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Volume fraction of the cerebellum in Parkinson's patients

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Abstract

Most investigations on Parkinson's disease (PD) focus on the basal ganglia and brainstem, whereas the cerebellum has often been overlooked. The cerebellum is critical for motor control and increasing evidence suggests that it may be associated with the pathophysiology of PD. The aim of this study was to describe cerebral and cerebellar volumes in patients with PD and to compare results with healthy subjects. In the present study, 18 patients with PD (8 female, 10 male) and 19 controls (9 females, 10 males) were included. Structural magnetic resonance (MR) imaging was performed in both groups with a 1.5 Tesla scanner. The images were analyzed using ImageJ software. Volumes were estimated via planimetry and threshold stereological methods. The mean total cerebral volumes were 943.19 ± 91.67 cm^3 in control group and 909.83 ± 95.88 cm^3 in patients. The mean total cerebellar volumes and the volume fractions were found 140.44 ± 21.68 cm^3, 14.94 ± 2.17 % in control group and 140.52 ± 15.96 cm^3, 15.52 ± 1.73% in patients, respectively. There were no significant differences found in terms of cerebral and cerebellar parameters. Our knowledge about cerebellum and PD interaction remains limited, although, the cerebellum is a potential target for some parkinsonian symptoms. Further investigations are needed to understand the role of cerebellum in PD using newly developing imaging techniques.

Keywords: Parkinson's disease, cerebellum, volume fraction, planimetry, magnetic resonance

1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder, leads to resting tremor, stiffness, slowness and impaired balance. Loss of dopaminergic neurons in pars compacta of subtantia nigra is regarded as the main pathophysiologic mechanism (1). However, this classic model of the disease is not adequate in explaining of all the symptoms of PD, for example resting tremor (2). It is likely that basal ganglia is not the only responsible structure in disease development (1-3). New researches determine different connections besides the traditional assumption that, the cerebellum and basal ganglia are separate anatomic structures and have indirect connections at the cortical level (4-5). Results from recent anatomical studies indicates direct synaptic pathways between the cerebellum and the basal ganglia structures (5). Both the cerebellum and the basal ganglia have a role in motor and non-motor behaviours. Because of their dense and reciprocal interactions suggest the involvement of cerebellum in disease manifestations (3). Most investigations on PD focused on the basal ganglia and other cortical structures, whereas the cerebellum has often been overlooked (6). Cerebellum may contribute to the symptoms or may be influenced by the PD (7).

Although Parkinson's disease is diagnosed clinically, brain imaging methods are used excluding the alternative pathologies (8). Magnetic resonance (MR) imaging, because of allowing *in vivo* accurate measurements, is under consideration to be helpful in understanding the morphological changes in the brain during the disease. In recent years, numerous volumetric studies were conducted using different measurement techniques on MR images (9). Nevertheless, the results remain inconsistent and studies on cerebellum are few (10, 11).

Therefore, the aim of this study was determined to describe and compare the cerebral volume and the cerebellar volume and the volume fractions in Parkinson's patients comparing with controls using MR imaging-based analysis.

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2. Material and Methods

2.1. Ethical Statement

This study was carried out with the permission of the Medical Research Ethics Committee of Ondokuz Mayıs University. Written informed consent was obtained from all subjects before the procedures.

2.2. Participants

In the present study the total of 37 subjects, 19 control (9 females, 10 males) and 18 Parkinson's patients (8 females, 10 males) were participated. The mean ages of males and females in controls and patients were 54.89±6.82, 55.50±6.67 and 54.50±6.43, 59.20±4.54 years-old, respectively

2.3. Exclusion criteria

Patients with Parkinsonian/Parkinson plus syndromes and other neurodegenerative diseases, dementia and history of prior neurological disorder were excluded from the study. Patients with motion artifacts on their brain scans were excluded, although they had fulfilled the inclusion criteria.

2.4. Image processing and sampling

Structural magnetic resonance imaging was done the subjects using 1.5 Tesla (T) scanner (Philips, Achieva, The Netherlands). The image thickness was 1.1 mm. DICOM images were transferred to the ImageJ software and then converted into stack, the images were in coronal plane, which used for the measurements of the cerebral hemispheres. Second stack was obtained in sagittal plane with 1 mm in thickness for the measurement of the cerebellum. Systematic random sampling was done. The sampling fraction was 1/10 and 1/5 for the cerebrum and the cerebellum, respectively.

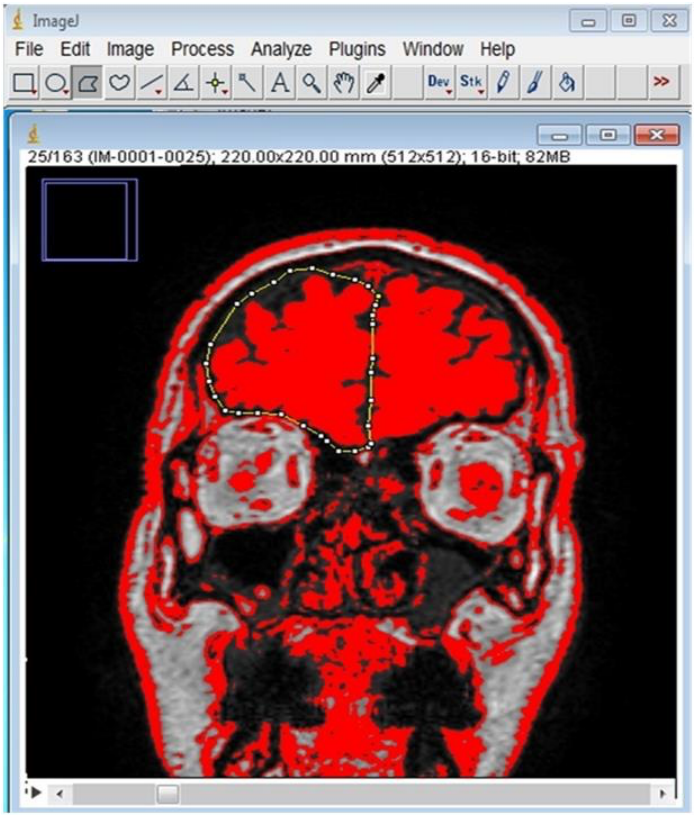

Fig. 1. Delineation of contour of the right cerebral hemisphere using the planimetry and the thresholding methods

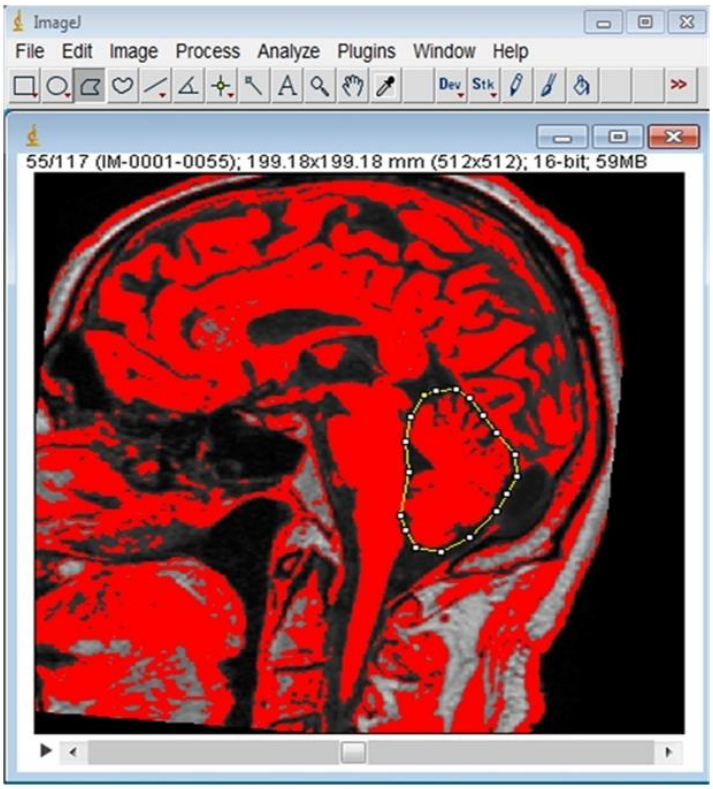

Fig. 2. Delineation of contour of the cerebellar hemisphere using the planimetry and the thresholding methods

Using thresholding, the cerebral and cerebellar hemispheres were determined using upper and lower limits of the structures. Delineations of the cerebral and the cerebellar hemispheres in coronal and sagittal sections on ImageJ software interface, respectively were given in Fig. 1 and 2. Planimetry method of the stereological techniques was done, the regions of interests were delineated (12). T1 weighted images were used for manual tracing of the borders of cerebrum and cerebellum. Finally, the delineated areas were measured and volume and volume fractions were calculated.

2.5. Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used for determining whether variables are normally distributed. Data are given as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Continuous variables were analysed with the two-way analysis of variances (ANOVA). Sex distribution between cases was evaluated with the Chi-square test. Two tailed p-values of less than 0.05 were considered statistically significant.

3. Results

We included 37 individuals (19 controls and 18 patients) into our study, mean age was 56.14 ± 6.20 (range 45 – 65). There was no significant difference between cases with regard to the age (p=0.421). There were 9 (47.37%) females and 10 (52.63%) males in the controls group while there were 8 (44.44%) females and 10 (55.56%) males in the patient's group. There was no significant difference between cases with regard to sex distribution (p=1.000). As a result of the analysis

of the cerebellar volumes, cerebral volumes and the volume fractions, we found no significant differences between the cases. Summary of the individuals' characteristics and measurements with regard to cases is given in Table 1.

Table 1. Summary of individuals' characteristics and measurements with regard to cases

	Cases			
	Control (n=19)	Patients (n=18)	Total	p
Age (year)	55.21 ± 6.56	57.11 ± 5.81	56.14 ± 6.20	0.421
Female	9 (47.37%)	8 (44.44%)	17 (45.95%)	1.000
Male	10 (52.63%)	10 (55.56%)	20 (54.05%)	
Right Hemisphere Cerebellar Volume (cm^3)	68.73 ± 10.67	68.50 ± 8.71	68.62 ± 9.63	0.910
Right Hemisphere Cerebral Volume (cm^3)	474.90 ± 45.65	455.65 ± 46.31	465.53 ± 46.36	0.111
Volume Fraction of the Right Cerebellum (%)	14.52 ± 2.17	15.09 ± 1.79	14.80 ± 1.98	0.375
Left Hemisphere Cerebellar Volume (cm^3)	71.72 ± 11.46	72.01 ± 7.82	71.86 ± 9.73	0.967
Left Hemisphere Cerebral Volume (cm^3)	468.29 ± 47.03	454.19 ± 51.28	461.43 ± 48.98	0.222
Volume Fraction of the Left Cerebellum (%)	15.37 ± 2.35	15.96 ± 1.85	15.66 ± 2.11	0.353
Total Cerebellar Volume (cm^3)	140.44 ± 21.68	140.52 ± 15.96	140.48 ± 18.85	0.968
Total Cerebral Volume (cm^3)	943.19 ± 91.67	909.83 ± 95.88	926.96 ± 93.96	0.153
Volume Fraction of the Cerebellum (%)	14.94 ± 2.17	15.52 ± 1.73	15.22 ± 1.97	0.345

Data are given as mean ± standard deviation and as frequency (percentage) for categorical variables; p values were obtained by two-way analysis of variances with cases and sex

Total cerebellar volume (mean ± standard deviation) with regard to the cases was given in Fig. 3. Volume fraction of the cerebellum (mean ± standard deviation) with regard to the cases were given in Fig. 4.

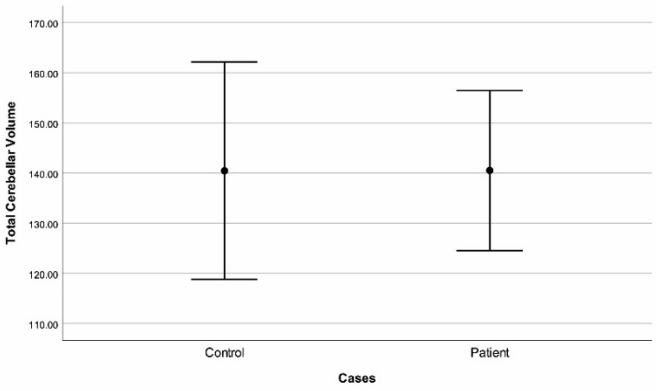

Fig. 3. Total Cerebellar Volume (mean ± standard deviation) with regard to the cases

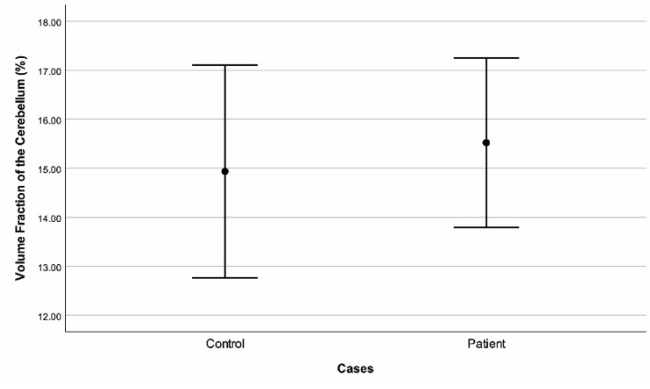

Fig. 4. Volume Fraction of the Cerebellum (mean ± standard deviation) with regard to the cases

The right hemisphere cerebral volume, left hemisphere cerebellar volume, left hemisphere cerebral volume, total cerebellar volume and the total cerebral volume were significantly higher in the males compared to females. On the other hand, there was no significant difference found between sexes with regard to age, right hemisphere cerebellar volume, volume fraction of the right cerebellum, volume fraction of the left cerebellum and volume fraction of the cerebellum.

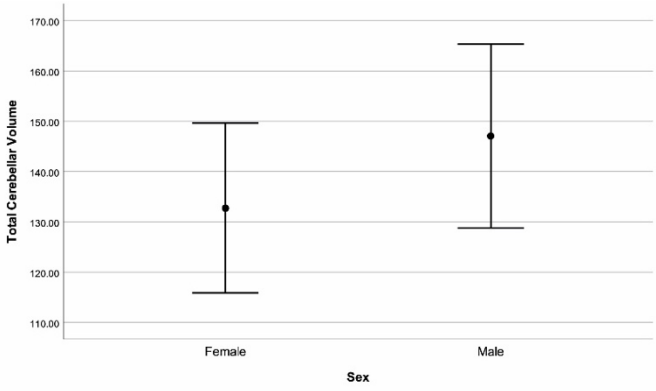

Fig. 5. Total Cerebellar Volume (mean ± standard deviation) with regard to sex

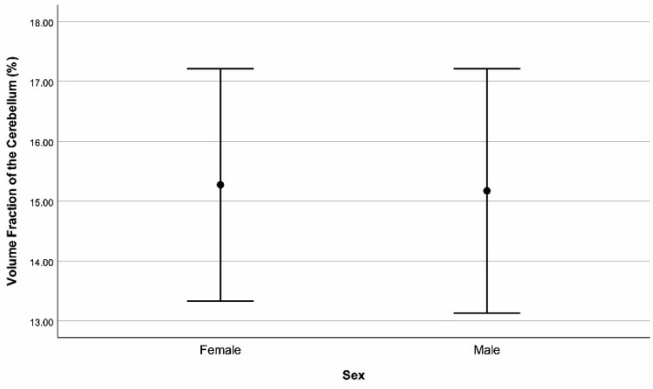

Fig. 6. Volume Fraction of the Cerebellum (mean ± standard deviation) with regard to sex

Also interactions between cases and sexes found as non-significant for all variables that means differences between sexes are independent from presence of Parkinson's disease (presence of Parkinson's disease has no effect on differences between sexes). Summary of individuals' characteristics and measurements with regard to sex is given in Table 2. Total

cerebellar volume (mean ± standard deviation) with regard to sex is given in Fig. 5. Volume fraction of the cerebellum (mean ± standard deviation) with regard to sex is given in Fig. 6

Table 2. Summary of individuals' characteristics and measurements with regard to sex

	Sex			
	Female (n=17)	Male (n=20)	p (sex)	p (cases*sex)
Age (year)	54.71 ± 6.44	57.35 ± 5.87	0.200	0.322
Right Hemisphere Cerebellar Volume (cm^3)	65.82 ± 9.15	70.99 ± 9.62	0.115	0.955
Right Hemisphere Cerebral Volume (cm^3)	438.68 ± 37.36	488.36 ± 41.28	<0.001	0.694
Volume Fraction of the Right Cerebellum (%)	15.04 ± 1.92	14.60 ± 2.07	0.496	0.757
Left Hemisphere Cerebellar Volume (cm^3)	66.90 ± 8.05	76.08 ± 9.15	0.004	0.700
Left Hemisphere Cerebral Volume (cm^3)	433.38 ± 40.74	485.27 ± 42.96	<0.001	0.225
Volume Fraction of the Left Cerebellum (%)	15.53 ± 2.11	15.77 ± 2.16	0.784	0.192
Total Cerebellar Volume (cm^3)	132.72 ± 16.89	147.07 ± 18.26	0.023	0.826
Total Cerebral Volume (cm^3)	872.06 ± 77.16	973.63 ± 82.01	<0.001	0.404
Volume Fraction of the Cerebellum (%)	15.27 ± 1.94	15.17 ± 2.04	0.839	0.401

Data are given as mean ± standard deviation and as frequency (percentage) for categorical variables
p values were obtained by two way analysis of variances with cases and sex

4. Discussion

Today, it is as of yet unknown whether cerebellar involvement is present in patients with PD (13). Conflicting results have been obtained in the few publications that have evaluated cerebellar volumes with volumetric MRI measurements (6). In this study, we aimed to address these controversial findings by comparing healthy subjects and patients with idiopathic PD in terms of volumetric MRI results. Our findings showed no significant differences between the two groups. Additionally, although we found that males had significantly larger right hemisphere cerebral volume, left hemisphere cerebellar volume, left hemisphere cerebral volume, total cerebellar volume and total cerebral volume when compared to females; detailed statistical analyses demonstrated that the presence of PD had no effect on these differences between the sexes. The study by Bharti et al., which was performed via voxel-based morphometry in 31 patients with PD, was in agreement with our results and showed no significant differences in the grey matter volume of cerebellar locomotor region, fastigial nucleus and dentate nucleus seed regions between Parkinson disease patients and healthy subjects. However, in the subgroup comparison of subjects with and without freezing of gait (FOG), the authors determined that PD patients had higher functional connectivity within these regions compared to healthy subjects (14). In another study, Ma et al. reported similar cerebellum volumes in patients with tremor-predominant PD and those with akinetic/rigidity-predominant PD (15).

There are also studies that report different results. For instance, in a voxel-based morphometry study, O'Callaghan et al. reported loss of grey matter throughout the cognitive and motor regions of the cerebellum in patients with PD, and more importantly, identified a significant inverse correlation between cerebellar connectivity and grey matter volume (16). Gao et al. also reported changes in volumetric measures in PD; their results showed that PD patients with normal cognition had loss in the posterior cerebellum, whereas those with mild cognitive impairment had loss in the anterior cerebellum (both comparisons relative to healthy subjects) (17). The cerebellar peduncle was also determined to demonstrate PD-related reduction in size when a subgroup of patients who had sleep disorder were compared with healthy subjects by Radziunas et al. (18).

We believe that the variations in previously reported results and the differences regarding our findings may be explained by several factors. The fact that the number of patients were higher in previous studies could have caused statistically-relevant differences; furthermore, in prior studies, the significant differences were mostly found in the comparison of healthy subjects with specific subgroups of patients with PD (such as those with FOG, mild cognitive impairment and sleep disorder). Today, it is well known that the cerebellum is not limited to the modulation of balance, with studies showing its relationships with cognition. For instance, several clinical/anatomical studies as well as functional MRI findings have shown that the posterior lobe of the cerebellum, particularly the crus I and crus II lobules, connect with the frontal cortex (19-21). Therefore, it is possible that more specific measurements of the effected regions could result in more accurate findings. Considering the limited number of patients and insufficient clinical data, we did not perform subgroup analyses in the present study. This characteristic may be identified as the primary limitation of our study; however, it must be noted that previous studies have not found any common results in terms of the change and localization of volumetric differences. Additionally, studies that determined significant alterations included considerably older PD patients, suggesting longer duration with disease; whereas, our results were performed in younger patients (average age: 57.1 years).

In this study, the cerebellum volumes were compared between Parkinson patients and healthy controls. No significant differences were found neither in the cerebrum volumes nor the cerebellum volumes between the groups as measured by a 1.5 Tesla MRI scanner. Lack of significance might be the result of relatively small sample size or limitations of the imaging method or volume estimations.

There are still controversial opinions about whether the

cerebellar volume is affected in PD. The literature data about the cerebellum and PD interaction remain limited, even though the cerebellum is potentially associated with the symptoms of PD. The further studies with higher number of subjects or more advanced imaging modalities are needed to clarify PD–related pathological alterations in the cerebellum and to determine the way in which cerebellar pathologic and compensatory effects change as the disorder progresses.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None to declare.

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