J Korean Med Sci 2002; 17: 530-6
ISSN 1011-8934

The Segmented Regional Volumes of the Cerebrum and Cerebellum in Boys with Tourette Syndrome

Neuropathological deficits are an etiological factor in Tourette syndrome (TS), and implicate a network linking the basal ganglia and the cerebrum, not a particular single brain region. In this study, the volumes of 20 cerebral and cerebellar regions and their symmetries were measured in normal boys and TS boys by brain magnetic resonance imaging. Brain magnetic resonance images were obtained prospectively in 19 boys with TS and 17 age-matched normal control boys. Cerebral and cerebellar regions were segmented to gray and white fractions using algorithm for semi-automated fuzzy tissue segmentation. The frontal, parietal, temporal, and the occipital lobes and the cerebellum were defined using the semi-automated Talairach atlas-based parcellation method. Boys with TS had smaller total brain volumes than control subjects. In the gray matter, although the smaller brain volume was taken into account, TS boys had a smaller right frontal lobe and a larger left frontal lobe and increased normal asymmetry (left>right). In addition, TS boys had more frontal lobe white matter. There were no significant differences in regions of interest of the parietal, temporal, or the occipital lobes or the cerebellum. These findings suggest that boys with TS may have neuropathological abnormalities in the gray and the white matter of the frontal lobe.

Key Words : *Tourette Syndrome; Magnetic Resonance Imaging; Frontal Lobe*

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Received : 11 January 2002
Accepted : 11 April 2002

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*This article was presented at the 47th annual meeting of the American Academy of Child and Adolescent Psychiatry, New York, October 24-29, 2000.

INTRODUCTION

Tourette syndrome (TS) is a childhood-onset movement disorder entailing vocal tics and multiple motor tics (1). Although the definite pathophysiology of TS is not yet known, there is a hypothesis that the basal ganglia and related thalamocortical circuitry are involved (2, 3).

Most of the existing structural neuroimaging studies on TS were on the basal ganglia, corpus callosum, and lateral ventricle (4-10). Functional neuroimaging studies of TS using positron emission tomography (PET) suggest that the cortical system (especially, the frontal lobe area) is related with the pathophysiology of TS (11-14). However, structural neuroimaging studies of TS on the cerebrum are rare, and a recent regional cerebral volumetric study reported that the broadly distributed cortical systems are involved in the pathophysiology of TS (15). Compared with controls, TS subjects were found to have larger volumes in the dorsal prefrontal regions, and larger volumes in the parieto-occipital regions, but smaller volumes in the inferior occipital regions. Nevertheless, the gray matter and white matter were not segmented in previous cerebral neuroimaging studies, needing studies on whether the pathophysiology of TS is related with the gray matter or the white matter. Previous studies posed many problems related with study methods since they did not control the effect of the disorders that frequently accompany TS including attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD), and various confounding variables including drug-effect, age, sex, and handedness that could affect neuroimaging studies (3).

Traditionally, the cerebellum has been viewed as a motor coordination center (16). Studies are also needed on the cerebellum related with TS since TS is basically a movement disorder and abnormality is reported in the cerebellar vermal area in patients with ADHD, which frequently accompany TS (17, 18). However, no neuroimaging study on TS related with the cerebellum has been reported according in the literature.

This structural neuroimaging study of segmented regional cerebral and cerebellar volumes tested the following three hypotheses; 1) The segmented cerebral regional volumes (especially, the frontal lobe, parietal lobe, and occipital lobe)

in patients with TS would be different from those in healthy subjects (11-15). 2) The segmented cerebellar regional volume in patients with TS would be different from that in healthy subjects. 3) The hemispheric asymmetry shown in healthy subjects would be reversed or decreased in patients with TS in each segmented regional volume in the cerebrum and cerebellum (3-5).

MATERIALS AND METHODS

Subjects

Nineteen male subjects with TS (mean±SD of age, 9.7±2.7 yr; range, 7 to 17 yr) were recruited from an outpatient clinic at Inha University Hospital in metropolitan Incheon, Korea. The diagnosis of TS in these patients was established according to the DSM-IV criteria (19), and by a consensus between two child psychiatrists (J.S.L. and S.J.C.). Seventeen age-matched male control subjects (mean±SD age, 9.8±1.9 yr; range, 7 to 13 yr) were recruited by advertisement at an elementary school.

Subjects were recruited from September 1998 to August 1999. Screening included detailed medical/developmental history, physical/neurological examinations, the 12 handedness items from the Revised Physical and Neurological Examination for Subtle Signs (20), and Korean Wechsler Intelligence Scale for Children-Revised (KWISC-R) (21). Ratings of the worst-ever severity of tic symptoms were obtained using the Korean Form of Yale Global Tic Severity Scale (22).

Exclusion criteria for TS subjects included any other history or current Axis I psychiatric disorder, with the exception of a history of mild hyperactivity (n=8) and a prior history of neuroleptic therapy. For control subjects, the exclusion criteria included any history or current Axis I psychiatric disorder and any first-degree relatives with major psychiatric disorders. Additional exclusion criteria for both groups were left-handedness, with the exception of ambidexter (n=2), a full-scale KWISC-R IQ of less than 80, and evidence of medical or neurological disorders on examination or history. Socioeconomic status was established using the Hollingshead Index of Social Status (23). The characteristics of the subjects and controls are summarized in Table 1.

Table 1. Demographic characteristics of boys with Tourette syndrome and controls

Characteristics	Tourette syndrome (n=19)		Controls (n=17)	
	Mean	SD	Mean	SD
Age (yr)	9.7	2.8	9.8	1.9
KWISC-R scores*	106.9	14.2	117.9	10.4
YGTSS scores†	46.1	14.4	0	
Social class	2.1	0.9	1.9	1.0
Right-handed, No. (%)	17 (89)		17 (100)	

Notes: KWISC-R, Korean Wechsler Intelligence Scale for Children-Revised: YGTSS, Korean Form of Yale Global Tic Severity Scale.
*t=-2.63, d.f.=34, $p<0.05$. †t=13.98, d.f.=18, $p<0.001$.

The study was explained to the subjects and their parents, and written consent was obtained from the child and written informed consent from the parents.

MRI protocol

Subjects were scanned on a 1.5-T GE Sigma Scanner (GE Medical System, Milwaukee, U.S.A.) at the Inha University Hospital. A three-dimensional spoiled gradient recalled echo in the steady-state imaging sequence (time to echo, 5 msec; time to repeat, 24 msec; flip angle, 45°; acquisition matrix, 256×256; number of excitations, 1; and field of view, 24 cm; slice thickness, 1.5 mm; 124 slices) was used to obtain T1-weighted images in the coronal plane. The head was aligned with laser cross-hairs referenced to the nasion and the midsaggital plane. Sedation with chloral hydrate (1.5 to 2.0 g by mouth) was used for five TS subjects.

Image analysis

Two clinical neuroradiologists (M.K.L. and C.H.S.) reviewed all scans. No gross abnormalities were noted in the subjects, and all MRI scans of the subjects and controls were rated in a blinded fashion.

The spoiled gradient echo image data were imported into the Brainimage program for semi-automated image processing, analysis, and quantification (24). Volumetric assessment of segmented image data in the Brainimage program requires a stepwise process of data importation, the removal of non-brain voxels, correction of image non-uniformities, position normalization, and fuzzy tissue segmentation, as described and validated elsewhere (25-28). Data from this image-processing pipeline were in the form of gray matter, white matter, and cerebrospinal fluid (CSF) volumes for the cerebral lobes and the cerebellum.

To specify regional differences, the brain was divided into lobes with using a semi-automated stereotactic-based parcellation method (27-30). Total brain volume measurement included cerebral tissue, cerebellar tissue, and ventricular CSF, but not extracerebral CSF. The interrater and intrarater intraclass correlation coefficients were greater than 0.98 for each of the cerebral and cerebellar subdivisions.

Statistical analysis

All statistical procedures were performed using SPSS 6.1 for Windows (31). Because the TS subjects had a significantly smaller total brain volume than the controls, volumetric measurements of the right and left brain regions were analyzed using two-way repeated-measures analysis of covariance (ANCOVA) with diagnosis as the between-subject factor, side (right and left) as the repeated factor, and total brain

volume (TBV) as the covariate. Percent asymmetry was defined as {(R−L)/(R+L)/2}×100. Since the diagnostic groups also differed significantly in IQ scores, all analyses were retested by ANCOVA with both IQ scores and TBV as covariates. Bonferroni tests were used to determine the post hoc significance of least-square adjusted means. Pearson's product-moment correlations were used to test relationships between volumetric measurements of the brain regions and clinical ratings of the Yale Global Tic Severity Scale. A p value of 0.05 (two-tailed) was chosen as the significance threshold. Age-related changes in regions that differed significantly between groups were examined by linear regression, as shown in Fig.1 and Fig. 2.

RESULTS

The TBV was significantly smaller in TS subjects (mean±SD, 1,417.4±119.9 cm^3) than normal controls (mean±SD, 1500.8±88.1 cm^3) on Student t-test (t=-2.35, d.f.=34, p=0.03). In the frontal lobe gray matter, although the smaller brain volume was taken into account with ANCOVA, TS subjects had a smaller right volume and a larger left volume and increased normal asymmetry (left> right). TS subjects had a larger frontal lobe white matter. These results are summarized in Table 2-5.

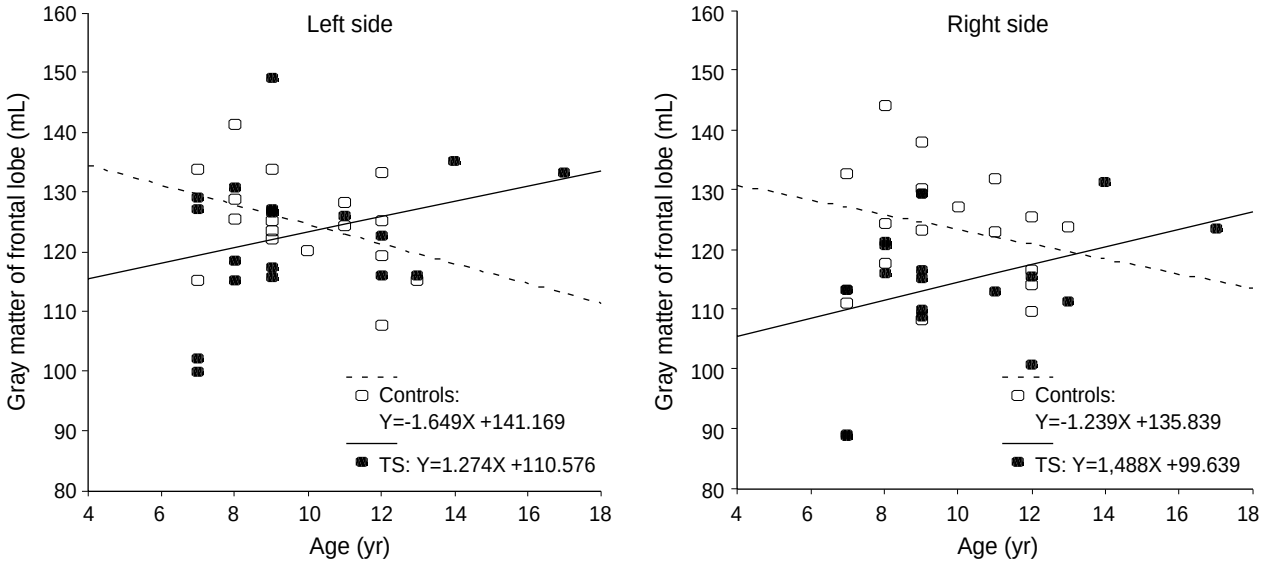

Fig. 1. Volumes of frontal lobe gray matter in relation to age in 19 boy with Tourette syndrome (TS) and 17 healthy control subjects.

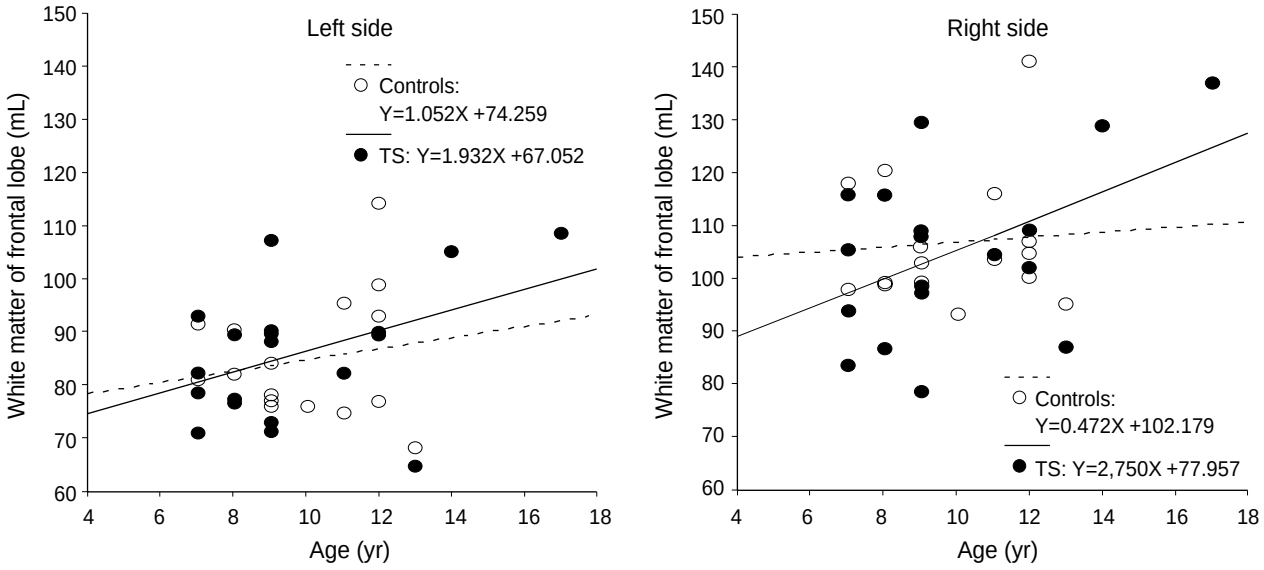

Fig. 2. Volumes of frontal lobe white matter in relation to age in 19 boys with Tourette syndrome (TS) and 17 healthy control subjects.

Group differences in tissue composition

Further segmentation of gray matter and white matter was undertaken to explore the group differences in terms of the regions of interest. Analysis of covariance for total brain volume demonstrated significant diagnosis by side interactions in the gray matter of the frontal lobe (F=8.181, d.f.=1, p=0.007). Boys with TS had approximately 3.3% less gray matter in the right frontal lobe and 3.3% more gray matter in the left frontal lobe than control subjects. The white matter volume of the frontal lobe was significantly larger in TS subjects (F=4.66, d.f.=1, p=0.038). No diagnostic differences were apparent between two groups in terms of the tissue composition for the cerebellar or the temporal, parietal, or occipital lobe volumes.

Table 2. Unadjusted mean volumes for boys with Tourette syndrome (TS) (n=19) and controls (n=17)

	Unadjusted mean (SD) in cm^3			
	Tourette syndrome		Control	
	Right	Left	Right	Left
Frontal lobe				
Gray	114.13 (11.7)	122.98 (11.4)	123.67 (10.0)	124.97 (8.2)
White	104.74 (16.0)	85.86 (12.4)	106.82 (11.8)	84.59 (11.4)
Parietal lobe				
Gray	73.51 (6.8)	71.88 (7.5)	76.57 (4.7)	74.87 (4.2)
White	54.21 (10.1)	51.68 (8.2)	57.87 (5.6)	54.64 (4.3)
Temporal lobe				
Gray	78.12 (6.6)	78.73 (8.6)	84.77 (6.3)	85.05 (6.6)
White	40.22 (7.6)	33.39 (4.1)	40.71 (5.5)	34.04 (4.1)
Occipital lobe				
Gray	40.44 (4.1)	36.81 (5.4)	41.14 (3.4)	41.47 (5.4)
White	18.36 (4.8)	22.81 (4.6)	17.61 (2.5)	24.30 (2.5)
Cerebellum				
Gray	49.00 (3.8)	43.13 (5.1)	53.37 (7.7)	48.49 (7.3)
White	12.51 (3.0)	19.47 (4.0)	11.99 (3.9)	18.67 (3.7)

Table 3. Adjusted mean volumes for boys with Tourette syndrome (n=19) and controls (n=17)

	Adjusted least square means*			
	Tourette syndrome		Control	
	Right	Left	Right	Left
Frontal lobe				
Gray	116.73	125.83	120.75	121.79
White	108.71	88.75	102.38	81.37
Parietal lobe				
Gray	74.80	73.76	75.13	72.78
White	56.42	53.64	55.41	52.46
Temporal lobe				
Gray	79.79	81.24	82.90	82.24
White				
Occipital lobe				
Gray	40.38	38.21	41.21	39.92
White	18.87	23.74	17.04	23.26
Cerebellum				
Gray	49.90	44.20	52.37	47.30
White	12.87	19.79	11.59	18.33

*Adjusted for total brain volume by Bonferroni post hoc tests.

Symmetry in tissue composition

Repeated measures ANCOVA was used to test group differences in the symmetry of the gray and white matter regions. Compared to the healthy subjects, subjects with TS showed

Table 4. Repeated measures ANCOVA for diagnosis, side and diagnosis by side interactions for regional brain volumes in boys with Tourette syndrome (n=19) and controls (n=17)*

	Diagnosis		Side		Diagnosis × side	
	F	p	F	p	F	p
Frontal lobe						
Gray	0.00	0.99	0.24	0.63	8.18	0.007‡
White	4.66	0.038†	8.10	0.008‡	0.24	0.63
Parietal lobe						
Gray	0.06	0.82	6.06	0.019†	0.95	0.34
White	0.42	0.52	1.22	0.28	0.02	0.90
Temporal lobe						
Gray	2.57	0.12	8.70	0.006‡	1.72	0.20
White	2.70	0.11	13.08	0.001‡	2.14	0.15
Occipital lobe						
Gray	1.92	0.18	15.5	0.000§	0.18	0.68
White	1.14	0.29	5.87	0.021†	1.86	0.18
Cerebellum						
Gray	2.29	0.14	0.38	0.54	0.16	0.69
White	1.32	0.26	0.08	0.79	0.03	0.86

Note: ANCOVA indicates analysis of covariance.
*The ANCOVA covaries for total brain volume, †p<0.05, ‡p<0.01.

Table 5. Unadjusted and adjusted means of symmetry for boys with Tourette syndrome (n=19) and controls (n=17)

Symmetry measures, %†	Unadjusted means (SD)		Adjusted least square means*	
	Tourette syndrome	Controls	Tourette syndrome	Controls
Frontal lobe				
Gray‡	-7.6 (6.5)	-1.2 (6.4)	-7.63	-1.09
White	19.7 (5.6)	23.5 (7.6)	20.07	23.03
Parietal lobe				
Gray	2.4 (5.9)	2.2 (4.8)	1.51	3.15
White	4.4 (7.0)	5.6 (5.6)	4.52	5.49
Temporal lobe				
Gray	-0.6 (6.9)	-0.3 (4.7)	-1.53	0.77
White	17.6 (12.1)	17.6 (8.8)	19.32	15.65
Occipital lobe				
Gray	9.9 (16.6)	-0.3 (18.0)	6.02	3.99
White	-22.6 (17.5)	-32.2 (13.5)	-24.12	-30.43
Cerebellum				
Gray	13.1 (10.0)	9.6 (8.4)	12.61	10.13
White	-43.5 (19.7)	-45.7 (20.4)	-42.36	-46.96

*Adjusted for total brain volume by Bonferroni post hoc tests. †Percentage of Asymmetry defined as {(R-L)/[(R+L)/2]}×100. ‡F=7.69, d.f.=1, p=0.009.

a significantly leftward predominance of the frontal lobe gray matter ($F=7.69$. d.f.=1, $p=0.009$), which was due to a relative increase in the left frontal lobe gray matter and a decrease in the right frontal lobe gray matter. No group differences in the symmetry of the tissue composition of the cerebellar or temporal, parietal, or occipital lobe volumes were evident.

Clinical correlates

No significant relationship was observed between clinical ratings of Yale Global Tic Severity Scale and volumetric measurements of the brain regions.

IQ-matched analysis

ANCOVA was performed for both IQ scores and TBV as covariates. The results were virtually identical to those shown in Table 2-5.

Age-related changes

No significant age-related changes in slope were seen for the TS subjects.

DISCUSSION

In this study, the volumes of 20 cerebral and cerebellar regions and their symmetries were measured in 19 boys with TS and 17 age-matched normal control boys by brain magnetic resonance imaging. In the gray matter, TS boys had a smaller right frontal lobe and a larger left frontal lobe and increased normal asymmetry (left>right). In addition, the TS subjects had a larger frontal lobe white matter.

The results of this study by segmenting the gray and white matter showed that the normal asymmetry was significantly increased in TS subjects (left>right) in the frontal lobe gray matter. Thus, the asymmetry of the leftward predominance in the frontal lobe was the effect of the gray matter. TS subjects also had a larger frontal lobe white matter. However, it is different from the previous studies on ADHD that reported decreased volumes of the right anterior frontal region (32-34) and a previous study on OCD that reported a decrease in the bilateral orbital frontal volume and overall volumetric decreases in the white matter (35-37). However, further studies are needed in the future since little study has been performed in TS by segmenting brain tissue in the literature.

The smaller TBV in TS boys suggests that the boys with TS may have a bigger lesion compared with the normal controls. The smaller TBV may indicate a greater non-specific central nervous system insult in TS subjects (2, 38). This result was also confirmed by a smaller total cerebral volume in patients with ADHD and childhood-onset schizophrenia than in healthy controls in the similar age group (32-34, 38). However, a smaller TBV is confounded by lower IQ score and possible selection bias in TS subjects (38).

On the other hand, when the cerebrum and cerebellum were analyzed for correlation according to the region of interest with age, the results showed that the white matter showed a positive correlation with age but the gray matter did not show a significant correlation with age. Thus, our result is very reliable compared with the previous studies done with the school age children between the ages of 7 yr to 17 yr, which reported that the volume of the white matter increased only in this age group (39, 40).

The small number of subjects and the inclusion of only male subjects were the limitations of the present study. We, however, controlled various confounding variables (age, sex, handedness, drug-effect, and comorbid diagnosis) indicated in other studies as much as possible (3). Although a few problems existed in the selection of the control subjects, they were eligible as study subjects.

Diagnosis of TS was established according to the DSM-IV and by a consensus between two child psychiatrists, and clinical ratings of Yale Global Tic Severity Scale were used to increase the reliability of diagnosis of each patient. Since TS is a psychiatric disorder that frequently accompanies ADHD and OCD, we limited the study patients to those only with TS through detailed history taking to exclude these comorbid psychiatric disorders. A mild hyperactivity was described by 8 guardians of the subjects of the present study. But, there were no differences in results of statistical analysis if we excluded the TS subjects who had mild hyperactive history in the past.

Because the overall IQ scores were significantly higher in the control subjects than in the patients, we performed AN COVA for both IQ scores and TBV as covariate to control the effect of IQ. And results were virtually identical to the result for only TBV as covariate.

The overall IQ scores were significantly higher in the control subjects than in the patients, suggesting that control subjects included boys with superior IQ. However, the boys in the TS patient group also had IQ higher than the average, suggesting the possibility that the strict guideline in patient and control selection had to do with the high IQ. There have been controversial studies on the relationship between IQ and the brain size (40, 41). Although we investigated the relationship between IQ and various parts of the brain in the present study, no relationship with IQ was present in regions other than the cerebellar gray matter.

In this study, we were able to confirm the volumetric differences in the frontal lobe gray and white matter between TS and healthy control subjects. The results of the present study suggest the possibility that the frontal lobe is implicated in the pathophysiology of TS. Further studies are needed to support this hypothesis through a more standardized and detailed stereotactic-based parcellation method with a larger number of samples.

ACKNOWLEDGEMENTS

This research was partially supported by the Inha University Research Grant (INHA-21074). The authors acknowledge Alex M.C. Liu, Stephan Eliez, and Allan L. Reiss for their contribution to this work.

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