfunction.
Methods: We retrospectively analyzed clinical data of 61 patients with MSA who underwent both [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET within 3 months of clinical evaluation, and who had ≤3 years of disease duration. Tracer uptake of the striatum on [^{18}F]FP-CIT-PET and glucose metabolism of the striatum on [^{18}F]FDG-PET were analyzed using eight striatal subregional volumes-of-interest templates. The patients were classified into two subgroups according to the predominant pre-synaptic tracer uptake loss of the posterior putamen on [^{18}F]FP-CIT-PET (MSA-SNpc, n = 21) and trans-synaptic dopaminergic dysfunction reflected by both [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET (MSA-STR, n = 40).
Results: Parkinsonian features were significantly more severe in the MSA-STR group than in the MSA-SNpc group (P = .005) and cerebellar ataxia was significantly more severe in the MSA-SNpc group (P = .036). The cerebellar type of MSA was significantly more common in the MSA-SNpc group (P = .001). There was no difference in age at onset, disease duration at the time of study, or Mini-Mental Status Examination scores between the groups.
Conclusions: Patients with MSA showed distinct clinical features depending on whether the pattern of nigrostriatal dysfunction was predominantly pre-synaptic or trans-synaptic.

1. Introduction

Multiple system atrophy (MSA) is an adult-onset, progressive neurodegenerative disorder that is characterized clinically by parkinsonism, cerebellar ataxia, autonomic failure, and corticospinal dysfunction of variable severity [1]. Parkinsonian features are caused by heterogeneous degeneration of the nigrostriatal systems in MSA [2–4]. Akinetic-rigid parkinsonism that is poorly responsive to levodopa is a typical clinical manifestation. However, some MSA patients may have parkinsonian features that are indistinguishable from those of Parkinson's disease (PD) [2,5]. A clinicopathological study reported that pre-synaptic parkinsonism caused by degeneration of dopaminergic neurons in the midbrain without degeneration of neurons in the striatum may occur in MSA, and can be indistinguishable from PD [6]. Those findings suggest that MSA with predominantly pre-synaptic nigrostriatal dysfunction may have clinical features distinct from those in their counterparts with combined dopaminergic and striatal neuronal dysfunction.

Dopamine transporter (DAT) imaging, ^{18}F-fluorinated-N-3-fluoropropyl-2-b-carboxymethoxy-3-b-(4-iodophenyl) nortropane ([^{18}F]FP-

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CIT) PET, and [^{18}F] fluorodeoxyglucose (FDG) PET provide useful information about the pathology of MSA. On [^{18}F]FP-CIT-PET, uptake of the DAT-binding tracer is a useful tool for evaluating the integrity of the pre-synaptic nigrostriatal system in MSA [7]. On [^{18}F]FDG-PET, decreased glucose metabolism in the striatum, pons, and cerebellum is correlated with pathological involvement in MSA [8,9]. There has also been a report of a correlation between decreased metabolism assessed by [^{18}F]FDG-PET and a decreased level of receptor binding assessed by [^{11}C]raclopride in the putamen of MSA [10]. [^{18}F]FDG-PET may indirectly reflect the post-synaptic nigrostriatal function in MSA. Therefore, [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET could be used to classify MSA into those with predominantly pre-synaptic nigrostriatal dysfunction and those who have both pre-synaptic and post-synaptic (trans-synaptic) nigrostriatal dysfunction, depending on the relative involvement of the nigrostriatal neuronal systems.

We aim to investigate the difference in clinical features between predominantly pre-synaptic and trans-synaptic nigrostriatal dysfunction in MSA using neuroimaging classification by [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET.

2. Methods

2.1. Subjects

The clinical data were retrospectively obtained from the medical records of MSA patients who were admitted under the care of the Department of Neurology at the Asan Medical Center, Seoul, Korea, between 1 January 2009 and 31 September 2015. All the patients fulfilled the clinical diagnostic criteria for MSA based on the second consensus statement for MSA and underwent both [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET within 3 months of clinical evaluation. All patients had ≤3 years of disease duration. The exclusion criteria were as follows: age under 30 years at the time of onset of symptoms; a positive family history of parkinsonism or cerebellar ataxia; a known genetic abnormality; supranuclear gaze palsy and focal cortical dysfunction; a suspected structural brain lesion on magnetic resonance imaging; antipsychotic medication; and a systemic disease that would impair judgment. Thirty-nine of the 132 MSA patients identified were excluded because they had undergone [^{18}F]FDG-PET or [^{18}F]FP-CIT-PET > 3 months after their clinical evaluation. Seven further patients were excluded for having a disease duration of > 3 years. A diagram showing the flow of patients through the study is provided in Supplementary Fig. 1.

To investigate the difference in clinical features between predominantly pre-synaptic and trans-synaptic nigrostriatal dysfunction in MSA, we selected two subgroups using the neuroimaging values. The pre-synaptic nigrostriatal function was evaluated by the normalized DAT binding ratio (%BR) in the posterior putamen on [^{18}F]FP-CIT-PET and the post-synaptic nigrostriatal function was evaluated by the normalized metabolic ratio (%MR) in the posterior putamen on [^{18}F]FDG-PET. The MSA-SNpc defined as MSA patients with predominantly pre-synaptic nigrostriatal dysfunction included 21 MSA patients who simultaneously had a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a preserved %MR (≥95%) in the posterior putamen on [^{18}F]FDG-PET. The MSA-STR defined as MSA patients with trans-synaptic nigrostriatal dysfunction included 40 MSA patients who simultaneously had a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a decreased %MR (< 90%) in the posterior putamen on [^{18}F]FDG-PET. To compare the extreme cases, a predominantly MSA-STR was defined that included 21 MSA patients who simultaneously had simultaneously a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a decreased %MR (< 80%) in the posterior putamen on [^{18}F]FDG-PET. The study protocol was approved by the institutional review board at Asan Medical Center.

2.2. Clinical assessment

All MSA patients were assessed by a neurologist specialized in movement disorders, and their medical records were made available. The Unified Multiple System Atrophy Rating Scale (UMSARS) was used to assess the clinical symptoms of MSA patients during the off state [11]. The Unified Parkinson's Disease Rating Scale (UPDRS) III was used to evaluate parkinsonism, which was categorized as tremor (Q20 + 21), rigidity (Q22), bradykinesia (Q23 + 24 + 25 + 26 + 27 + 31), and axial motor features (Q18 + 19 + 27 + 28 + 29 + 30) [4]. Cerebellar ataxia was evaluated using the finger-to-nose, heel-to-shin, and ocular motor tests. The finger-to-nose and heel-to-shin tests were scored bilaterally (0, normal; 1, mildly dysmetric and ataxic; 2, moderately dysmetric and ataxic; 3, severely dysmetric and ataxic; 4, can barely perform the task). The ocular motor test, including broken-up smooth pursuit, gaze-evoked nystagmus at an eye position of > 45 degrees, gaze-evoked nystagmus at an eye position of < 45 degrees, and saccadic hypermetria, was scored as follows: 0, none; 1, one abnormal ocular motor sign; 2, two abnormal ocular motor signs; 3, three abnormal ocular motor signs; or 4, four abnormal ocular motor signs.

Orthostatic blood pressure (BP) was assessed by the systolic and diastolic BP values in the supine position and after 3 min of standing. The Mini-Mental State Examination (MMSE) was used to assess cognitive function. The responsiveness to levodopa was classified as poor or good. Some MSA patients were not evaluated for response to levodopa because of intolerable side effects or life-long minimal parkinsonism,

The control groups included healthy individuals with no psychiatric illness or neurological disease and normal findings on [^{18}F]FDG-PET (19 men, 10 women; mean age 52.2 ± 7.1 years) or [^{18}F]FP-CIT-PET (5 men, 16 women; mean age 61.6 ± 14.2 years) who were selected from the normal PET data pool maintained at our institution.

2.3. [^{18}F]FP-CIT-PET

[^{18}F]FP-CIT-PET was performed in 86 MSA patients and in 21 healthy controls using a Biograph 40 TruePoint PET/CT camera (Siemens/CTI, Erlangen, Germany) that provides an ordered subsets expectation maximization using a point spread function-based high-resolution reconstruction algorithm called True-X (resulting in 2 mm full-width at half-maximum spatial resolution in air at the center of the field of view). The PET slice thickness was 1.5 mm and the matrix size was 336 × 336 (transaxial field of view 30 cm, resulting voxel size 0.9 × 0.9 × 1.5 mm). Antiparkinsonism drugs were stopped 12 h before the scans were obtained. Image acquisition was started 3 h after intravenous injection of 185 MBq of [^{18}F]FP-CIT. [^{18}F]FP-CIT-PET images were reconstructed from CT-based attenuation-corrected PET raw data using the TrueX algorithm and an all-pass filter.

[^{18}F]FP-CIT-PET was synthesized using a protic solvent (t-butanol or t-amyl alcohol) as a reaction solvent and N-[3′-(tosyloxy) propyl]-2β-carbomethoxy-3β-(4´iodophenyl)nortropane as a precursor. The radiochemical purity was > 98% after purification by high-performance liquid chromatography and the specific activity was 64.4 ± 4.5 GBq/μmol at the end of synthesis.

2.4. [^{18}F]FDG-PET

[^{18}F]FDG-PET was performed in 86 MSA patients and 29 healthy controls. All subjects had fasted for at least 6 h before the scan. PET scan were performed in a quiet and dimly lit room. PET images were acquired 40 min after intravenous injection of 370 MBq [^{18}F]FDG on a Discovery 690 or Discovery STE scanner (GE Healthcare, Milwaukee, WI, USA). The scanner imaged 47 planes with a slice thickness of 3.27 mm simultaneously for a longitudinal field of view of 15.5 cm. The transaxial field of view was 25 cm and the matrix size was 128 × 128 (resulting voxel size 1.96 × 1.96 × 3.27 mm). All emission images were reconstructed from CT-based attenuation-corrected PET raw data

Table 1
Comparison of clinical and imaging characteristics between multiple system atrophy with predominantly presynaptic (MSA-SNpc[a]) nigrostriatal dysfunction and trans-synaptic (MSA-STR[b]) nigrostriatal dysfunction.

Characteristic	MSA-SNpc (n = 21)	MSA-STR (n = 40)	P-value
Male sex, n (%)	11 (52.4)	19 (47.5)	0.717
Age at onset (years), mean ± SD (range)	54.6 ± 8.2 (42.0–74.0)	58.0 ± 7.9 (41.0–74.0)	0.122
Disease duration at time of study (years), mean ± SD (range)	1.7 ± 0.7 (0.4–3.0)	1.7 ± 0.9 (0.3–3.0)	0.996
MMSE, mean ± SD (range)	26.5 ± 3.2 (17.0–30.0)	26.7 ± 3.5 (18.0–30.0)	0.837
Cerebellar type of multiple system atrophy, n (%)	16 (76.2)	12 (30.0)	0.001
UMSARS part I score, mean ± SD (range)	14.7 ± 5.1 (3.0–24.0)	17.9 ± 7.0 (5.0–39.0)	0.072
UMSARS part II score, mean ± SD (range)	12.9 ± 7.1 (1.0–26.0)	17.9 ± 8.6 (3.0–33.0)	0.025
UMSARS part III			
Change in systolic BP, mean ± SD (range)	25.6 ± 17.5 (−6.0, 63.0)	30.1 ± 18.0 (−-1.0, 70.0)	0.353
Change in diastolic BP, mean ± SD (range)	13.4 ± 18.2 (−-13.0, 61.0)	15.5 ± 12.9 (−-9.0, 43.0)	0.6
Change in heart rate, mean ± SD (range)	−-8.8 ± 8.3 (−-30.0, 6.0)	−-9.1 ± 8.4 (−-27.0, 6.0)	0.872
UMSARS part IV score, mean ± SD (range)	1.3 ± 0.7 (1.0–3.0)	2.2 ± 1.2 (1.0–5.0)	0.001
UPDRS part III score, mean ± SD (range)	17.3 ± 11.8 (0.0–54.0)	29.5 ± 16.8 (0.0–59.0)	0.005
Tremor subscore, mean ± SD (range)	1.1 ± 1.3 (0.0–6.0)	2.3 ± 2.0 (0.0–6.0)	< 0.001
Rigidity subscore, mean ± SD (range)	2.3 ± 2.3 (0.0–11.0)	5.4 ± 4.2 (0.0–15.0)	0.015
Bradykinesia subscore, mean ± SD (range)	8.6 ± 6.9 (0.0–28.0)	14.0 ± 8.5 (0.0–28.0)	0.031
Axial motor subscore, mean ± SD (range)	5.3 ± 3.8 (0.0–12.0)	7.7 ± 4.6 (0.0–17.0)	0.047
Cerebellar ataxia score, mean ± SD (range)	3.7 ± 2.1 (0.0–7.0)	2.5 ± 2.2 (0.0–9.0)	0.036
Good responsiveness to levodopa, n (%)[c]	3 (17.6%)	3 (9.4%)	0.65
%BR of the posterior putamen in [^{18}F]FP-CIT-PET, mean ± SD (range)	53.4 ± 14.0 (34.9–78.6)	58.9 ± 15.9 (34.5–89.7)	0.183
%MR of the posterior putamen in [^{18}F]FDG- PET, mean ± SD (range)	102.5 ± 7.7 (94.9–128.0)	78.6 ± 8.1 (64.9–89.9)	< 0.001

Abbreviations: BP, blood pressure; MMSE, Mini-Mental State Examination; %MR and %BR (described in the Methods section); SD, standard deviation; UMSARS, Unified Multiple System Atrophy Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] MSA-SNpc was defined as patients who simultaneously had a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a preserved %MR (≥95%) in the posterior putamen on [^{18}F]FDG-PET.

[b] MSA-STR was defined as patients who simultaneously had a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a decreased %MR (< 90%) in the posterior putamen on [^{18}F]FDG-PET.

[c] Responsiveness to levodopa was evaluated in 49 patients with multiple system atrophy.

using ordered subsets expectation maximization (two iteration and 24 subsets with post-smoothing of 2 mm full-width at half-maximum).

2.5. Quantitative analyses

The images were processed using the SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, UK) within MATLAB 2013a (MathWorks, Inc., Natick, MA). Quantitative analyses were based on volumes of interest (VOIs), as described previously. All reconstructed PET images were spatially normalized to Montreal Neurology Institute (MNI) template space using standard [^{18}F]FDG-PET (MNI PET template) and in-house [^{18}F]FP-CIT-PET templates to remove intersubject anatomic variability. The [^{18}F]FP-CIT-PET template was constructed using the [^{18}F]FP-CIT-PET images from 13 normal controls (four men, nine women; mean age 55.2 ± 9.2 years), as described elsewhere [12,13]. Similar to our previous study, bilateral striatal subregions were defined as target VOIs and one occipital VOI was defined as a reference VOI on the [^{18}F]FP-CIT template [13].

The positions of the automatically defined template VOIs (by SPM 8 spatial normalization onto [^{18}F]FP-CIT template) were adjusted manually by our in-house ANIQUE (AMC NM Image Quantification Toolkit of Excellence) VOI editing software to ensure the accuracy of registration [14]. The [^{18}F]FDG-PET images were analyzed similarly after spatial normalization. We defined the [^{18}F]FP-CIT template on MNI space and also adjusted the VOI position on both PET images so that we could assure the VOI positions of the striatum VOIs were identical between these two modalities. The activity concentration in each VOI on the [^{18}F]FDG and [^{18}F]FP-CIT-PET images was calculated and normalized by that of the reference region (i.e., occipital VOI); thus, the uptake ratio was used for the statistical analysis. The subregional glucose metabolic ratio (MR_{gluc}) and the subregional DAT binding ratio (BR_{DAT}) were defined as follows: MR_{gluc} = subregional VOI count/whole brain count on [^{18}F]FDG-PET; BR_{DAT} = (subregional VOI count − occipital VOI count)/occipital VOI count on [^{18}F]FP-CIT-PET. The normalized MR_{Gluc} (%MR) and normalized BR_{DAT} (%BR) were defined as follows: %MR = 100 × (MR_{gluc} for patient/mean MR_{gluc} for healthy controls); %BR = 100 × (BR_{DAT} for patient/mean BR_{DAT} for healthy controls). The count was defined as counts per voxel in each VOI in Bq/mL.

2.6. Statistical analysis

The continuous data are shown as the mean ± standard deviation and the categorical data as the count and percentage. The continuous data were compared using the independent t-test or nonparametric Mann-Whitney test. The categorical data were compared using the χ^2 test or Fisher's exact test. A P-value < .05 was considered statistically significant. The statistical analysis was performed using SPSS version 21.0 software (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Subjects

We investigated 61 MSA patients categorized into MSA-SNpc and MSA-STR. The imaging characteristics on [^{18}F]FDG-PET and [^{18}F]FP-CIT-PET of all 61 MSA patients are summarized in Supplementary Table 1. The patients were diagnosed with probable MSA (n = 45, 73.8%) or possible MSA (n = 16, 26.2%).

3.2. Comparison of clinical and imaging features between the MSA-SNpc and MSA-STR

The clinical and imaging features are compared between the MSA-SNpc and MSA-STR in Table 1. There was no significant difference in sex, age at onset, disease duration at the time of study, or MMSE scores between the MSA-SNpc and MSA-STR. The cerebellar type of MSA was significantly more common in the MSA-SNpc than in the MSA-STR (P = .001). Parkinsonian features, including tremor, rigidity,

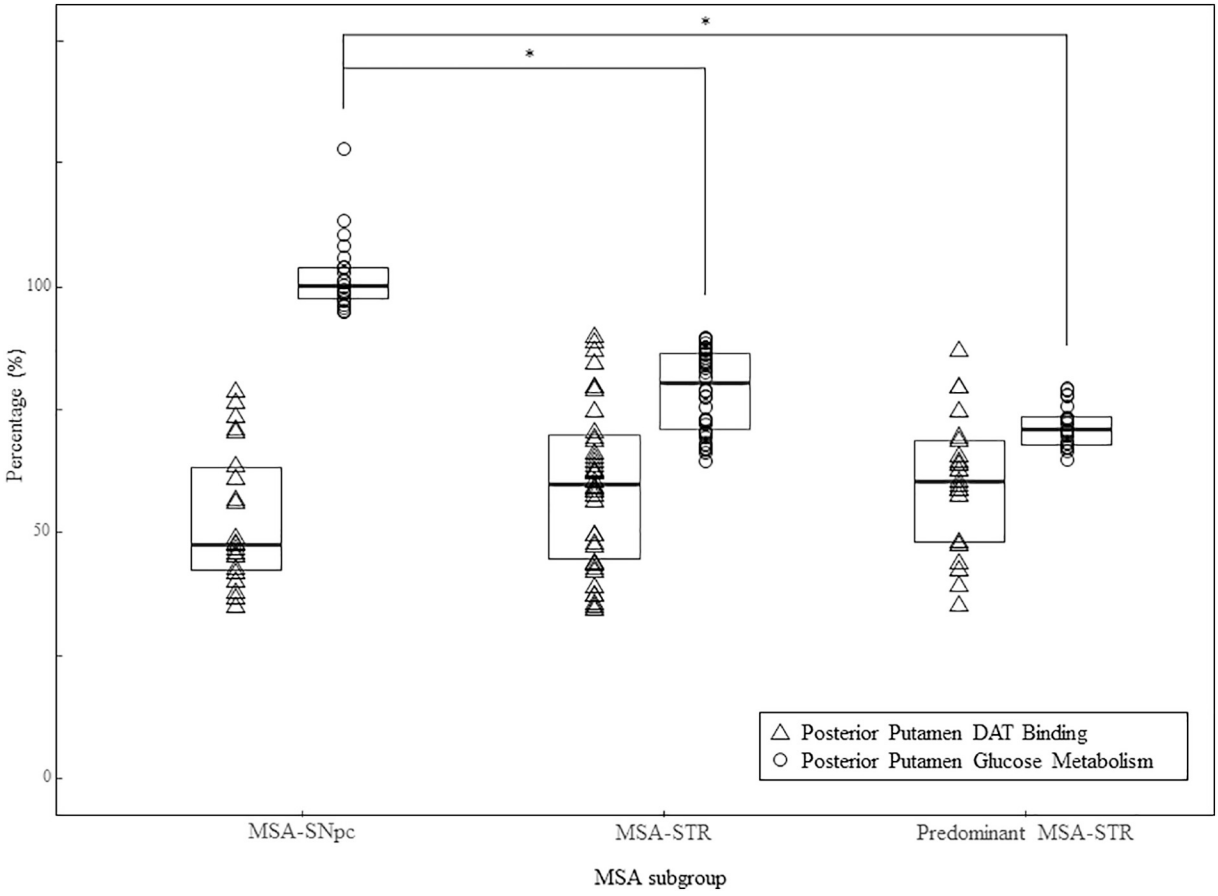

Fig. 1. Normalized DAT binding ratio (%BR) and normalized metabolic ratio (%MR) of the posterior putamen. The %MRs of the posterior putamen are significantly lower in patients with MSA-STR and predominant MSA-STR than in those with MSA-SNpc. *$P < .001$.

bradykinesia, and axial motor features, were significantly more severe in the MSA-STR than in the MSA-SNpc ($P < .001$, $P = .015$, $P = .031$, and $P = .047$, respectively). However, cerebellar ataxia was significantly more severe in the MSA-SNpc than in the MSA-STR ($P = .036$). There was no significant difference in the orthostatic change in BP or responsiveness to levodopa between the MSA-SNpc and the MSA-STR. The mean %BR in the posterior putamen was 53.4% in the MSA-SNpc and 58.9% in the MSA-STR. The mean %MR in the posterior putamen was 102.5% in the MSA-SNpc and 78.6% in the MSA-STR (Fig. 1). Fig. 2 shows representative [^{18}F]FDG-PET and [^{18}F]FP-CIT-PET images in MSA patients categorized as MSA-SNpc or MSA-STR.

3.3. Comparison between extreme cases with predominantly MSA-STR or MSA-SNpc

The extreme cases in a predominantly MSA-STR subgroup ($n = 21$) that included patients who simultaneously had a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a decreased %MR (< 80%) in the posterior putamen on [^{18}F]FDG-PET (Table 2). The part I, II, and IV UMSARS scores were significantly more severe in the predominantly MSA-STR than in the MSA-SNpc ($P = .028$, $P = .002$, and $P = .002$, respectively). Parkinsonian features, assessed by UPDRS part III scores, including tremor, rigidity, bradykinesia, and axial motor features, were significantly more severe in the predominantly MSA-STR than in the MSA-SNpc ($P = .008$, $P < .001$, $P < .001$, and $P = .022$, respectively). However, the score for cerebellar ataxia was significantly higher in the MSA-SNpc than in the predominantly MSA-STR ($P = .006$). There was no difference in sex, age at onset, disease duration at the time of study, MMSE, orthostatic change in BP, or responsiveness to levodopa between the MSA-SNpc and the predominantly MSA-STR (Table 2).

4. Discussion

In this study, we demonstrated a distinct difference in clinical features between MSA patients with predominantly pre-synaptic (MSA-SNpc) nigrostriatal dysfunction and those with trans-synaptic (MSA-STR) nigrostriatal dysfunction. Patients in the MSA-SNpc had significantly less severe parkinsonism but more severe cerebellar ataxia than those in the MSA-STR. These findings may aid our understanding of the heterogeneous neuropathology in MSA.

The parkinsonian features in the MSA-SNpc was less severe than those in the MSA-STR, although there was no significant difference in age at onset, disease duration at the time of study, or sex distribution between the two groups. Bradykinesia and rigidity in MSA originate principally from the combination of nigral and striatal degeneration. However, their relative importance in producing parkinsonism, and whether the degenerative process starts in one or both regions, is unclear [2]. One possible explanation is that the pre-synaptic parkinsonism is alleviated by other clinical manifestations, such as cerebellar ataxia, which may mask parkinsonism to be predominant. Rivest et al. reported that cerebellar strokes reduced parkinsonian rigidity on the ipsilateral side [15]. Another potential compensatory mechanism is the role of the subthalamic nucleus (STN) in MSA. Schöls et al. suggested that neurodegeneration in the motor territory of the STN prevents parkinsonism caused by degeneration of the substantia nigra in types 2 and 3 spinocerebellar ataxia [16]. Similarly, the anti-parkinsonian effects of high-frequency stimulation of the motor territory of the STN in PD point to a common pathophysiological explanation [17]. Recently,

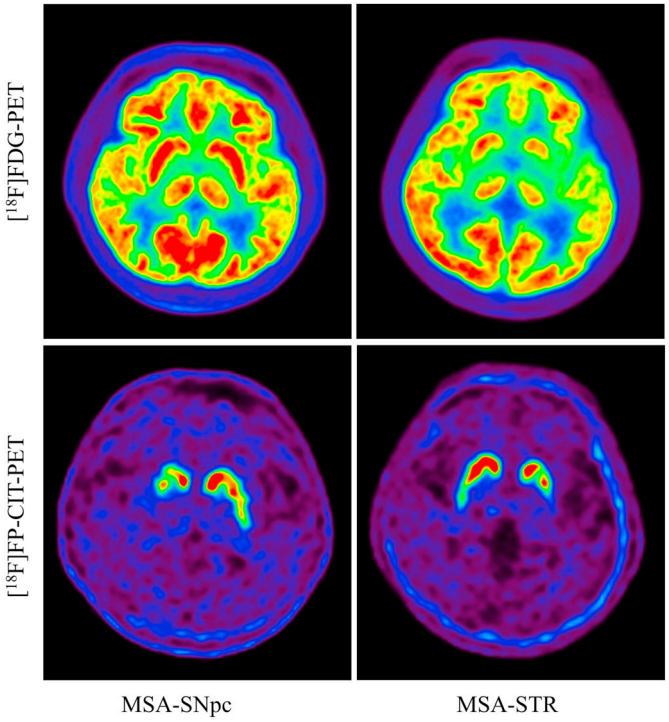

Fig. 2. Representative [^{18}F]FDG and [^{18}F]FP-CIT-PET images in patients with MSA. Patients in the MSA-SNpc group showed decreased uptake on [^{18}F]FP-CIT-PET images and normal glucose metabolism on [^{18}F]FDG-PET images. Patients in the MSA-STR group showed decreased glucose metabolism on [^{18}F]FDG-PET images and decreased uptake on [^{18}F]FP-CIT-PET images.

Cykowski et al. demonstrated that alpha-synuclein-positive pathologic inclusions were present in the STN in MSA, even though the macroscopic appearance of STN in MSA is typically reported to be normal [18,19]. In this study, the MSA-SNpc showed more severe cerebellar ataxia, which may be associated with alleviation of pre-synaptic parkinsonism. Further studies are needed to investigate the potential role of the STN in MSA.

Although the therapeutic response to levodopa is poor in a large proportion of MSA patients, up to 40% of these patients may show, at least initially, a good or even excellent response to dopaminergic medications, so that a trial of levodopa up to a target dose of 1 g/day if necessary and tolerated is recommended [2,20–22]. In clinical practice, exacerbation of orthostatic hypotension, nausea, or sleepiness often limits the administration and augmentation of levodopa [20,23]. Therefore, it is important that we find a biomarker that predicts the responsiveness to levodopa of MSA patients on an individual basis. Wenning et al. reported that levodopa was highly effective in patients in whom the putamen was relatively conserved in relation to the degree of nigral neuronal loss and that the effect of levodopa was negatively correlated with the degree of nigral degeneration [5]. In this study, there was no significant difference of response to levodopa between MSA-STR and MSA-SNpc irrespective of [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET findings.

These findings suggest that MSA patients with good response to levodopa might not have been included in this retrospective study and some patients with early-stage MSA that resembled PD might not have been evaluated by [^{18}F]FDG-PET. The frequency of good response to levodopa was approximately 12% in this study, which is lower than that in previously reported studies [20]. The significant difference in the proportion of MSA-C between MSA-SNpc and MSA-STR could also influence the result of the response to levodopa. Another possible explanation is that considering degeneration of the nigrostriatal pathway alone might not be enough to predict levodopa responsiveness in MSA, suggesting a high variability of severity and regional distributions of neurodegeneration beyond the nigrostriatal system. Further studies are needed to confirm the exact relationship between the integrity of the nigrostriatal pathway and responsiveness to levodopa in MSA.

In this study, the existence of the PET imaging-based classification

Table 2
Comparison of clinical characteristics between multiple system atrophy with predominant presynaptic (MSA-SNpc[a]) and trans-synaptic (MSA-STR[b]) nigrostriatal dysfunction.

Characteristic	MSA-SNpc (n = 21)	Predominant MSA-STR (*n* = 21)	*P*-value
Male sex, n (%)	11 (52.4)	11 (52.4)	> 0.999
Age at onset (years), mean ± SD (range)	54.6 ± 8.2 (42.0–74.0)	59.1 ± 7.8 (46.0–74.0)	0.074
Disease duration at time of study (years), mean ± SD (range)	1.7 ± 0.7 (0.4–3.0)	1.6 ± 0.9 (0.4–3.0)	0.860
MMSE, mean ± SD (range)	26.5 ± 3.2 (17.0–30.0)	26.3 ± 4.0 (18.0–30.0)	0.751
Cerebellar type of multiple system atrophy, n (%)	16 (76.2)	5 (23.8)	0.001
UMSARS part I score, mean ± SD (range)	14.7 ± 5.1 (3.0–24.0)	18.4 ± 5.6 (5.0–29.0)	0.028
UMSARS part II score, mean ± SD (range)	12.9 ± 7.1 (1.0–26.0)	19.6 ± 6.3 (4.0–31.0)	0.002
UMSARS part III score			
Systolic BP change, mean ± SD (range)	25.6 ± 17.5 (−6.0, 63.0)	27.5 ± 15.7 (−6.0, 63.0)	0.705
Diastolic BP change, mean ± SD (range)	13.4 ± 18.2 (−13.0, 61.0)	13.9 ± 12.5 (−13.0, 61.0)	0.597
Heart rate change, mean ± SD (range)	−8.8 ± 8.3 (−30.0, 6.0)	−9.9 ± 8.5 (−27.0, 3.0)	0.662
UMSARS part IV score, mean ± SD (range)	1.4 ± 0.7 (1.0–3.0)	2.3 ± 1.0 (1.0–4.0)	0.002
UPDRS part III score, mean ± SD (range)	17.3 ± 11.8 (0.0–54.0)	34.3 ± 12.6 (0.0–54.0)	< 0.001
Tremor subscore, mean ± SD (range)	1.1 ± 1.3 (0.0–6.0)	2.4 ± 1.7 (0.0–6.0)	0.008
Rigidity subscore, mean ± SD (range)	2.3 ± 2.3 (0.0–11.0)	6.4 ± 3.6 (0.0–11.0)	< 0.001
Bradykinesia subscore, mean ± SD (range)	8.6 ± 6.9 (0.0–28.0)	17.3 ± 6.1 (0.0–28.0)	< 0.001
Axial motor subscore, mean ± SD (range)	5.3 ± 3.8 (0.0–12.0)	8.2 ± 3.9 (0.0–12.0)	0.022
Cerebellar ataxia score, mean ± SD (range)	3.7 ± 2.1 (0.0–7.0)	1.9 ± 1.9 (0.0–7.0)	0.006
Good responsiveness to levodopa, n (%)[c]	3 (17.6%)	1 (5.3%)	0.326
%BR in the posterior putamen on [^{18}F]FP-CIT-PET, mean ± SD (range)	53.4 ± 14.0 (34.9–78.6)	60.2 ± 13.9 (35.2–86.8)	0.122
%MR in the posterior putamen on [^{18}F]FDG- PET, mean ± SD (range)	102.5 ± 7.7 (94.9–128.0)	71.7 ± 4.3 (64.9–79.2)	< 0.001

Abbreviation: SD, standard deviation; MMSE, Mini-Mental State Examination; MSA-C type, cerebellar type of MSA; %MR and %BR (described in method); UMSARS, Unified Multiple System Atrophy Rating Scale; UPDRS, Unified Parkinson's disease rating scale; SD, standard deviation.

[a] MSA-SNpc was defined as patients who simultaneously had a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a preserved %MR (≥95%) in the posterior putamen on [^{18}F]FDG-PET.

[b] MSA-STR was defined as patients who simultaneously had a decreased %BR (< 90%) in the posterior putamen on [^{18}F]FP-CIT-PET and a decreased %MR (< 80%) in the posterior putamen on [^{18}F]FDG-PET.

[c] Responsiveness to levodopa was evaluated in 36 patients with MSA.

of MSA-SNpc and MSA-STR suggests that there may be multiple ways MSA pathology spreads throughout the brain. Wenning et al. suggested a nigrostriatal-specific grading scheme that could interpret the spread of MSA pathology [24]. Jellinger et al. proposed semi-quantitative assessment of the distribution of neuronal loss, astrocytosis, and glial cytoplasmic inclusions (GCIs) in various brain areas, distinguished four degrees of severity of both striatonigral degeneration and olivopontocerebellar atrophy [25]. Halliday et al. graphically depicted the two major types of MSA, as well as the overlap between olivopontocerebellar atrophy and striatonigral degeneration [26]. Recent evidence suggests that toxic alpha-synuclein spreads through the brain in a prion-like manner in alpha-synucleinopathies to other functionally connected neuronal networks [27]. In addition, high variability of both neuronal loss and density of GCIs should be considered in MSA. Some regions, such as the motor cortex, have a high density of GCIs even though they are histologically unremarkable, indicating that neurodegeneration is not a prerequisite for developing GCIs [28]. Furthermore, the substantia nigra, despite severe neuronal loss, usually shows a relatively low density of GCIs in MSA patients. Other factors might contribute to neuronal loss in certain areas or these may be affected earlier in the disease course and have already been burned out [29].

Interestingly, some MSA patients categorized as MSA-SNpc showed striatal hypermetabolism in this study (Fig. 1 and Supplementary Table 1), although it has been widely accepted that glucose metabolism in the striatum of MSA is decreased [30]. We included the MSA patients who had within 3 years of disease duration and predominatly pre-synaptic nigrostriatal dysfunction as MSA-SNpc, which could be a explanation for this discrepancy. In addition, the cause of striatal hypermetabolism in some MSA patients is unknown. In patients with PD, striatal hypermetabolism might be explained as a compensatory mechanism against pre-synaptic dopaminergic dysfunction [31]. Likewise, we suggest that the striatal hypermetabolism might be a compensatory effort to maintain motor function in early stage MSA patients with predominantly pre-synaptic nigrostriatal dysfunction.

This study has several strengths and limitations. To our knowledge, it is the first study to investigate the correlation between the clinical features and reciprocal integrity of the pre-synaptic and trans-synaptic nigrostriatal pathway using [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET in MSA. Second, it investigated patients with early-stage MSA to determine the early pathological changes in MSA. However, its retrospective design is an inherent limitation, and the study is limited by the diagnoses being made clinically rather than at autopsy diagnosis. The patients selected according to the neuroimaging criteria could not represent the MSA patients as a whole. These methodological limitations might be associated with selection bias. Therefore, further studies are needed to confirm our findings. In conclusion, a combination of [^{18}F]FP-CIT-PET and [^{18}F]FDG-PET is useful in help to explain the variable clinical features in patient with early stage MSA. We expect this study could provide useful information on understanding the heterogeneous phenotype associated with variable nigrostriatal dysfunction in early stage MSA patients.

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Relevant conflict of interest statement

All authors have no actual or potential conflicts of interest.

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Author contributions

Professor Chung contributed to the conception, organization and execution of the research project, design, execution, review, and critique of the statistical analysis, writing of the first draft, and review and critique of the manuscript. Dr. Ryu contributed to the execution of the research project, design, execution, review and critique of the statistical analysis, writing of the first draft, and review and critique of the manuscript. Professor Jae Seung Kim contributed to the conception, organization, and execution of the research project, design, execution, review and critique of the statistical analysis, review and critique of the manuscript. Dr. Minyoung Oh contributed to the conception, organization, and execution of the research project, design, execution, review, and critique of the statistical analysis, and review and critique of the manuscript. Professor Jongsu Oh contributed to the conception, organization, and execution of the research project, design, execution, review, and critique of the statistical analysis, and review and critique of the manuscript. Hyojeong Moon contributed to the conception, organization, and execution of the research project, design, execution, review, and critique of the statistical analysis, and review and critique of the manuscript. Dr. Park contributed to the conception, organization, and execution of the research project, design, execution, review, and critique of the statistical analysis, and review and critique of the manuscript. Dr. Lee contributed to the conception, organization, and execution of the research project, design, execution, review, and critique of the statistical analysis, and review and critique of the manuscript. Professor You contributed to the execution of the research project, design, execution, review, and critique of the statistical analysis, and review and critique of the manuscript. Professor Mi-Jung Kim contributed to the execution of the research project, design, execution, review and critique of the statistical analysis, and review and critique of the manuscript. Dr. Young Jin Kim contributed to the execution of the research project, design, execution, review, and critique of the statistical analysis, and review and critique of the manuscript. Dr. Juyeon Kim contributed to execution of the research project, the design, execution, review and critique of the statistical analysis, and review and critique of the manuscript. Dr. Kiju Kim contributed to the execution of the research project, design, execution, review and critique of the statistical analysis, and review and critique of the manuscript.

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All coauthors have seen and agree with the contents of the manuscript, that the ICMJE requirements for authorship have been met, and that each author believes that the manuscript represents honest work.

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