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Evaluation of cortical thickness and volume differences of the cerebellum in Parkinson's cases

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Abstract

Parkinson's disease (PD) is the most common neurodegenerative disease after Alzheimer's disease. PD causes degenerative changes in the cerebellum. It is known that the cerebellum does not have a symmetrical anatomy and some pathological disorders may cause asymmetric changes in the cerebellum. In this study, our aim is evaluate whether or not cases with PD show age and gender dependent cerebellar changes and cerebellar asymmetry comparing with healthy subjects. We also aimed to depict the probable cortical thickness differences in cases with PD by using a stereological technique. The study evaluated the volumetric assesment of each cortical cerebellar hemisphere and total cerebellum by applying a stereological technique on magnetic resonance images. The age and gender-matched study was composed of 47 adult cases with PD and 47 healthy subjets as control. In the PD group, right and left cerebellar hemisphere volume, total cerebellum volume, and cortical thickness of the right and left cerebellar hemispheres were significantly lower than the control group ($p<0.01$). Although there was significant cerebellar atrophy and asymmetry in PD cases with age between 40-71, the study showed no statistically significant cerebellar asymmetry in cases over 70 years of age. However, no significant difference was detected depending on gender. Our findings suggest that in PD, cerebellum's cortical thickness and volume decreases. The decrease in the volume and cortical thickness of the cerebellum increases with age, regardless of gender, compared to healthy individuals. However, this difference begins to close with age.

Keywords: Parkinson's disease, cerebellar atrophy, asymmetry, cortical thickness

Introduction

Recent studies have focused on defining brain compartments and finding Magnetic Resonance Imaging (MRI)-detectable discriminators of healthy and pathological ageing in neurodegenerative diseases [1]. Parkinson's disease (PD) is a progressive neurodegenerative disorder and manifests resting tremor, bradykinesia, rigidity, cogwheel sign, postural instability. The disease involves basal nuclei, principaly the degeneration of dopaminergic neurons in substantia nigra pars compacta. It has been revealed that the basal nuclei are not the only structure responsible for PD and that they interact with the cerebellum through connections at the cortical level. Subcortical systems such as the basal ganglia and cerebellum influence cerebral cortical activity via the thalamus and are connected to the cerebral cortex via recurrent circuits [2,3]. In recent years, it has been described that the basal ganglia and the cerebellum are anatomically connected to each other, and the existence of a disynaptic projection and reciprocal projections from the cerebellum to the basal ganglia [3]. In this way, it affects many aspects of motor, cognitive and emotional behavioral skills.

Although the exact cause of neuronal degeneration in PD remains unclear, the cause of this degeneration has been attributed to the simultaneous interaction of multiple factors [4]. The main pathology in the emergence of motor symptoms in PD is the

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degeneration of dopaminergic neurons in the substantia nigra pars compacta. However, the damage that occurs is not only in dopamine; it also causes the effects of different neurotransmitters such as serotonin, noradrenaline, acetylcholine and glutamate. This degeneration that occurs in PD affects not only the regions of the brain responsible for motor function, but also non-motor areas [5]. There are two connections between the cortex and basal ganglia as direct and indirect. While dopamine has an inhibitory effect on the indirect pathway, it has a stimulating effect on the direct pathway. The balance between the direct and indirect pathways disrupted in PD causes the thalamo-cortical connections and brainstem connections to be suppressed, thus causing PD symptoms [6].

Previous studies have frequently represented changes in the cerebellum [7]. According to literature the cerebellum does not have a symmetric morphology, and that some diseses like cerebellar hypoplasia, schizophrenia, epilepsy, hemimegalencephaly, dyslexia, autism, alcoholism, drug abuse, bipolar disorders, brain injuries and tumors may cause cerebellar asymmetrical differences. Evaluation of the cerebellar changes in cross-sectional MRI using the stereological technique is relevant for morphologist as it broadens the existing data of brain structures [2,8]. In literature information regarding cortical thickness and volumetric changes in the cerebellum is limited. Quantitative assessment of cerebellar volume and asymmetry can be performed mainly by manual measurement methods, which are time-consuming and laborious.

We thought that the present study may provide morphometric data to the literature and be significant in terms of determining the cerebellum as a clinical diagnostic and treatment target in terms of PD.

Material and Methods

Clinical and Neuroradiological Measurements

Demographic retrospective clinical data of all participants, such as age and gender, were evaluated through archive scanning. Retrospective archival clinical data were examined and selected among the cases followed up in the neurology clinic of Akdeniz University Medical School with a diagnosis of PD. The study evaluated the volumetric assesment of each cortical cerebellar hemisphere and total cerebellum by applying a stereological technique on MR images. The first MRI scans of patients diagnosed with PD before the start of treatment were used in the study. The age- and gender-matched study was composed of 47 right handed adult cases (age between 40-90) with PD and 47 right handed healthy subjets as control. The inclusion criteria was a diagnosis of PD according to the neurology clinic data bank diagnostic criteria. The exclusion criteria were severe concomitant diseases, current psychiatric illness, a history of head trauma, stroke, central nervous system infection, a structural lesion or hydrocephalus, diagnosed dementia, moderate-to-severe head rest tremor, the patients' experienced seizures before, secondary Parkinsonism and motion artifacts on the brain scans. All diagnosis and patient selection was managed by the professional neurologist and neurosurgeon. This study was approved by the Medical Ethics Committee of the Akdeniz Medical University, per the Declaration of Helsinki.

Image Processing and Sampling

MR imaging was performed on a 1.5 T MR machine (Philips Systems, Netherlands). T1-weighted axial and sagittal plane (5 mm) slices were obtained retrospectively for each subject. DICOM images were transferred to the ImageJ software and then converted into stack, the images were in sagital plane, which used for the measurements of the cerebellar hemispheres. Systematic random sampling was done. The sampling fraction was 1/5 for the the cerebellum. Planimetry method of the stereological techniques was done, the regions of interests were delineated. T1 weighted images were used for manual tracing of the borders of cerebellum [9]. Finally, the delineated areas were evaluated. Volume and volume fractions as cortex (gray matter) of cerebellum were calculated.

Stereological Method

This principle enables the calculation of values such as total volume, volume ratios and volume density. The basis of the Cavelieri principle is to divide the structure whose volume we want to calculate into slices with a certain thickness from beginning to end by taking parallel sections. The surface area of each slice facing the same direction is first calculated. As a result, the total volume of the structure is calculated objectively by multiplying the calculated total surface area values of the slices with the determined slice thickness [10-12]. The point counting method was used when volumetric evaluation of the cerebellum was performed on magnetic resonance images of all groups. The method was apply using a transparent scale marked with equally spaced points called "grid". This grid was randomly placed on the cerebellum in each MRI slice. Both whole and cortical cerebellar volumes calculated. All measurements were performed blindly. The smallest diameter of the anisotropic structures was taken that could be measured for volumetric analysis of sagittal and axial cranial MRI sections. Each image were measured in double by two observers using a stereological method. The points falling on the cerebellum were counted and recorded by two blinded medical observers (Figure 1). The slice thickness was determined as 0.5 cm, and sequential progression of images was ensured. Sagittal magnetic resonance image sections of individuals in the cases with PD and control groups were recorded and cerebellum boundaries were determined on the images. By randomly positioning the grid on the images, the number of points within the borders of the cerebellum was manually measured in the right and left hemispherium cerebelli, and the numbers were recorded. Points on the cerebellum cortex were also counted in order to determine possible changes in cerebellum cortical thickness, which is another parameter we measured. The area where dot counting was performed was determined according to contrast discrimination. This area was determined based on the contrast difference between substantia alba and substantia grisea.

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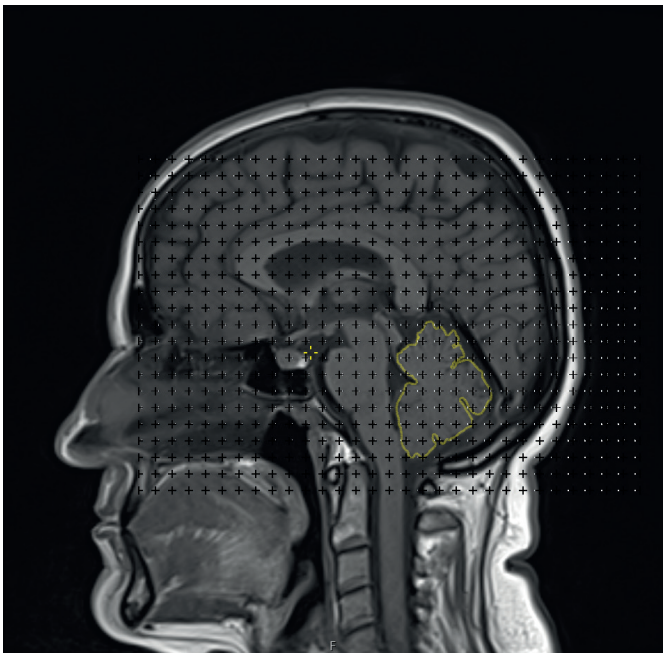

Figure 1. A grid superimposed mid-sagittal cross sectional image of cerebellum

The number of points counted in each section was recorded by creating different Excel files for cortical thickness and volume values. The counted points were collected and multiplied by the section thickness, and the volume calculation was completed. Using the "Grid" plug-in installed with Image-J, a uniform point grid with an area of 0.625 cm2 was randomly superimposed on each MR image. Points hitting the cerebellum were manually counted for volume estimation. Volume estimation was performed according to the Cavalier principle, as described previously, and the calculations are mathematically formulated as follows: $V=t \times [((SU) \times d)/SL]2 \times \Sigma P$

The calculations are mathematically formulated as follows; In the formula; t- corresponds to the section thickness, SU- corresponds to the MR scale unit, d- the distance between two points on the grid, SL- the scale length and p- the number of points counted [1,9-11].

Cerebellum volume and cortical thickness values of the cases in both the cases with PD and control groups were calculated separately for the right and left hemispheres and recorded in the Excel file. In distinguishing between the right and left hemispheres, the section where the aqueductus cerebri was most clearly visible was accepted as the midline. The boundaries of the area we determined for cerebellum volume and cerebellum cortical thickness measurement were checked by two medical doctor anatomists with a stereology certificate. The results obtained were evaluated depending on the ages and genders of the cases in both the patient and control groups. The data obtained were described statistically.

Statistical Analysis

Since all values to be analyzed in the study exhibited normal distribution, independent sample T test was used when comparing paired groups. ANOVA test was used to compare groups of three. Post Hoc tests were used to determine the difference between age groups. Since the data exhibited normal distribution, Pearson tests were used in correlation analysis. Two tailed p-values of less than 0.05 were considered statistically significant. Data analysis was carried out with SPSS Statistics 26 version.

Results

We conducted our study on a total of 94 adult people as age and gender matched 47 PD patients and 47 healthy control cases.

Of the 47 PD cases, 23 were women (mean age 62.86) and 24 were men (mean age 62.87). Considering the distribution by age groups, there were 16 patients between the ages of 40-54, 15 patients between the ages of 55-70, and 16 patients between the ages of 71-90.

Of the 47 healthy individuals selected as the control group, 23 were women (mean age 62.82) and 24 were men (mean age 62.41). Considering the distribution by age groups, there were 16 patients between the ages of 40-54, 15 patients between the ages of 55-70, and 16 patients between the ages of 71-90.

When the results obtained are analyzed; it was found that right cerebellar hemispheric volume, left cerebellar hemispheric volume, total cerebellum volume, right cortical thickness, left cortical thickness showed a statistically significant difference between the control group and the PD group ($p<0.05$). The five different independent variables analyzed showed significant differences according to the groups. When the value averages were examined by groups, it was determined that all value averages of PD patients were lower than the control group averages (Table 1). According to age groups, evaluation of right cerebellum volume value of both PD and control groups were as follows; in the 40-54 age range, the right cerebellar hemispheric volume of the PD group (12.44±1.44) was found to be significantly lower than the control group (13.8±1.38) ($p=0.01$); in the 55-70 age range, the right cerebellar hemispheric volume of the PD group (12.15±1.38) was found to be significantly lower than the control group (13.14±1.16) ($p=0.043$).

Table 1. Parameters and results measured in PD and control groups

	PD Group Mean±SD	Control Group Mean±SD	p
Right cerebellar volume	12.2±1.38	13.14±1.29	**0.001****
Left cerebellar volume	13.47±1.28	14.37±1.58	**0.003****
Total cerebellar volume	25.67±2.5	27.5±2.59	**0.001****
Right cortical thickness	0.71±0.14	0.82±0.19	**0.003***
Left cortical thickness	0.60±0.13	0.72±0.22	**0.002***

$p<0.05$ value was considered significant and marked with an asterisk; PD: Parkinson's disease, SD: standard deviation; Asterisks are used to identify statistically significant

According to age groups, evaluation of left cerebellum volume value of both PD and control groups were as follows; in the

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40-54 age range, the left cerebellar hemispheric volume of the PD group (13.93±1.26) was found to be significantly lower than the control group (14.97±1.49) (p=0.041); in the 55-70 age range, the left cerebellar hemispheric volume of the PD group (13.23±1.34) was found to be significantly lower than the control group (14.63±1.52) (p=0.012). According to age groups, evaluation of total cerebellum volume value of both PD and control groups were as follows; in the 40-54 age range, the total cerebellum volume of the PD group (26.37±2.50) was found to be significantly lower than the control group (28.77±2.71) (p=0.014); in the 55-70 age range, the total cerebellum volume of the PD group (25.38±2.57) was found to be significantly lower than the control group (27.77±2.26) (p=0.011). There was no statistically significant difference between the PD and control groups in the 71-90 age range in terms of right hemisphere (p=0.277); left hemisphere (p=0.576) and total cerebellar volume (p=0.370). Evaluation of cerebellum volume value of both PD and control groups according to age groups was shown in Table 2. Age-related right and left cerebellar cortical thickness value in PD and control groups was as follows; the right cortical thickness value of the PD group (0.75±0.14) was found to be significantly lower than the control group in the 40-54 age range (0.99±0.14) (p=0.00); the left cortical thickness value of the PD (0.67±0.1) was found to be significantly lower than the control group in the 40-54 age range (0.88±0.25) (p=0.006). When the 55-70 age (p=0.134) and 71-90 (p=0.733) age ranges were examined, no significant difference was found between the PD and control groups for the right hemisphere cortical thickness value. When the 55-70 age (p=0.150) and 71-90 (p=0.176) age ranges were examined, no significant difference was found between the PD and control groups for the left hemisphere cortical thickness value. Evaluation of age-related right and left cerebellar cortical thickness value in PD and control groups was shown in Table 3. According to gender, evaluation of right and left cerebellum volume value in PD and control groups was as follows; although the right cerebellum volume value of women in both the PD (p=0.127) and control (p=0.271) groups was smaller than men, it was not statistically significant. Although the left cerebellum volume value of women in control (p=0.271) groups was smaller than men, it was not statistically significant. Similarly, although the total cerebellum volume value of women in control (p=0.135) groups was smaller than men, it was not statistically significant. Hovewer, a significant difference was detected between the left cerebellum volume value of women in the control group (13.75±1.45) and men (14.95±1.51) (p=0.008) and also a significant difference was detected between the total cerebellum volume value of women in the control group (26.68±2.38) and men (29.3±2.59) (p=0.03). Briefly, according to gender, left cerebellar hemisphere and also total cerebellar volume was measured to be larger in both PD and control cases for male subjects (Table 4).

Table 2. Right, left and total cerebellum volume value of both PD and control groups according to age groups

	Age ranges	Right cerebellar volume (Mean±SD)	Left cerebellar volume (Mean±SD)	Total cerebellar volume (Mean±SD)
PD group	40-54	12.44±1.44	13.93±1.26	26.37±2.50
	55-70	12.15±1.38	13.23±1.34	25.38±2.57
	71-90	12.01±1.36	13.25±1.20	25.26±2.45
Control group	40-54	13.8±1.38	14.97±1.49	28.77±2.71
	55-70	13.14±1.16	14.63±1.52	27.77±2.26
	71-90	12.47±0.99	13.51±1.44	25.99±2.07

PD: Parkinson's disease, SD: standard deviation

Table 3. Age-related right and left cerebellar cortical thickness value in PD and control groups

	Age ranges	Right cerebellar cortical thickness (Mean+SD)	Left cerebellar cortical thickness (Mean+SD)
PD group	40-54	0.75±0.14	0.67±0.1
	55-70	0.75±0.1	0.59±0.13
	71-90	0.63±0.14	0.54±0.14
Control group	40-54	0.99±0.14	0.88±0.25
	55-70	0.74±0.13	0.67±0.17
	71-90	0.63±0.14	0.60±0.12

PD: Parkinson's disease, SD: standard deviation

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Table 4. According to gender right and left cerebellum volume value in PD and control groups

	Gender	Right cerebellar volume (Mean±SD)	Left cerebellar volume (Mean±SD)	Total cerebellar volume (Mean±SD)
PD group	**Female**	11.89±1.36	13.23±1.01	25.11±2.2
	Male	12.50±1.36	13.71±1.48	26.21±2.7
Control group	**Female**	12.93±1.16	13.75±1.45	26.68±2.38
	Male	13.34±1.39	14.95±1.51	29.3±2.59

PD: Parkinson's disease, SD: standard deviation

Discussion

PD is a neurodegenerative disease with a progressive course that occurs due to loss of dopaminergic neurons in the nigrostriatal region. Clinical symptoms appear when neuronal loss reaches 60 to 80%. PD is characterized by rigidity, bradykinesia, postural balance disorders, rest tremor and various sensory anomalies [13,14].

Loss of dopaminergic neurons in the substantia nigra pars compacta is considered the main pathophysiological mechanism, but this classical model of the disease is not sufficient to explain all symptoms of PD, such as rest tremor. It is possible that the basal ganglia are not the only structure responsible for the development of the disease. Increasing evidence suggests that the cerebellum may have specific roles in the pathophysiology of PD [9]. Recent studies have identified interconnections between the basal ganglia and cerebellum. However, pathological changes due to PD are observed in the cerebellum [15]. In PD, the amount of gray matter in the cerebellum decreases, and it is thought that this condition may be functionally related to widespread cognitive functions. Findings from recent studies indicate that reduced gray matter volume and cortical thickness may be biological indicators for cognitive impairments in PD [16].

The effects of the cerebellum, which is considered to be important in voluntary movement, gait, distal extremity muscle activity, posture, and coordination of fine and complicated motor functions, in PD have generally been ignored [17]. It has not been fully clarified whether there is cerebellum involvement in PD patients. As a result of our literature review, it was seen that the number of studies on the subject was low and there were contradictions among the data obtained. Data obtained in many neuroanatomical and neurophysiological studies conducted in recent years have drawn attention to volumetric differences in different regions of the cerebellum due to PD [15]. Basal nuclei and the cerebellum are connected reciprocally, and PD-related morphological abnormalities have been displayed in both animal models and humans [18]. Cerebellum volume, along with other structures in the brain, atrophy with advancing age in humans [19]. Atrophy in the cerebellum may vary depending on many factors and diseases [20,21]. In their meta-analysis study where they evaluated cerebellum atrophy in 7 different neurodegenerative diseases, Gellersen and colleagues [22] reported that there is no involvement in the motor areas of the cerebellum in PD, but atrophy is observed in areas related to cognitive processes, depending on the severity of symptoms. These include various neurodegenerative diseases, traumas, developmental and vascular diseases, as well as factors such as age and gender. The data we obtained as a result of our literature review via neuroanatomical and radiological studies shows that the cerebellum undergoes many morphological changes due to PD [15,16,23,24]. Therefore, more studies are needed to elucidate the relationship between volume differences between the cerebellum and PD. By examining possible asymmetrical volumetric and cortical changes in the cerebellum in our study, we predicted that these changes would be useful in elucidating the role of the cerebellum in PD.

In their study with 21 individuals with PD with postural instability and gait disorders and 23 individuals in the healthy control group, Gardoni and colleagues [25], evaluated cerebellum gray matter using an atlas-based method and confirmed cerebellum atrophy as a result of the study. Deng and colleagues [26], reported a decrease in cortical volume and thinning in cortical thickness in the cerebellum in their study on 100 sporadic PD patients and a 40-year-old and gender-matched control group using the voxel-based morphometry method. They stated that this extensive cortex loss (reduction in cortical volume, thinning in thickness) that occurs in sporadic PD leads to dysfunction of the corresponding brain regions and creates a series of complex clinical symptoms.

In the study conducted by Zeng et al. [23], they aimed to separate 45 individuals in the possible patient group from 40 age and gender-matched healthy control groups by looking at the morphological change in the cerebellum, using the voxel-based morphometry method in PD patients. They reported that the gray matter volume in crus I and vermis III decreased, while there was an increase in the gray matter volume in vermis VIII and right lateral crus I. They stated that morphological changes in the cerebellum may cause depressive mood in patients and tremor in the head and neck. Unlike this study, we detected right and left hemispheric cortex thickness differences in both PD and control cases depending on age and gender parameteres.

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Li et al. [24] measured gray matter as cortical thickness volume with the voxel-based morphometry method and cortical thickness with the surface-based morphometry method on 23 individuals with mild cognitive impairment and diagnosed with PD without cognitive impairment and 23 matched healthy control group individuals. In their study, they found decreased gray matter volume and cortical thinning in individuals in the patient group compared to individuals in the control group. In the present study both right and left hemispheric cortical thickness in young adults between the ages of 40-54 was found to be lower in PD cases than in healthy controls. This stuation can be explained by the rapid cortical cell loss due to PD. On the other hand, cortical thickness decreased in patients with PD above the age of 55, but it was not found to be statistically significant. This can be explained by the fact that the difference in age-related neuronal losses is similar with the healthy controls due to cortical atrophy in aging.

Sahin et al. [9] found that males had significantly larger left hemisphere cerebellar volume and total cerebellar volume when compared to females and also they claimed that presence of PD had no effect on these differences between the sex. When the overall value averages were examined by our study groups, it was seen that all value averages of PD patients were lower than the control group averages. However, when we examined the patient and control groups according to age ranges; differences were varied according to age ranges. In the healthy control group, left cerebellar volume and total cerebellar volume in men were found to be statistically significantly larger than in women. The left hemisphere was found to be larger in both control and PD patients, although it was not statistically significant in women.

In their voxel-based morphometry study on 42 PD patients and 29 control groups, O'Callaghan and colleagues [27] reported gray matter loss in the cognitive and motor regions of the cerebellum in PD. However, they found a significant inverse correlation between cerebellar connectivity and gray matter volume.

In their study using voxel-based morphometry on 14 PD cases with rest tremor and 10 PD patients without tremor, Benninger and colleagues [28] reported that there was a decrease in volume in the quadrangular lobe and declive in the right cerebellum of patients with rest tremor. They stated that, in line with physiological and functional imaging studies, this study confirmed the involvement of the cerebellum in the pathogenesis of rest tremor.

Nyatega and colleagues [18] claimed that the left cerebellum has seen a substantial contraction, while the right quadrangular lobe's of cerebellar gray matter volume has decreased. They also explained that these alterations might be brought on by degeneration of dopaminergic neurons. We think that this situation can be clarified with further clinical and experimental studies that will determine the cortical neural synaptic connections of the left cerebellar hemisphere in right-handed patients.

Many methods are used to calculate the volumes of biological structures like cerebellum. One of these methods, the stereological method, stands out as being highly reliable and unbiased. Stereology allows us to obtain quantitative information about the real dimensions of three-dimensional structures, based on two-dimensional cross-sections (such as MRI) [29]. Stereology is a scientifically reliable, mathematically proven and highly accepted method. At the same time, it is easy to apply, economical, unbiased and reliable [30]. The basis of stereological methods is impartiality and effectiveness. The expression indicating measurements that do not deviate from the true value in a statistical sense with the application of repeated measurements is expressed as neutrality. In order to achieve accurate results in the measurement method applied, the application must be unbiased. The efficiency principle refers to obtaining data with less variability in a short period of time. Stereological methods enable reducing the workload and achieving the desired accurate results in a short time [31]. While the boundaries of biological structures must be clear when measuring with the stereological method, their shapes do not have to be smooth.

Conclusion

In conclusion, we predict that there is significant cerebellum involvement in PD and that morphometric and volumetric changes in the cerebellum may contribute to the motor and cognitive symptoms of the disease through neuronal, that is, cortical losses. The findings of our study show that the cerebellum undergoes significant volumetric and morphological changes due to PD. Based on our clinical observations and the results of the present study, we believe that cerebellar asymmetry and cortical atrophy may be a factor in the aetiology of PD or on cause and effect relationship of PD as well. Using stereology, it is easy to make quality, rapid, safe and accurate measurements on MRI scans in a short time by adhering to the principles of impartiality and effectiveness. We think that stereological examination of the volumetric and morphometric changes caused by PD in the cerebellum, especially in the cortex, will contribute to similar studies in the literature, both clarifying the role of the cerebellum in the disease and determining it as a treatment target in the clinic.

Conflict of Interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical Approval

This study was approved by the Clinical Research Ethics Committee of Akdeniz University (Ethics committee approval: KAEK-634).

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