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Topographic distribution of cortical thinning in subtypes of multiple system atrophy

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ABSTRACT

Background and purpose: Despite the predominant degeneration of subcortical structures, recent studies have suggested the evidence of cortical involvement in multiple system atrophy (MSA). This study aimed to identify the different topographic pattern of cortical thinning in MSA according to clinical subtypes, and the association of cortical thinning with cerebellar atrophy and other disease related metrics.
Materials and methods: We used cortical thickness analysis in 53 non-demented probable MSA patients (29 with MSA-C, 24 with MSA-P) and 35 healthy subjects and modeled local cortical thickness as a linear association with cerebellar volume and disease related metrics including age, disease duration, cognition and disease severity.
Results: We found five clusters (left ventromedial prefrontal, bilateral ventrolateral prefrontal cortex, right parahippocampal and lingual gyrus) exhibiting significant cortical thinning in MSA-C and two clusters (right primary sensory motor and left ventromedial prefrontal cortex) exhibiting a thinning tendency in MSA-P compared with the control group. In correlation analysis, we identified no cluster exhibiting a significant correlation with cerebellar atrophy in both of the MSA groups. However, cortical thickness in right parahippocampalgyrus and left ventrolateral prefrontal cortex showed significant negative correlation with International Cooperative Ataxia Rating Scale subscore of speech disorder in MSA-C group.
Conclusions: We identified different topographic distributions of cortical thinning in MSA subtypes. Our study suggests that cortical thinning of MSA occurs independently of cerebellar atrophy as a primary disease process rather than secondary deafferentation.

1. Introduction

Multiple system atrophy (MSA) is a sporadic, adult-onset disease characterized by progressive neurodegeneration in various parts of the central nervous system [1,2]. The neuropathology of MSA is characterized by selective neuronal loss, gliosis and the development of myelin pathology and α-synuclein positive glial cytoplasmic inclusions (GCI) as histologic hallmarks largely affect the substantianigra, striatum, inferior olivary nucleus, pontine nuclei and cerebellum.

Infratentorial and subcortical structures such as the cerebellum, brainstem and basal ganglia are primarily affected in MSA, and hence past studies had focused on those structures whereas cortical pathology has received little attention. Despite the predominant subcortical degeneration in MSA, progressive cerebral cortical atrophy involving frontal lobes, motor-related areas and the temporal lobe has been reported [3–5]. Furthermore, various MRI techniques have become available to describe the morphological changes and patterns of MSA during the last decade, suggesting that cortical involvement may be more extensive in MSA than previously recognized [3,6–8]. However, the results of previous studies revealed heterogeneity in reported structural changes as detected using VBM analyses of MRI data collected in MSA subjects. The exact nature, topographical distribution and the reason of cortical

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thinning in MSA are unknown. Furthermore, a consensus conference on diagnosis held in 1998 defined two categories of MSA; MSA with predominant parkinsonism (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C) [9,10]. These MSA subtypes reveal differences in various point of views, however, there were less data available on topographical pattern of cortical thinning in the MSA subtypes.

Cortical thickness analysis has an advantage over VBM for the detection of cerebral cortical changes [11–13]. VBM results roughly reflect volume changes that might be caused either by changes in thickness or changes in surface area, or both. The limited specificity of VBM for thickness is critical in highly convoluted structures of cerebral cortex. The cortical thickness measurement is consistent with VBM results in general, but the thickness measurement is more sensitive in detecting regional morphological changes. This study aimed to address two issues: identifying the different topographic patterns of cortical thinning in MSA according to clinical subtypes using more sophisticated cortical thickness analysis, and whether this cortical thinning pattern could be associated with cerebellar atrophy and other disease related metrics.

2. Methods

2.1. Patients

We recruited 88 non-demented right-handed subjects: 29 patients with MSA-C, 24 patients with MSA-P and 35 control subjects (matched for age and sex). MSA-C patients who showed predominant cerebellar ataxia and MSA-P patients who showed predominant parkinsonism were enrolled. Clinical diagnosis of MSA was made by consensus criteria, and all patients fulfilled the clinically probable MSA criteria [9] and showed autonomic dysfunction documented by objective autonomic nervous function test. All patients underwent clinical interviews and neurological examinations by an experienced neurologist (J.W.C.) to evaluate their motor function. The motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr (H & Y) stage of MSA-P, International Cooperative Ataxia Rating Scale (ICARS) [14] of MSA-C and the Korean version of the Mini Mental Status Examination (K-MMSE) scores of all subjects were measured within 1 month of the MRI study. Patients who had infarction, hemorrhage, tumors, trauma, or severe white matter hyperintensity [15,16] were excluded from the study. We also excluded patients who scored lower than 24 on K-MMSE. This study was approved by Institutional Review Board of the Samsung Medical Center, Seoul, Korea and each patient provided informed consent to participate.

2.2. Magnetic resonance imaging acquisition and analysis

All subjects were scanned from anatomical MRI. Details of the imaging acquisition can be found in Supplemental material 1. T1-weighted brain scans of the sample of 35 NC, 29 MSA-C, and 24 MSA-P participants were automatically processed using CIVET – Montreal Neurological Institute (MNI) image processing software to produce the cortical surface and to measure the cortical thickness [17]. The hemispherical surfaces of the inner and outer cortex were automatically extracted using the Constrained Laplacian-based Automated Segmentation with Proximities algorithm [18,19], which was used to estimate the surface consisting of 40,962 vertices on each hemisphere for each subject. Cortical thickness was measured as the Euclidean distance between linked vertices of the inner and outer surfaces using the t-link method [13]. Segmentation of cerebellar region was automatically performed using T1WI by inhouse software. (Supplemental materials 1, 2) Intracranial volume (ICV) was defined as the total volume of gray matter, white matter, and cerebrospinal fluid. To account for differences in individual brain size, we adjusted local cortical thickness by using ICV as a covariate.

2.3. Statistical analysis

Statistical analyses for demographic characteristics of subjects were performed with SPSS Statistics 18.0 (Predictive Analysis Software, Chicago, IL). The age and MMSE were compared using Kruskal-Wallis test, disease duration was analyzed by Mann-Whitney test, and the cerebellar volume and ICV in each group was assessed by ANOVA with a Bonferroni post hoc test.

Statistical analyses were implemented using SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/), for Matlab (R2008b, The MathWorks, Inc.) [20]. We performed a multiple linear regression analysis adjusted for age, sex, and ICV to examine the group differences in cortical thickness at each vertex following contrasts: (1) MSA-C versus NC, (2) MSA-P versus NC, (3) MSA-C versus MSA-P. The regression equation was given as follows: $Y = b_0 + b_1\text{Group} + b_2\text{Age} + b_3\text{Sex} + b_4\text{ICV} + \varepsilon$. Where Y is the cortical thickness, b_0 is the Y intercept, b_{1-4} are the regression coefficients, and ε is the residual error. The multiple comparisons problem was corrected by random field theory (RFT, $p < 0.05$) [20]. The resultant thresholded t-value and p-value maps of b_1 regression coefficient were projected on an average surface template generated from the ICBM152 data set for visualization. We further examined the correlation between mean thickness of the cluster and cerebellar volume, disease severity, cognition, disease duration for controlling age, sex and ICV.

3. Results

3.1. Demographic and clinical features

Table 1 presents the demographic characteristics of each group. There were no significant differences of age, sex and time since disease onset and MMSE scores between patients and control groups. Mean ICARS total score of MSA-C was 31.28 ± 11.25 and subscores of posture and gait disturbances, kinetic functions, speech disorders and oculomotor disorders were 14.07 ± 8.03, 13.10 ± 5.48, 2.31 ± 1.14 and 1.41 ± 1.32. UPDRS off score and H & Y stage of MSA-P were 26.69 ± 8.45 and 2.52 ± 0.54.Cerebellar volume of MSA-C was smaller than those of MSA-P and normal controls. Cerebellar volume showed negative correlation with ICARS total score ($r = -0.427$, $p < 0.05$), subscores of posture and gait disturbances ($r = -0.521$, $p < 0.01$) and speech disorders ($r = -0.470$, $p < 0.05$) in MSA-C group, and Hoehn and Yahr stage ($r = -0.411$, $p = 0.046$) in MSA-P group (Table 2).

3.2. Distribution of focal areas with reduced cortical thickness

There was no significant reduction of whole brain mean thickness in MSA-C and MSA-P group compared with control group (mean cortical thickness in the MSA-C group = 3.01 ± 0.11 mm, in the MSA-P group = 2.96 ± 0.11 mm, in the NC group = 3.04 ± 0.12 mm). We found five clusters exhibiting a significant cortical thinning ($p < 0.05$ RFT corrected) associated MSA-C compared with control group: in left ventromedial prefrontal (VMPFC) and bilateral ventrolateral prefrontal cortex (VLPFC), right parahippocampal and lingual gyrus (Fig. 1A). In MSA-P group, there were two clusters exhibiting cortical thinning ($p < 0.001$, uncorrected) compared with the control group: in right primary sensory motor cortex (PMC) and left VMPFC (Fig. 1B). Direct comparison of MSA-C and MSA-P with cortical thickness analysis showed no significant thinning areas (Fig. 1C).

Table 1
Demographic characteristics of MSA-C, MSA-P and normal controls.

	MSA-C ($n = 29$)	MSA-P ($n = 24$)	NC ($n = 35$)	p
Age (yrs)	61.48 ± 7.49	67.88 ± 9.92	63.54 ± 4.26	0.066
Sex (M:F)	15:14	18:6	18:17	0.139
Duration (yrs)	2.86 ± 1.90	3.33 ± 1.83		0.292
MMSE	27.28 ± 2.99	26.58 ± 3.24	28.51 ± 1.82	0.056
ICV (mm^3)	1378,884.47 ± 131,761.19	1,384,289.33 ± 118,063.27	1,352,763.29 ± 126,770.93	0.578
Cbll vol. (mm^3)	102,605.21 ± 14,052.04*	117,630.89 ± 17,094.91*	124,075.90 ± 13,992.88*	<0.001

yrs, years; ICV, intracranial volume; cbll vol, cerebellar volume.
*Post hoc analysis of cerebellar volume revealed that cerebellar volume of MSA-C was smaller than those of MSA-P and normal controls.