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RESEARCH

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Regional Volume Analysis of the Parkinson Disease Brain in Early Disease Stage: Gray Matter, White Matter, Striatum, and Thalamus

BACKGROUND AND PURPOSE: Loss of dopaminergic neurons in the nigrostriatal pathway is well-documented in PD, whereas neuronal changes beyond the nigrostriatal pathway are uncertain. The purpose of our study was to estimate volume changes in the striatum and thalamus, which are areas of the basal ganglia, as well as in GM and WM located beyond the nigrostriatal pathway, in early-stage PD.

MATERIALS AND METHODS: We enrolled 30 participants (15 healthy controls and 15 patients with PDND with H & Y stage I or II). Cognitive function was assessed by using the MMSE. ICV and the volumes of the caudate nucleus, putamen, thalamus, GM, and WM were calculated via 3D volume analysis by using MR imaging.

RESULTS: A comparison of the PD group with the control group revealed an absence of significant differences between them regarding age and MMSE scores. Comparison of the volumes of regional brain structures of patients with PD with those of controls revealed the presence of significant differences in the caudate nucleus, thalamus, and WM ($P < .05$) between the groups. However, there were no significant differences in the volumes of the putamen and GM or in ICV between patients with PD and controls. The results of ANCOVA by using the covariates of age and ICV showed a significant difference in the caudate nucleus, thalamus, and WM between patients with PD and controls ($P < .05$).

CONCLUSIONS: We suggest that loss of WM volume may occur in early disease stages and that variation of the volumes of the caudate nucleus and thalamus may be an early phenomenon of disease progression.

ABBREVIATIONS: ANCOVA = analysis of covariance; GABA = gamma aminobutyric acid; GM = gray matter; H & Y = Hoehn & Yahr; ICV = intracranial volume; max = maximum; min = minimum; MMSE = Mini-Mental State Examination; PD = Parkinson disease; PDD = Parkinson disease with dementia; PDND = Parkinson disease without dementia; PIGD = postural instability and gait disturbance; TD = tremor dominant; TFE = turbo field echo; UPDRS = Unified Parkinson's Disease Rating Scale; WM = white matter

PD is a neurodegenerative disease that is caused by degenerative changes in the dopaminergic neurons of the substantia nigra.¹ The pathologic changes of PD progress beyond the nigrostriatal pathway,²⁻⁴ and PD is now considered a multi-systemic disease that affects cognition, even in early stages, rather than a strict movement disease.⁵

Several reports have addressed the structural changes of PD, with special focus on brain atrophy.⁶⁻⁸ Studies of variation of regional brain volume, such as striatal volume, have yielded inconsistent results.⁹⁻¹²

In patients with PD, the natural balance of the basal ganglia circuitry is functionally lost because of dopamine depletion. Sequential imbalances lead to overexcitation of inhibitory GABAergic neurons in the globus pallidus interna/subthalamic nucleus via direct and indirect pathways, which results in profound inhibition of the thalamus.¹³ The striatum and

thalamus represent important structures that comprise the motor, cognitive, and limbic loops, which are responsible for various motor and nonmotor symptoms of PD. Nigrostriatal neurons synapse with medium-sized spiny neurons within the striatum, which in turn project to direct and indirect pathways.¹³ Significant loss of attenuation and length of the dendritic spines of medium-sized spiny neurons located in the striatum of patients with PD has been reported.¹⁴ In addition, neuronal degeneration (40%–50%) has been observed in the intralaminar thalamic nuclei of PD brains, which is suggested to occur in early disease stages.^{15,16}

The major hypotheses of the present study were that a lack of brain atrophy in PD implies a low likelihood of detecting brain changes by using imaging analysis and that a high likelihood of detecting brain changes by using imaging means that overall, the brain atrophy is too developed to allow the differentiation of vulnerable areas; therefore, early changes in the most vulnerable brain regions constitute an ideal tool to discriminate variations in different brain structures.

On the basis of these concepts, we hypothesized that the decrease in the dopaminergic tone of the nigrostriatal pathway results in structural changes that are not restricted to the basal ganglia but extend beyond this structure and that the severity of the structural changes varies according to brain region or time of examination. To address these hypotheses, we enrolled

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Table 1: Demographic features of patients with PD and healthy subjects

Demographics	Patients with PD (<i>n</i> = 15)	Control Subjects (<i>n</i> = 15)	<i>P</i> Value
Mean age (min–max, yr)	66.4 ± 7.05 (54–76)	61.4 ± 7.77 (52–75)	>.05
Sex	All female	All female	–
Smoking (No.)	0	0	>.05
Hypotension (No.)	2	0	–
Diabetes mellitus (No.)	0	0	>.05
Handedness	Right	Right	–
TD/PIGD (No.)	11/4	–	–
MMSE	27.4 ± 1.8	27.8 ± 1.4	>.05
UPDRS part 3	15.3 ± 4.9	–	–
H & Y stage	1.6 ± 0.5	–	–
Duration of illness (yr)	1.2 ± 0.8	–	–

– indicates not applicable.

patients with relatively early-stage PD. Subsequently, we analyzed the volume of the striatum and thalamus of patients with PD by using 3D volume analysis. The rationale for choosing these areas was that these structures play an important role in input and output pathways, respectively, in basal ganglia circuits and that loss of these structures reportedly represents an early disease period.^{13–16} We also calculated the total volume of the GM and WM in whole brains of patients to evaluate structural changes that occur beyond the basal ganglia in early-stage PD.

Materials and Methods

Subjects

Fifteen de novo patients were recruited from the department of neurology at the Kangwon National University Hospital. To avoid sex bias in brain volume, we enrolled only women. H & Y staging was restricted to stages I or II.¹⁷ All participants were right-handed. None of the patients had a history of alcohol dependency or smoking. The inclusion criterion was a diagnosis of PD according to the United Kingdom Parkinson's Disease Society brain bank diagnostic criteria.¹⁸ Exclusion criteria were the following: a history of head trauma, stroke, exposure to antidopaminergic drugs, central nervous system infection, abnormal thyroid function, a structural lesion or hydrocephalus on brain MR imaging, and red flag signs suggestive of PD Plus syndrome or dementia (MMSE score of <24).¹⁹ Fifteen sex-, handedness-, and age-matched healthy volunteers were used as control subjects. The clinical assessment of patients included MMSE, UPDRS part III, and H & Y staging. The present study was approved by the Ethics Committee of the Kangwon National University Hospital, and all patients and volunteers provided informed consent to participate in the study. Table 1 summarizes the demographic features of patients and control subjects.

Data Acquisition

All subjects were scanned by using a 1.5T MR imaging scanner (Gyrosan ACS-NT; Philips Healthcare, Best, the Netherlands). To achieve consistent positioning of the head of individuals, we acquired pilot images of coronal, sagittal, and axial fast-field echo T1 MR images by using the following scanning variables: thickness = 10 mm, gap = 10 mm, TR/TE = 15/5.2 ms, matrix = 256 × 256, FOV = 25 × 25 cm, 4 sections in each orientation, and flip angle = 20°.

On the basis of the pilot images, coronal 3D T1-weighted TFE MR imaging was performed by using the following scanning variables: thickness = 1.3 mm, no gap, 160 sections, scanning time = 10 min-

utes 13 seconds, TR/TE = 10/4.3 ms, number of signal-intensity averages = 1, matrix = 256 × 256, FOV = 22 × 22 cm, 160 sections, and flip angle = 8°. Coronal sections were obtained perpendicular to the long axis extending from the anterior commissure to the posterior commissure in the midsagittal pilot. The final voxel size was 0.86 (x) × 0.86 (y) × 1.30 (z) mm.

Volumetry

The volumes of the caudate nucleus, putamen, and thalamus were measured by 1 of the authors (W.-S.T.) who had experience in brain anatomy and volumetry. The rater was blinded to the clinical information of all participants. The boundaries of each substructure were traced manually by using ITK-SNAP 1.6 (www.itksnap.org).²⁰ Coronal T1 MR imaging data were loaded onto ITK-SNAP and zoomed 3-fold. We used the interactive labeling function with simultaneous coronal, sagittal, and axial views and surface rendering of the labeled substructures. On the basis of manual tracing guidelines (www.psychiatry.uiowa.edu/mhrc/IPLpages/manual_tracing.htm) and on a brain atlas,²¹ the boundaries of the substructures were defined as follows: 1) For the thalamus, the mammillary body was used as the anterior boundary, the third ventricle was used as the medial boundary, the internal capsule was used as the lateral boundary, the inferior border of the third ventricle was used as the inferior boundary, the main body of the lateral ventricle was used as the superior boundary, and the posterior boundary was defined as the area where the thalamus merged under the crus of fornix. 2) The tracing of the caudate nucleus started at a section where it was first visualized in the frontal horn of the lateral ventricles and ended at the section where it was no longer identifiable; the nucleus accumbens was used as the ventral boundary, the lateral ventricle was used as the medial boundary, and the internal capsule was used as the lateral boundary. 3) For the boundary of the putamen, the medial boundary was the internal capsule (anterior putamen) and the external pallidum (posterior putamen); the lateral boundary was defined by the external capsule (Fig 1).

Without clinical information, we included all MR imaging data from healthy subjects and patients in the same directory before measurements. To test the reproducibility of thalamus volumetry, we again measured both thalami of 5 healthy subjects and 5 patients. The intraclass correlation coefficients (Cronbach α) obtained for the volumetry of the thalami (right, 0.96; left, 0.97), caudate nuclei (right, 0.94; left, 0.96), putamina (right, 0.94; left, 0.92), and the intracranial volume (ICV, 0.998) were high.

Fig 1. A–G, Volumes of interest of the caudate nucleus, putamen, and thalamus. Each substructure was traced manually and labeled separately, according to the predefined boundary criteria. The most anterior caudate nuclei (A), putamina (B), and thalami (D) are displayed. 3D rendering of the volumes of interest of both caudate nuclei, putamina, and thalami (H). Red indicates the right caudate nucleus; green, the left caudate nucleus; blue, the right putamen; yellow, the left putamen; sky blue, the right thalamus; and purple, the left thalamus.

ICV and GM/WM Volume Measurements

ICV was used to normalize thalamic volumes.²² To measure ICV, we reconstructed coronal T1-weighted TFE MR imaging data to 5-mm-thick sagittal images, which were then magnified 2-fold. The cerebrum, cerebellum, and midbrain were included in the ICV volume, together with the outer boundary of the dura mater.^{23–26} The lateral limits of the ICV were defined as the rightmost and leftmost sections of the brain parenchyma on sagittal images, and the lower tip of the cerebellum was defined as the lower limit. We increased the brightness of the image to improve the visual clarity of the boundary of the dura mater. The dura mater of the cerebrum, cerebellum, and midbrain (with the exception of the inferior boundary) were traced manually by using established measurement criteria.²⁶ To establish the inferior boundary on the head-tilt-corrected sagittal images, we drew a horizontal line across the midbrain to include the lower tip of the cerebellum.

GM and WM volumes were calculated separately by using SPM2 software (Wellcome Department of Imaging Neuroscience, London, United Kingdom) implemented in Matlab (MathWorks, Natick, Massachusetts). To create customized templates and prior images of GM, WM, and CSF, we spatially normalized all MR images to the standard T1 template. On the basis of a modified Gaussian mixture model,²⁷ normalized images were segmented into GM, WM, and CSF and were subsampled into a voxel size of $2 \times 2 \times 2$ mm. To remove isolated voxels of 1 tissue class that were unlikely to be members of this tissue type, a hidden Markov Random Field model was applied in all segmentation processes.²⁸ The spatially normalized raw images and segmented GM, WM, and CSF images were averaged and saved into the customized T1 template and into GM, WM, and CSF prior images, respectively. Three prior images and the customized T1 template were smoothed by using an 8-mm full width at half maximum isotropic Gaussian kernel.

Table 2: Results of MR imaging volumetry

	Healthy Controls	PD	T test (P)	ANCOVA (P ^a)
ICV (cm ³)	1,389 ± 78.2	1,347 ± 101.8	0.211	— ^b
GM volume (cm ³)	662 ± 45.3	611.5 ± 102	0.513	.582
WM volume (cm ³)	396 ± 28.6	354 ± 39.8	0.003	.017
Caudate nuclei volumes (cm ³)				
Right	3.32 ± 0.41	2.82 ± 0.36	0.001	.020
Left	3.24 ± 0.44	2.67 ± 0.35	0.001	.008
Putamina volumes (cm ³)				
Right	3.82 ± 0.53	3.47 ± 0.34	0.043	.328
Left	3.74 ± 0.54	3.26 ± 0.35	0.008	.067
Thalamic volumes (cm ³)				
Right	5.75 ± 0.52	4.96 ± 0.56	0.0004	.003
Left	5.67 ± 0.64	4.78 ± 0.47	0.0002	.006

^a Indicates ANCOVA covariate with ICV and age.

^b — indicates not applicable.

To calculate GM and WM volumes, we automatically segmented the raw T1 images of all subjects into GM, WM, and CSF partitions in native space. The GM image of an individual was spatially normalized to the customized GM template and the raw T1 image of the subject was then transformed to Montreal Neurologic Institute space by using the spatial normalization parameter. The normalized raw T1 MR images were segmented into 3 brain tissues on the basis of a Bayesian rule.²⁷ The use of the hidden Markov random field model and Bayesian rule in the segmentation process improves the clear brain tissue separation with other brain tissues. Finally, the segmented GM images were reversely normalized to native space by using a voxel size of 0.86 (x) × 0.86 (y) × 1.30 (z) mm, and the GM volumes were calculated.

Statistical Analyses

It was important to reduce the variability within the control group to compare the variable volumes of brain structures between groups. The following methods have been introduced to overcome this problem: inclusion of the covariates in the statistical analyses and selection of controls that matched the patient group regarding demographic parameters²⁹ (though the relative reliability of the approaches is inconclusive). In the current study, we used ANCOVA as a general linear model to compare groups and attempted to select controls with demographic parameters that matched those of the patients.

The Kolmogorov-Smirnov test showed that the ICV and the volumes of the caudate nuclei, putamina, thalami, GM, and WM exhibited a normal distribution ($P > .1$). A parametric *t* test was used to compare the volumes of the caudate nucleus, putamen, thalamus, GM, and WM between patients with PD and controls. Correlations between the volumes of both sides of the thalamus were assessed by using the Pearson correlation test.

A general linear model was used because the ICV and the volumes of the caudate nucleus, putamen, thalamus, GM, and WM exhibited a normal distribution. The ANCOVA with the covariates of age and ICV was used to compare the focal brain volume between groups because age, sex, and ICV were expected to influence volume.²⁹ A sex effect was absent in the current study because only female participants were recruited. ANCOVA by using covariate age and ICV was applied to compare the volumes of the caudate nucleus, putamen, thalamus, GM, and WM between patients with PD and controls. Significance was set at $P < .05$. Statistical analyses were performed by using the Statistical Package for the Social Sciences, Volume 18.0 (SPSS, Chicago, Illinois).

Results

The mean age of the subjects in the PD group was 66.4 ± 7.05 years versus 61.4 ± 7.77 years in the control group. The MMSE scores of patients with PD and controls were 27.4 ± 1.8 and 27.8 ± 1.4 , respectively. There was no significant difference in age and MMSE score between patients with PD and control subjects. Although MMSE is a method that is used to screen for cognitive decline and has pitfalls in the detection of the executive dysfunction of PD, we considered that the cognitive function of all participants was grossly within normal limits. The mean UPDRS part III scores and mean H & Y stages of patients with PD were 15.3 ± 4.9 and 1.6 ± 0.5 , respectively. As expected, most patients with PD had motor symptoms without cognitive decline. All patients with PD exhibited a relatively early stage of disease, and the maximal UPDRS part III score was 24.

Correlation analysis revealed the presence of a significant correlation between the volume of the right and left structures within the basal ganglia (caudate nucleus, putamen, and thalamus; $P < .001$). This result implies that the regions of interest of the caudate nucleus, putamen, and thalamus were adequately traced by using manual drawing and that there was no morphologic asymmetry.

The comparison of the ICV and the volumes of the striatum, thalamus, GM, and WM revealed a significant difference in both caudate nuclei (right, $P = .001$; left, $P = .001$), both putamina (right, $P = .043$; left, $P = .008$), both thalami (right, $P = .0004$; left, $P = .0002$), and WM ($P = .003$) between PD subjects and controls. The results of ANCOVA by using covariates of age and ICV showed a significant difference in both caudate nuclei (right, $P = .020$; left, $P = .008$) and thalami (right, $P = .003$; left, $P = .006$) and WM ($P = .017$) between patients with PD and controls. However, the findings for the putamen were not significant ($P > .05$). These results are summarized in Table 2.

Discussion

The PD group had the following characteristics: absence of cognitive decline, female sex in all patients, and a relatively early disease stage (ie, H & Y stage I or II).

Our study yielded 3 interesting findings: First, the volumes of the caudate nucleus and thalamus of patients with PD were

Table 3: Comparison of the present study with previous ones

Author	Age	Sex	MMSE	UPDRS Part III	H & Y Stage	Duration of Illness
Burton et al ⁷	75.2 ± 5.2	Mixed	26.4 ± 1.9			43.5 ± 34.2 (mo)
Karagulle Kendi et al ⁸	62.1 ± 12.7	Mixed	28.2		1.8 ± 0.4	5.8 ± 4.5 (yr)
Krabbe et al ⁹	57.5 ± 9.6	Mixed	28.2 ± 1.8	39 ± 21	2.3 ± 1	8.1 ± 5.5 (yr)
Gattellaro et al ¹²	63.8 ± 15.7	Mixed	28.3 ± 1.5	20.5 ± 8.3	I or II	3.4 ± 2.9 (yr)
Beyer et al ³⁰	72.5 ± 8.5	Mixed	28.2 ± 2.1		2.4 ± 0.6	12.0 ± 6.3 (yr)
Summerfield et al ³¹	72.77 ± 4.90	No info.	28.54 ± 1.05	24.50 ± 12.04	2.73 ± 0.72	10.61 ± 7.41 (yr)

smaller than those of control thalami. Second, the ICV and the volume of the GM of patients with PD were not significantly different from those of control subjects. Third, the volume of the WM of patients with PD was smaller than that of controls. Nonspecific brain atrophy in regions with atrophic changes associated with/without dementia has been reported in several previous studies, with an absence of consistent results.^{6-11,30-32} The cause of the variability among these findings remains uncertain. However, the results of our study showed that the loss of volume of brain structures in PD varies according to region. The comparison of our results with those of previous studies revealed that the stage of PD in the current report was relatively earlier than that of other studies, though there was some variability among the individual studies (Table 3). Therefore, we speculate that the inconsistency of previous results may stem from the variability of the stage of PD at examination.

Although the precise region of the WM that had loss of volume was uncertain because the volume of the entire WM was measured automatically, our result implies that structural changes occur in early disease stages, before clinical manifestations become apparent. In other words, PD may not be a disease that is restricted to the nigrostriatal pathway but may involve structures beyond this pathway, even at early stages. Accordingly, another study revealed the presence of widespread microstructural damage in the frontal and parietal WM in early-stage PD, though the authors used diffusion tensor imaging as the analytic method, not volume analysis.¹² The cause of the loss of WM volume remains uncertain. Nevertheless, we assumed that a decreased dopaminergic tone, which results in a breakdown of corticostriatal connections¹⁴ or impairment of various neurochemicals in broad areas,³³ may be 1 of the mechanisms involved in WM changes.

We also found that the GM volume and the ICV of patients with PD were not different from those observed for healthy controls. Age is a main factor affecting cortical GM structures, and loss of cerebral WM occurs later than the loss of GM during the aging process.³⁴ In this study, there was no age difference between patients with PD and controls. Moreover, age was defined as a covariate in the statistical design of the study. Our results suggest that the effects of PD on the GM in early disease stages were not as marked as its effects on the WM. Several studies suggest that the risk of dementia is 6 times greater in patients with PD compared with controls,³⁵ and the prevalence of PDD is estimated as ~25%.³⁶ PDD was associated with greater GM reduction compared with PDND on morphologic MR imaging studies.^{30,31} None of the patients showed cognitive decline, and all patients exhibited a normal range of MMSE scores in our study. Therefore, the lack of reduction of the volume of GM in the whole brain was compatible with the condition of the patients enrolled.

In the present study, the significant volume change detected in PDND implies that the caudate nucleus and thalamus, which act as input and output pathways of the basal ganglia system, respectively, may be affected in early-stage disease. Although it has been shown that the loss of dopaminergic neurons in the nigrostriatal pathway results in the depletion of dopamine in the striatum, the loss of nondopaminergic neurons, including cholinergic, serotonergic, and noradrenergic cells, has also been recognized.³⁷ The reason underlying the observation that the volume change of the caudate nucleus and thalamus in basal ganglia in PDND was definitive, whereas that of the putamen in PDND was not, remains obscure. Loss of volume of the putamen was reported in previous studies^{9,11}; therefore, examination time is a possible explanation for this discrepancy because the stage of PD may have been too early to allow the discrimination of morphologic changes in the putamen.

In the current study, the overall GM did not differ between the groups, whereas the local volume of the GM, including the caudate nucleus and thalamus, was reduced in PD brains. The fact that the proportion of striatum and thalamus to whole-brain GM was strikingly low (<1%) is a possible explanation for this result.^{9,38}

The asymmetric involvement of motor symptoms is a typical clinical feature of PD.¹⁷ This characteristic may reflect an asymmetric dysfunction of the nigrostriatal pathway.³⁹ However, to our knowledge, there are no outstanding structural studies addressing the association between the asymmetric motor involvement observed in PD and brain atrophy, though several meaningful studies used positron-emission tomography or single-photon emission CT.⁴⁰⁻⁴² In the present study, we found no significant asymmetric volume changes in regional structures within the basal ganglia.

The limitations of the present study were as follows: First, cognitive impairment is an important feature of PD. Dysfunction of attention and executive function is seen in most patients with PDND.⁴³ However, this study exhibited a limitation regarding cognitive dysfunction because the sensitivity of MMSE was low for the diagnosis of PDD, despite the fact that MMSE is a general screening tool for cognitive impairment.⁴⁴ Second, although the patients with PD were selected strictly according to the United Kingdom Parkinson's Disease Society brain bank diagnostic criteria,¹⁸ the selection of patients with atypical parkinsonism was an unavoidable risk, especially those with an early disease stage.⁴⁵

Conclusions

In summary, the major aim of this study was to evaluate volume changes in several areas of the basal ganglia, as well as in the GM and WM located beyond the nigrostriatal dopaminergic

gic system in an early PD stage, because more advanced stages may involve nonspecific brain atrophy. Our results showed that the volumes of the putamen and GM and the ICV in patients with PD were not different compared with controls, whereas the volumes of the caudate nucleus, thalamus, and WM were decreased in patients with PD compared with controls. We suggest that though the clinical manifestations were obscure, loss of WM volume may occur in early disease stages and that change in the volume of the caudate nucleus and thalamus, which represents a structural change in input and output in the basal ganglia, may also be an early phenomenon of disease progression. Additional functional and pathophysiologic studies are required to provide complementary explanations regarding the PD structural changes reflected on neuroimaging.

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