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Clinical and imaging characteristics of dementia in multiple system atrophy

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ABSTRACT

Background: Recent reports show that dementia occurs in 5–26% of multiple system atrophy (MSA) patients. However, the structural or pathological correlates of dementia in MSA are unclear yet.
Methods: Of 152 patients with MSA, 59 fulfilled the criteria of probable MSA and 9 (15%) had dementia. Six of those patients and 9 without dementia, in addition to 10 controls, were included. All subjects underwent clinical evaluation including UMSARS, neuropsychological examinations, 3T-MRI, and Pittsburgh Compound B (PIB) PET imaging. The cortical thickness was assessed using surface-based morphometry.
Results: Age and disease duration were similar between MSA with dementia and without dementia, while motor disability was more severe in MSA with dementia. In neuropsychological tests, attention, visuospatial function, and language function were impaired in MSA with dementia. Mean PIB binding was similar among the three groups. Cortical thickness was reduced in precuneus/cuneus, uncus, and posterior cingulate in MSA with dementia compared to the controls, and in parahippocampal and lingual cortices compared to MSA without dementia.
Conclusions: Dementia was found in 15% of the probable MSA patients, which was similar to those reported in previous studies. It appears that amyloid pathology has limited role in dementia in MSA, although some patients had increased cortical amyloid burden. Cortical thinning in MSA-D was observed in areas where cortical thinning was reported in Alzheimer disease or Parkinson disease dementia, but its pathological relevance is unclear. The neuropathological processes leading to the development of dementia in MSA appears to be multifactorial and heterogenous.

1. Introduction

Although mild decline in cognition has repeatedly been described in patients with multiple system atrophy (MSA) [1–4], it has been thought that frank dementia is not a feature of MSA. However, dementia has been reported even in patients with pathologically-proven MSA [3,5,6] and recent reports have shown that dementia occurs in 5–26% of patients with MSA [7–9].

Until now, the structural or pathological correlates of dementia in MSA are unclear yet. Several pathological studies have described neuronal loss and atrophy of the frontal regions coupled with the accumulation of glial cytoplasmic inclusions (GCIs) in patients with MSA [10–12], but its association with dementia is not well understood. Neuroimaging studies also have shown atrophy, hypoperfusion, and hypometabolism of the frontal regions in patients with MSA [7,8,13–16].

Previous Pittsburgh Compound B (PIB) PET studies on Lewy body (LB) synucleinopathies have found that some proportion of patients with Parkinson's disease dementia (PDD) and dementia with LB (DLB) showed increased amyloid burden [17–20]. In MSA, a non-LB synucleinopathy, although β-amyloid pathology has been

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described by some authors [5,21], it is not a common finding and its effect on cognitive function has not been explored.

In this study, we evaluated the clinical, neuropsychological, and neuroimaging characteristics of MSA dementia (MSA-D) compared with those of MSA without dementia (MSA-ND) and normal controls (NC). To this end, detailed neuropsychological evaluations were administered to all subjects and cortical amyloid burden was measured using PIB PET imaging. We also assessed cortical thickness using surface-based morphometry (SBM).

2. Methods

2.1. Patients

This study included patients with probable MSA who were followed up at Seoul National University Hospital (SNUH) Movement Disorder Clinic (MDC). The diagnosis of MSA was based on the consensus criteria [22], except for dementia. From December 2010 to February 2011, 152 patients with MSA (possible or probable) (age 64.9 ± 9.2 years, disease duration 5.1 ± 3.0 years: MSA with predominant parkinsonism (MSA-P) 112, MSA with predominant cerebellar dysfunction (MSA-C) 40) were evaluated at SNUH MDC and 59 patients fulfilled the criteria of probable MSA. Since no diagnostic criteria for MSA-D was available, we referred to the diagnostic criteria and guidelines for PDD: diagnosis of MSA-D was made when a patient had a mini-mental state examination (MMSE) score less than 26 in association with impairment of activities of daily living and met the DSM-IV criteria for dementia. Nine of the 59 (15%) patients were diagnosed with MSA-D and six of them agreed to participate. Three patients refused to participate due to severe motor impairment. Of the 50 remaining nondemented patients, 9 patients were selected to match the overall distribution of sex and age (MSA-ND group). We also included 10 healthy subjects as controls (NC group). None of the participants were taking medications which may influence the cognitive evaluation. Written informed consent was obtained from all subjects. The Institutional Review Board of SNUH approved this study.

2.2. Clinical evaluation and neuropsychological testing

The severity of MSA was evaluated using the Unified Multiple System Atrophy Rating Scale (UMSARS).

Neuropsychological evaluation was done by a trained rater blinded to the clinical evaluation, MRI, and PIB PET results. The global cognitive state was determined with MMSE. Verbal memory was assessed with Seoul Verbal Learning test (SVLT), language function with the Korean version of the Boston Naming Test (K-BNT), visuospatial function with the copying score of the Rey Complex Figure Test (RCFT), attention with forward and backward digit span test, and frontal executive function with the letter fluency test. Additional measures included the Mayo Fluctuation Questionnaire, the hallucination subscale of Neuropsychiatric Inventory (NPI), and the Beck Depression Inventory (BDI).

2.3. PIB PET

PIB PET imaging was performed with a Siemens Biograph 40 (Siemens, Erlangen, Germany) scanner. A CT attenuation scan was performed with the lowest pitch allowed by the scanner and a 20-min emission scan was started after injection of 740 MBq of [^{11}C]PIB.

The PIB PET data of each subject were coregistered to individual volumetric MRI and then automatically spatially normalized into the Montreal Neurological Institute template. For quantitative normalization of ^{11}C-PIB uptake values, the cerebellum was used as a reference region, and ^{11}C-PIB retention maps were generated by dividing regional uptake values by the individual mean cerebellar uptake values in the same images. The automatic anatomic labeling algorithm and a region combining method were applied to set ROIs to characterize ^{11}C-PIB retention in the frontal, medial temporal, lateral temporal, precuneus/cuneus, lateral parietal, and occipital regions, and in the caudate, putamen, thalamus, and cerebellum. Mean cortical PIB retention was measured with an ROI covering the entire gray matter. A comparison of the global and regional ^{11}C-PIB retention values between groups was done with the Kruskal–Wallis test with Bonferroni-corrected post hoc Mann–Whitney test. The level of statistical significance was set at a two-tailed $p < 0.05$.

2.4. MRI

Three-dimensional T-1 weighted spoiled-gradient echo images were obtained from all participants using a 3.0-T MR scanner (Signa EXCITE; GE, Milwaukee, WI) with the following parameters: TR = 1500 ms, TE = 1.9 ms, flip angle = 9°, field of view = 25 cm, acquisition matrix = 256 × 256, slice thickness = 1.0 mm, and NEX = 1.

For cortical thickness measurements, the native MRI images were spatially registered into standardized stereotaxic space after intensity non-uniformity correction. The registered and corrected volumes were classified into gray matter, white matter, cerebrospinal fluid, and background. The surfaces of the inner and outer cortex were automatically extracted, using the Constrained Laplacian-Based Automated Segmentation with Proximities algorithm. The cortical thickness was defined as the Euclidean distance between the linked verticles of the inner and outer surfaces after transforming back into the subject's native space. To compare the thicknesses of the corresponding regions between the groups at a vertex level, the thickness values were spatially normalized using surface-based 2-dimensional nonlinear registration with a sphere-to-sphere warping algorithm. Using the transformation, thickness information on the vertices was transformed to an average template.

Diffusion smoothing with a full-width half-maximum of 20 mm was used to blur each cortical thickness map. To estimate the differences in cortical thickness between groups, a general linear model was estimated at an each vertex across the cortical surface, with cortical thickness as the dependent variable, and age, gender, and intracranial volume as the covariates. Initially, p-maps were thresholded to yield an expected FDR at a q value of 0.05 to correct for multiple comparisons. However, since nothing significant was found at $p < 0.05$ FDR corrected, to show less robust differences, the threshold was lowered to $p < 0.001$ uncorrected for multiple comparisons. In addition, we also analyzed the correlation between cortical thickness and clinical or neuropsychological variables within MSA patients.

3. Results

3.1. Clinical and neuropsychological data

The demographic and clinical characteristics of the subjects are summarized in Table 1. There was no significant difference in age, sex, and education among the groups. Age at onset and disease duration were similar between the MSA-ND and MSA-D groups. Compared with the MSA-ND group, the MSA-D group had more severe motor dysfunction measured by UMSARS II (motor function). The results of autonomic examination showed that the systolic blood pressure drop on standing was greater in the MSA-ND group.

The results of the neuropsychological tests showed that there were no group differences between the NC and MSA-ND groups for any of the tests (Table 2). The MSA-D group performed worse in SVLT immediate recall compared with the NC and MSA-ND groups and in RCFT and K-BNT compared to the MSA-ND group. The MSA-D

Table 1
Demographics and clinical characteristics.

	NC ($n = 10$)	MSA-ND ($n = 9$)	MSA-D ($n = 6$)
M:F	4:6	6:3	2:4
Age	59.2 ± 7.8	62.8 ± 8.3	61.7 ± 5.8
Age at onset	NA	59.2 ± 9.3	56.5 ± 7.3
Duration (yr)	NA	3.6 ± 1.7	5.2 ± 2.3
Education (yr)	10.8 ± 4.8	13.4 ± 3.7	10.5 ± 4.5
MSA-P:MSA-C	NA	5:4	4:2
UMSARS I	NC	18.0 ± 5.6	24.8 ± 11.8
UMSARS II	NC	16.8 ± 6.2	27.7 ± 8.1[b]
Global disability (range 1–4)	1.0 ± 0.0	2.4 ± 0.9[a]	3.2 ± 1.0[a]
Supine SBP (mmHg)	117.6 ± 10.4	125.2 ± 9.0	128.8 ± 13.8
Supine DBP (mmHg)	73.8 ± 6.9	80.2 ± 10.2	77.0 ± 8.7
Supine hypertension (n)	NC	1	2
Orthostatic hypotension (n)	NC	6	1
Max. SBP drop (mmHg)	NC	31.2 ± 19.4	8.3 ± 9.4[b]
Max. DBP drop (mmHg)	NC	16.9 ± 12.9	6.5 ± 11.2

Values are expressed as mean ± SD.
NC, normal control; MSA-ND, multiple system atrophy without dementia; MSA-D, multiple system atrophy with dementia; NA, not applicable; MSA-P, MSA with predominant parkinsonism; MSA-C, MSA with predominant cerebellar dysfunction; UMSARS, unified multiple system atrophy rating scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; NC, not checked.
Values between groups were compared using Kruskal–Wallis test with Bonferroni-corrected post hoc Mann–Whitney test. The level of statistical significance was set at two-tailed $p < 0.05$.
[a] $p < 0.05$ vs control.
[b] $p < 0.05$ vs MSA-ND.

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