

Effects of disease duration on the clinical features and brain glucose metabolism in patients with mixed type multiple system atrophy

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To study the effect of disease duration on the clinical, neuropsychological and [¹⁸F]-deoxyglucose (FDG) PET findings in patients with mixed type multiple system atrophy (MSA), this study included 16 controls and 37 mixed-type MSA patients with a shorter than a 3-year history of cerebellar or parkinsonian symptoms. We classified the patients into three groups according to the duration of parkinsonian or cerebellar symptoms (Group I = ≤ 1 year; II = 13–24 months; III = 25–36 months). We performed UPDRS, international cooperative ataxia rating scale (ICARS), and a neuropsychological test battery. We compared the FDG PET findings of each group of patients with controls. Group I patients frequently had memory and frontal executive dysfunction. They showed hypometabolism in the frontal cortex, anterior cerebellar hemisphere and vermis. They had parkinsonian motor deficits, but no basal ganglia hypometabolism. Group II and III patients frequently had multiple domain cognitive impairments, and showed hypometabolism in the frontal and parieto-temporal cortices. Hypometabolism of the bilateral caudate and the left posterolateral putamen was observed in Group II, and whole striatum in Group III. In summary, the cortical hypometabolism begins in the frontal cortex and spreads to the parieto-temporal cortex in MSA. This spreading pattern coincides with the progressive cognitive decline. Early caudate hypometabolism may also contribute to the cognitive impairment. Parkinsonian motor deficits precede putaminal hypometabolism that begins in its posterolateral part. Cerebellar hypometabolism occurs early in the clinical courses and seems to be a relevant metabolic descriptor of cerebellar deficits.

Keywords: multiple system atrophy; cognitive impairment; positron emission tomography

Abbreviations: COWAT = controlled oral word association test; FDG = [¹⁸F]-deoxyglucose; FWHM = full-width half-maximum; GCI = glial cytoplasmic inclusion; ICARS = international cooperative ataxia rating scale; IQR = interquartile range; K-BNT = Korean version of the Boston naming test; MSA = multiple system atrophy; PET = positron emission tomography; RCFT = Rey–Osterrieth complex figure test; SVLT = Seoul verbal learning test; TE = echo time; TR = repetition time; UPDRS = unified Parkinson's disease rating scale.

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Introduction

Patients with multiple system atrophy (MSA) usually present with a variable mixture of parkinsonian, cerebellar, pyramidal and autonomic symptoms and signs (Wenning *et al.*, 1997). Pathological studies of MSA show degeneration of the substantia nigra, striatum, pallidum, cerebellum, pontine nuclei, inferior olivary nucleus, pyramidal tract and intermediolateral cell column of the spinal cord. In addition to neuronal loss and gliosis, glial and neuronal inclusion

bodies occur in cerebral white matter and cortices, as well as the striatonigral and olivopontocerebellar systems (Papp *et al.*, 1989; Papp and Lantos, 1994). However, post-mortem pathological findings usually represent the end result, but not the early evolution of the disease.

In vivo examinations of MSA patients with positron emission tomography (PET) and single photon emission computed tomography studies have shown hypometabolism and hypoperfusion in the frontal cortex, striatum,

cerebellum and brainstem (De Volder *et al.*, 1989; Eidelberg *et al.*, 1993; Perani *et al.*, 1995; Antonini *et al.*, 1997; Taniwaki *et al.*, 2002; Juh *et al.*, 2004; Cilia *et al.*, 2005; Matsui *et al.*, 2005). However, most studies showed a sum of neuronal functional changes in a small number of patients without controlling for age, age at the onset of disease, duration of disease and severity of clinical deficits.

Duration of the disease is an important factor that would influence topographical distribution and severity of pathological changes of neurodegenerative diseases (Apaydin *et al.*, 2002). To understand the pattern of evolution of pathological changes, we investigated the effect of disease duration on the findings of [¹⁸F]-deoxyglucose (FDG) PET studies in patients with early MSA.

Patients

From July 2004 to May 2007, 75 MSA patients, who fulfilled consensus criteria for possible or probable MSA (Gilman *et al.*, 1999), were admitted to Youngdong Severance Hospital, Yonsei University, Seoul, Korea. Of these, 55 patients were recruited with a shorter than a 3-year history of parkinsonian or cerebellar symptoms, regardless of the duration of autonomic symptoms. Of the 55 patients, 36 patients had probable MSA and the remaining 19 patients had possible MSA. During the follow-up period (mean = 12.9 months), twelve of 19 patients with possible MSA developed autonomic dysfunction sufficient for the diagnosis of probable MSA. Of the 48 probable MSA patients, we excluded three patients with pure cerebellar type MSA and five patients with pure parkinsonian type MSA to include rather homogeneous patients. We also excluded three patients with the Korean version of Mini Mental State Examination (K-MMSE) score lower than 24. Among the 37 patients with mixed type MSA, 19 patients (predominated by parkinsonism = 11, predominated by cerebellar deficits = 8) were receiving a single levodopa treatment (mean daily dose = 739.5 mg) or a combination with selegiline (daily dose = 5 mg).

Thus, this study included 37 patients with mixed type MSA and 16 age-matched healthy controls [median age = 61.0 years, interquartile range (IQR) = 58.0–64.3 years, 5 males and 11 females]. According to the duration of parkinsonian or cerebellar symptoms, patients were classified into three groups (Group I = duration 1 year or shorter; Group II = duration between 13 and 24 months; Group III = duration between 25 and 36 months). In all subjects, PET studies were performed after written informed consents.

Methods

Evaluation of parkinsonian and cerebellar deficits

We measured the unified Parkinson's disease rating scale (UPDRS) motor score to assess the degree of parkinsonian deficits and the international cooperative ataxia rating scale (ICARS) scores to evaluate the severity of cerebellar deficits (Trouillas *et al.*, 1997).

Evaluation of cognitive function

Thirty-five of the 37 patients underwent a standardized neuropsychological test battery (Seoul Neuropsychological Screening Battery) (Kang and Na, 2003). The battery consists of various tests evaluating attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructional function, verbal and visual memory, and frontal executive functions. Among them, numerical tests were digit span test (forward and backward), Korean version of the Boston Naming Test (K-BNT) (Kim and Na, 1999), Rey–Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-min delayed recall and recognition), Seoul Verbal Learning Test (SVLT; three learning-free recall trials of 12 words, 20-min delayed recall trial for these 12 items and a recognition test), phonemic and semantic Controlled Oral Word Association Test (COWAT) and Stroop Test (word and colour reading of 112 items during a 2-min period). Age-, sex-, and education-specific norms for each test based on 447 healthy subjects were available.

We classified the cognitive function domain into four categories; memory, language, visuospatial function and frontal executive function and the pattern of cognitive dysfunction as single domain or multiple domain impairments. Memory function was evaluated with the delayed recall on the SVLT or the RCFT, language function with K-BNT and visuospatial function with copying score of the RCFT. The results of these numerical cognitive tests were considered as abnormal when the scores were below the 16th percentiles of the norms for the age-, sex- and education-matched controls (Kang and Na, 2003). The patients were considered to have frontal executive dysfunction if they showed impairment in at least two of the following three tests: motor executive function tests (contrasting programme, Go/no-go, fist-edge-palm, alternating hand movement, alternative square and triangle drawing and Luria loop), the COWAT and the Stroop Test.

Brain FDG PET studies

Acquisition of FDG PET scan images

After overnight fasting and withdrawal of all anti-parkinsonian medications, FDG PET study was performed in a quiet and dimly lit room with the subjects' eyes open. After injecting 5.18 MBq/kg of FDG into the antecubital vein, radial arterial blood was sampled nine times at 5 to 10-s intervals for 1 min and then sampled 15 times at 30 s to 10 min of progressively increasing intervals. The [¹⁸F]-radioactivity curve was obtained for quantification. Using an Allegro PET scanner (Philips Medical Systems; gadolinium oxyorthosilicate crystals), PET scanning was performed at 45–55 min after injecting FDG. After 1.5 min of transmission, 17 min of emission and a final 1.5 min of transmission scans, three-dimensional (3D) PET image was reconstructed by 3D-RAMLA (3D version of the row action maximum likelihood algorithm).

Brain magnetic resonance imaging (MRI) studies

On the day of PET scan studies, brain MRI studies were performed using 3D spoiled gradient-recalled (3D-SPGR) sequences on 3.0 Tesla MR scanner (Signa EXCITE, GE Medical Systems, Milwaukee, WI). We obtained 160 slices of axial T₁-weighted images with a repetition time (TR) of 6.8 ms, a minimum of echo time (TE) between 1.6 and 11.0 ms, a prep time of 300 msec, a flip angle of 20°,

Table 1 Clinical characteristics of the 37 patients with MSA with different disease duration

	Group I <i>n</i> = 13	Group II <i>n</i> = 12	Group III <i>n</i> = 12	Total <i>n</i> = 37
MSA-P: MSA-C	4 : 9	6 : 6	7 : 5	17 : 20
Male: Female	9 : 4	7 : 5	6 : 6	22 : 15
Age (years)	58.0 (51.0–65.0)	60.5 (49.8–69.0)	61.0 (57.8–64.5)	61.0 (55.0–64.5)
Age of onset (years)	57.0 (50.5–64.5)	59.5 (48.5–67.3)	58.5 (55.8–61.8)	59.0 (53.5–62.5)
Duration (months)	8.0 (7.0–12.0)	15.5 (14.0–21.0)	32.0 (27.0–34.5)	15.0 (12.0–27.0)
UPDRS motor score	22.0 (16.5–25.0)	23.0 (18.3–32.3)	32.5 (20.8–39.5)	23.0 (19.0–33.5)
ICARS score	19.0 (14.0–30.5)	26.5 (18.5–34.8)	28.5 (20.5–37.5)	23.0 (18.0–34.5)
Urinary incontinence	6 → 9	8 → 10	8 → 9	22 → 28
Orthostatic hypotension	7 → 10	3 → 4	8 → 8	18 → 22

Data are presented as median (interquartile range) and number of patients. The numbers shown in the urinary incontinence and orthostatic hypotension lines represent the number of patients with autonomic dysfunction fulfilling the criteria of probable MSA (Gilman *et al.*, 1999) at the initial evaluation and follow-up visits. (*n* = number of patients; MSA-P = MSA with predominantly parkinsonian features; MSA-C = MSA with predominantly cerebellar deficits; UPDRS = Unified Parkinson's Disease Rating Scale; ICARS = International Cooperative Ataxia Rating Scale).

a matrix of 256 × 256 and a slice thickness of 1 mm. The resulting 3D-MR image was reformatted parallel to the anterior and posterior commissures (AC-PC) line and centred at the midpoint of AC-PC line. Finally, the image was resampled with a voxel size of 1 × 1 × 1 mm for normalization. We also obtained 32 slices of axial T₂-weighted images (TR = 5,250 ms, TE = 120 ms, flip angle = 90°, matrix = 512 × 512 and slice thickness = 5 mm).

Pre-processing of PET and MR images

Individual MR images were used for spatial normalization of the FDG PET image. Normalization was performed automatically with the PFUS module in the software PMOD version 2.75 (PMOD technologies Ltd., Zurich, Switzerland). The subject's FDG PET image was co-registered to individual MR image. Using affine transformation and 12 non-linear iteration by 7 × 8 × 7 basis function, the MR image was transformed to MNI-152 (Montreal Neurological Institute) T₁-weighted MRI template. During this step, the individual transformation matrix was obtained and applied to the co-registered FDG PET image. Finally, a spatially normalized FDG PET image was obtained. The fitness of normalized PET and MR images was verified visually in each normalization step.

The parametric PET image was generated by the PMOD with FDG-autoradiography method (lump constant = 0.437, *k*₁ = 0.102, *k*₂ = 0.130, *k*₃ = 0.062, *k*₄ = 0.0068) (Huang *et al.*, 1980). Subsequently, an isotropic Gaussian kernel of 12 mm full-width half-maximum (FWHM) was applied to the parametric PET image to improve the signal-to-noise ratio. Finally, this normalized and smoothed parametric PET image was used for statistical analysis.

Statistical parametric mapping

Using the group comparison model covaried with age in SPM2 (Statistical Parametric Mapping; Wellcome Department of Cognitive Neurology, London, UK) implemented to MATLAB 7.0 (MathWorks, Natick, MA), we compared the cerebral glucose metabolism of each subgroup of MSA patients with the controls. A family wise error (FWE)-corrected *P*-value <0.05 was considered statistically significant.

Results

Characteristics and clinical features of patients (Table 1)

Of the 37 patients with mixed type MSA (22 men and 15 women), 17 patients had predominantly parkinsonian features (MSA-P) and the other 20 patients predominantly cerebellar deficits (MSA-C). There were 13 patients in Group I (MSA-P = 4, MSA-C = 9), 12 patients in Group II (MSA-P = 6, MSA-C = 6) and 12 patients in Group III (MSA-P = 7, MSA-C = 5).

The ages of the patients (median age = 61.0 years, IQR = 55.0–64.5 years) and controls were not different (Mann–Whitney Test, *P* > 0.05). In addition, the ages of the three groups of MSA patients [median (IQR) age: Group I = 58.0 (51.0–65.0), Group II = 60.5 (49.8–69.0), Group III = 61.0 (57.8–64.5) years] and controls were not significantly different (Kruskal–Wallis Test, *P* = 0.851). The *post hoc* comparison between each group and controls also did not show difference (Mann–Whitney Test, *P* > 0.05). The median (IQR) age of disease onset was 59.0 (53.5–62.5) years. The median (IQR) of disease duration was 15.0 (12.0–27.0) months [Group I = 8.0 (7.0–12.0) months, Group II = 15.5 (14.0–21.0) months, Group III = 32.0 (27.0–34.5) months].

The median (IQR) UPDRS motor score was 23.0 (19.0–33.5) and the median (IQR) ICARS score was 23.0 (18.0–34.5). There was significant difference in the UPDRS motor scores among the three groups (Kruskal–Wallis Test, *P* = 0.037). However, the ICARS scores were not significantly different among the three groups (Kruskal–Wallis Test, *P* = 0.164).

Cognitive dysfunction (Table 2)

The median (IQR) K-MMSE score of the 37 patients was 29.0 (27.5–30.0). No patient satisfied the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for dementia.

Table 2 Results of neuropsychological tests of the 35 patients with MSA with different disease duration

	Group I	Group II	Group III	Total
K-MMSE score	<i>n</i> = 13	<i>n</i> = 12	<i>n</i> = 12	<i>n</i> = 37
	29.0 (28.0–30.0)	29.0 (27.0–29.0)	28.0 (26.0–30.0)	29.0 (27.5–30.0)
Neuropsychological test	<i>n</i> = 13	<i>n</i> = 12	<i>n</i> = 10	<i>n</i> = 35
Normal	4 (30.8%)	1 (8.3%)	1 (10.0%)	6 (17.1%)
Single domain	5 (38.5%)	6 (50.0%)	3 (30.0%)	14 (40.0%)
Multiple domain	4 (30.8%)	5 (41.7%)	6 (60.0%)	15 (42.9%)
Impaired domain				
M	7 (53.8%)	9 (75.0%)	7 (70.0%)	23 (65.7%)
E	4 (30.8%)	7 (58.3%)	6 (60.0%)	17 (48.6%)
V	2 (15.4%)	3 (25.0%)	4 (40.0%)	9 (25.7%)
L	1 (7.7%)	1 (8.3%)	0 (0%)	2 (5.7%)

Data are presented as median (interquartile range) and number of patients. (*n* = number of patients; M = memory dysfunction; E = executive dysfunction; V = visuospatial dysfunction; L = language dysfunction; K-MMSE = Korean version of Mini Mental State Examination).

Among 35 patients who underwent neuropsychological tests, only six (17.1%) showed a normal cognitive function in all four domains tested (memory, frontal, visuospatial and language functions). Four of them were in Group I, and the remaining two were in Group II and III. Twenty-nine patients (82.9%) had impairments in at least one cognitive domain. Twenty-three patients (65.7%) had memory impairment, 17 (48.6%) had frontal dysfunction, nine (25.7%) had visuospatial dysfunction and two (5.7%) had language dysfunction. Fourteen of the 35 patients (40.0%) had an impairment in a single domain (either memory, frontal, visuospatial or language dysfunction). Fifteen patients (42.9%) had impairments in at least two domains. The individuals with multiple domain impairments were found more frequently in Group III (six patients, 60.0%) than in Group I (four patients, 30.8%) and Group II (five patients, 41.7%).

T₂-weighted brain MRI findings (Table 3)

Of the 37 patients with MSA, 34 patients had cerebellar cortical atrophy and 23 patients had hot cross bun sign in the pons. They were frequently found even in Group I patients. About one-third of the patients showed more than moderate degree of atrophy of the posterior putamen. The putaminal rim sign (high signal intensity lines lateral to the putamen) was observed in 13 of the 37 patients. It was found in patients with duration longer than 12 months.

PET findings (Table 4, Figs 1 and 2)

Patients in Group I showed decreased glucose metabolism in the right lateral and medial frontal cortex (Brodmann area; BA6, 8, 9, 45 and 47), left lateral and medial frontal

Table 3 The T₂-weighted brain MRI findings related to MSA

	Group I <i>n</i> = 13	Group II <i>n</i> = 12	Group III <i>n</i> = 12	total <i>n</i> = 37
Atrophy of cerebellar cortex				
Normal	2 (15%)	1 (8%)	0	3 (8%)
Mild	7 (54%)	4 (33%)	7 (58%)	18 (49%)
Moderate	4 (31%)	7 (58%)	5 (42%)	16 (43%)
Hot cross bun sign	7 (54%)	7 (58%)	9 (75%)	23 (62%)
Atrophy of posterior putamen				
Normal	1 (8%)	0	0	1 (3%)
Mild	10 (77%)	5 (42%)	8 (67%)	23 (62%)
Moderate	2 (15%)	6 (50%)	2 (17%)	10 (27%)
Severe	0	1 (8%)	2 (17%)	3 (8%)
Putaminal rim sign	0	7 (58%)	6 (50%)	13 (35%)

cortex (BA6, 8, 9, 44 and 45), cerebellar vermis and bilateral anterior cerebellar hemispheres. Group II patients showed hypometabolism in the right lateral frontal cortex (BA4, 6, 8, 9, 10, 45 and 47), left lateral and medial frontal cortex (BA4, 6, 8, 9, 10, 11, 45, 46 and 47), right superior, middle and inferior temporal cortex (BA20, 21, 22 and 42), left superior, middle and inferior temporal cortex (BA21, 37, 39 and 42), left fusiform gyrus (BA20 and 37), right post-central gyrus (BA3, 1 and 2), left angular gyrus (BA39), left precuneus (BA19) and right posterior cingulate cortex (BA31). There were also hypometabolic areas involving bilateral caudate nucleus and left posterolateral putamen. Also, the cerebellar vermis and bilateral cerebellar hemispheres were involved. Comparing to the Group II patients, the basal ganglia hypometabolic area in the Group III patients spread anteromedially to involve the entire putamen and globus pallidus.

Discussion

Cerebral cortical dysfunction in early MSA

FDG PET studies of MSA patients have reported normal or reduced cerebral cortical glucose metabolism (De Volder *et al.*, 1989; Kume *et al.*, 1992; Perani *et al.*, 1995; Taniwaki *et al.*, 2002; Juh *et al.*, 2004; Juh *et al.*, 2005). However, MSA patients with shorter than a 3-year history of cerebellar or parkinsonian symptoms may show glucose hypometabolism in the primary motor, premotor and prefrontal cortices (De Volder *et al.*, 1989; Otsuka *et al.*, 1996).

In the present study, MSA patients with disease duration shorter than 1 year showed frontal hypometabolism, and patients with disease durations longer than a year showed hypometabolism in more widespread cerebral cortical areas involving the frontal, temporal, parietal and cingulate cortices. In contrast to patients with Parkinson's disease, the parieto-temporal association and occipital cortices were preserved (Eidelberg *et al.*, 1994; Hu *et al.*, 2000). The partial volume effect of the grey matter atrophy can affect

Table 4 Results of statistical parametric mapping analysis showing brain areas of reduced glucose metabolism (family wise error corrected $P < 0.05$)

	Group I					Group II					Group III				
	BA	x	y	z	T	BA	x	y	z	T	BA	x	y	z	T
Rt superior frontal	6, 8, 9	20	39	48	6.3	6, 8, 9, 10	36	28	48	7.7	6, 8, 9, 10	20	11	64	10.5
Rt middle frontal	6, 8	44	22	43	6.0	10	42	58	-10	6.8	6, 8, 9, 10, 46	24	22	58	8.5
Rt inferior frontal	45, 47	57	21	3	6.8	10, 45, 47	53	35	4	8.1	9, 45	61	9	22	5.4
Rt medial frontal	6	2	-8	69	5.5						6, 10	12	-8	69	7.3
Rt precentral						4, 6	50	1	53	6.4	6	40	-8	63	7.9
Lt superior frontal	6, 8	-4	43	46	6.3	6, 8, 9, 11	-30	28	48	7.0	6, 8, 9	-24	1	66	8.9
Lt middle frontal	6	-28	15	60	5.3	6, 8, 46, 47	-51	44	-9	7.0	6, 9	-28	5	64	9.4
Lt inferior frontal	9, 44, 45	-59	14	1	5.1	9, 45, 47	-55	31	2	6.1	9, 45	-57	15	31	6.7
Lt medial frontal	8	-2	47	42	6.2	10	0	61	6	5.9	6, 10	-6	-8	69	9.2
Lt precentral	6	-48	-7	57	5.6	4, 6	-36	-10	65	5.7	4, 6	-30	-8	67	8.3
Rt superior temporal						22, 42	69	-15	10	8.7	22, 42	69	-15	10	6.8
Rt middle temporal						21	57	0	-34	7.4	21	65	-2	-2	6.3
Rt inferior temporal						20	65	-32	-20	6.1	20	61	-9	-31	5.7
Rt fusiform											20	63	-9	-28	5.7
Lt superior temporal						42	-71	-25	10	5.8	42	-71	-17	8	5.6
Lt middle temporal						21, 39	-67	-41	-11	5.8	21	-69	-12	-1	5.4
Lt inferior temporal						37	-59	-61	-9	6.5	20	-67	-26	-21	6.0
Lt fusiform						20, 37	-50	-61	-22	6.9	20	-63	-15	-30	7.4
Rt postcentral						3, 1, 2	65	-20	34	6.9	3, 1	26	-35	72	6.7
Rt precuneus											31	20	-55	27	7.0
Lt postcentral						2, 5	-38	-41	65	5.7	2, 5	-34	-45	67	6.2
Lt precuneus						19	-34	-76	35	5.5					
Lt angular						39	-51	-62	33	5.9					
Rt posterior cingulate						31	16	-51	25	5.4					
Rt putamen												31	4	5	7.5
Rt caudate							16	14	9	6.2		19	20	8	5.7
Lt putamen							-34	-6	6	5.5		-32	-4	6	7.7
Lt caudate							-16	14	7	6.6		-19	14	9	5.3
Rt cerebellar hemisphere		48	-52	-29	6.1		38	-79	-23	6.5		36	-55	-46	6.3
Lt cerebellar hemisphere		-48	-52	-26	5.1		-24	-83	-24	6.5		-46	-48	-28	5.7
cerebellar vermis		0	-64	-41	5.3		-2	-74	-37	6.5		0	-70	-34	5.3

Rt = right, Lt = left, BA = Brodmann's area; x, y, z = Talairach coordinate; T = t-value.

the glucose metabolism studied with the brain FDG PET scan. However, in accordance with previous studies (Brenneis *et al.*, 2003, 2006), voxel-based morphometry of the MR images of the patients included in this study showed atrophy of the perisylvian and orbitofrontal cortical areas. Therefore, cortical atrophy is unlikely to play a major role in the cerebral cortical hypometabolism found in the present study.

In pathological studies of MSA, cerebral cortical changes have not received much attention and inconsistent results on neuronal loss and gliosis of the cerebral cortex have been reported. Some pathological studies showed mild to moderate neuronal loss and adjacent white matter changes in the superior and middle frontal gyri, supplementary motor area, precentral gyrus, postcentral gyrus and inferior parietal lobule (Spargo *et al.*, 1996; Wakabayashi *et al.*, 1998; Konagaya *et al.*, 1999; Tsuchiya *et al.*, 2000; Su *et al.*, 2001). Neuronal loss and astrocytosis in the layer V of the precentral gyrus was found, even in MSA patients with the disease duration shorter than 3 years (Tsuchiya *et al.*, 2000;

Su *et al.*, 2001). However, a review of 203 pathologically proven MSA patients reported that about 78.4% of the patients had no abnormalities in the cerebral cortex, and only 8.9% had moderate to severe abnormalities (Wenning *et al.*, 1997).

Glial cytoplasmic inclusions (GCIs) were found in the frontal lobe, particularly in the supplementary motor, cingulate, primary motor and premotor cortices (Papp and Lantos, 1994). The distribution pattern of cerebral cortical GCI is similar to that of cortical neuronal loss (Papp *et al.*, 1989; Papp and Lantos, 1994; Inoue *et al.*, 1997; Su *et al.*, 2001). GCI is known to precede neuronal loss and gliosis (Wenning *et al.*, 1994; Inoue *et al.*, 1997; Wenning and Jellinger, 2005). Indeed, a patient who died 15 months after the onset of cerebellar type MSA had GCIs in the precentral gyrus (Wakabayashi *et al.*, 2005).

We postulate that the early widespread cortical glucose hypometabolism observed in the present study is more likely caused by cortical GCI than by cortical neuronal loss. Another possible explanation may be damage to the afferent

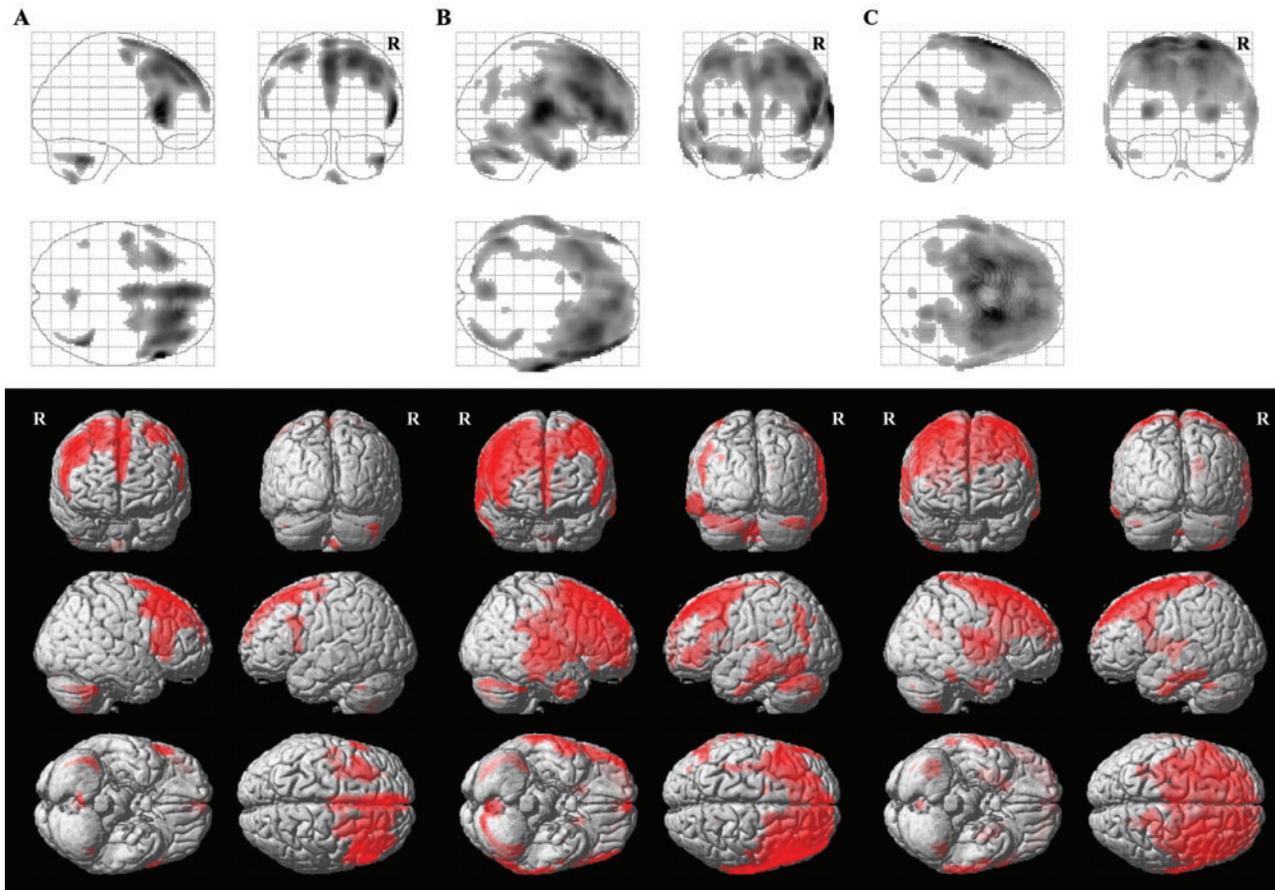


Fig. 1 The projection view (upper) and three-dimensional surface rendering images (lower) of statistical parametric mapping (SPM) analysis show brain areas of reduced glucose metabolism (family wise error-corrected $P < 0.05$). (A = Group I, B = Group II, C = Group III) Note that hypometabolic brain regions extend from the frontal cortex to the parieto-temporal cortex as the disease duration increases.

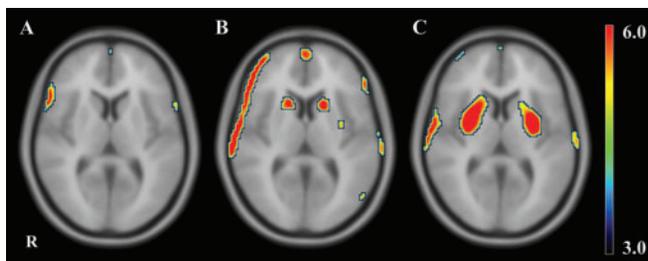


Fig. 2 The result of statistical parametric mapping co-registered on the T_1 -weighted axial magnetic resonance brain image at the level of the basal ganglia. (A) There is no hypometabolic basal ganglia area in Group I patients. (B) There are hypometabolic areas in the left posterolateral putamen and caudate nucleus of Group II patients. (C) In Group III patients, hypometabolism involves whole striatum and extends to the bilateral globi pallidi. (family wise error-corrected $P < 0.05$; colour bar = t -value).

cortical inputs arising from the subcortical nuclei (e.g. locus ceruleus and substantia nigra) (Papp *et al.*, 1989; Wenning *et al.*, 1994).

Previous studies on cognitive changes in patients with MSA consistently reported frontal executive dysfunction

(Robbins *et al.*, 1992, 1994; Monza *et al.*, 1998; Berent *et al.*, 2002; Bak *et al.*, 2005; Paviour *et al.*, 2005; Bürk *et al.*, 2006). Accordingly, the present study showed that about half of the MSA patients develop frontal dysfunction within a year after the onset of cerebellar or parkinsonian symptoms. These findings coincide with our FDG PET results showing early medial and lateral frontal glucose hypometabolism.

A previous study reported that about 40% of MSA patients have memory impairment (Bak *et al.*, 2005). In the present study, 8 (22.9%) of 35 patients had a single amnesic and 15 (42.9%) had multiple amnesic cognitive impairments. The early memory impairment in patients with MSA can be attributed to the hypometabolism of the prefrontal and inferior frontal cortex (Tulving *et al.*, 1994; Buckner and Koutstaal, 1998; Buckner *et al.*, 1999). The proportion of patients with multiple amnesic cognitive impairments was 30.8% in Group I, and it increased up to 60% in Group III.

Only a small proportion of patients with MSA are known to have visuospatial dysfunction (Bak *et al.*, 2005, 2006; Bürk *et al.*, 2006). However, a longitudinal study showed

progressive deterioration of visuospatial function in MSA (Soliveri *et al.*, 2000). In the present study, no one had a single visuospatial function domain impairment. However, as the duration of disease increased, the proportion of patients who had visuospatial dysfunction as a component of their multiple domain impairments increased up to 40%. This is in accordance with the spread of frontal hypometabolism to involve parieto-temporal areas.

Language impairment has rarely been reported in patients with MSA (Robbins *et al.*, 1992; Bak *et al.*, 2005). Two (5.7%) of our patients had language impairment. Our FDG PET studies showed preserved cortical motor and sensory language areas, except left angular gyrus involvement in Group II patients.

Basal ganglia dysfunction in early MSA

Although post-mortem pathological studies of MSA have consistently reported damage to the basal ganglia, its evolution from early disease to the final outcome of neurodegeneration found at autopsy is largely unknown (Fearnley and Lees, 1990; Wenning *et al.*, 1995; Ozawa *et al.*, 2004; Jellinger *et al.*, 2005). In previous literatures, we identified post-mortem pathological findings of 10 MSA patients who died within 3 years after the onset (Papp *et al.*, 1989; Fearnley and Lees, 1990; Kume *et al.*, 1993; Su *et al.*, 2001; Wakabayashi *et al.*, 2005). Except one patient with pure olivopontocerebellar pathology (Wakabayashi *et al.*, 2005), the others had variable degree neuronal loss in the putamen, caudate and substantia nigra.

Although our Group I patients had parkinsonian motor deficits ranging from 9 to 38 on UPDRS motor score, they showed no striatal hypometabolism. In MSA, calcineurin positive medium spiny striatal neurons are depleted severely in the dorsolateral part of the posterior putamen, but choline acetyltransferase positive striatal neurons are preserved (Sato *et al.*, 2007). The nigrostriatal dopaminergic terminals comprise less than one-fifth of the striatal synapses (Tennyson *et al.*, 1974; Pickel *et al.*, 1981). Therefore, in early MSA, the additive effect of selective striatal neuronal loss and partial damage to the nigrostriatal neurons may cause parkinsonian deficits, but too small changes in striatal synaptic activity to be detected by FDG PET studies. A multi-tracer PET study of the nine MSA patients also showed no correlation between the degree of putaminal FDG uptake and the severity of parkinsonian motor deficits (Antonini *et al.*, 1997). Another possible explanation may be non-specific contamination of UPDRS motor scores by cerebellar motor slowing (Tison *et al.*, 2002).

In our study, as expected, Group II and III patients had more severe parkinsonian motor deficits than Group I patients. In Group II, glucose metabolism was reduced in the caudate nucleus and posterolateral putamen. It is interesting to note the early involvement of the posterolateral putamen, where the somatic motor inputs from the cerebral cortex and the nigrostriatal dopaminergic terminals are

connected (Hedreen and DeLong, 1991). The caudate receives afferent fibres mainly from the prefrontal cortex (Hedreen and DeLong, 1991; Lehericy *et al.*, 2004). Therefore, dysfunction of the caudate may contribute to frontal executive dysfunction observed in our patients (Alexander and Crutcher, 1990).

In Group III, the basal ganglia hypometabolic area extended to involve whole putamen and globus pallidus. Such changes may be caused by reduced activities of afferent inputs to the pallidum and striatum, as well as loss of striatal and pallidal intrinsic neurons (Papp *et al.*, 1989).

Cerebellar dysfunction in early MSA

In MSA, there is neuronal loss in the pontine nuclei, inferior olivary nucleus, cerebellar hemisphere and cerebellar vermis (Papp and Lantos, 1994; Wenning *et al.*, 1996; Jellinger *et al.*, 2005). There is a deposition of many GCIs and extensive myelin loss in the cerebellar white matter, middle cerebellar peduncle and basis pontis (Papp *et al.*, 1989; Papp and Lantos, 1994; Inoue *et al.*, 1997; Tsuchiya *et al.*, 1998; Su *et al.*, 2001; Wakabayashi *et al.*, 2005). Such changes are remarkable even in the early stage of the disease, when the loss of Purkinje cells in the cerebellar cortex is not evident or mild (Papp *et al.*, 1989; Inoue *et al.*, 1997; Su *et al.*, 2001; Wakabayashi *et al.*, 2005).

In the present study, the cerebellar vermis and the anterior cerebellar hemisphere were involved within 1 year after the onset of parkinsonian or cerebellar symptoms. These findings are in accordance with pathological studies that have shown predominant involvement of anterior cerebellar hemisphere (Kume *et al.*, 1991; Wenning *et al.*, 1996).

In summary, this is the first *in vivo* FDG PET study showing a pattern of progression of metabolic changes in the brains of mixed type MSA patients. However, community-based longitudinal FDG PET studies are needed to verify the results of the present study.

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