Statistical Shape Analysis of the Corpus Callosum and the Cerebellum in Migraine Patients

Migren Hastalarında Korpus Kallozum ve Serebellumun İstatistiksel Şekil Analizi

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ABSTRACT Objective: The aim of this study was to investigate the shape differences in the corpus callosum and cerebellum of migraine patients compared with healthy controls and to assess whether migraine attack frequency and disease duration are indicators for brain abnormalities in migrain cases. **Material and Methods:** This study included magnetic resonance imaging scans of 25 control subjects and 38 migraine patients. The data were obtained from the coordinate of landmarks analyzed with statistical shape analysis. A generalized Procrustes analysis was used to investigate shape differences. Witelson subdivision was used to further assess the regional shape differences in corpus callosum. **Results:** The shape of the corpus callsoum in controls was significantly different from the shape in migraine patients. Migraine patients had deformations in corpus callosum compared to control patients where the most prominent deformations were seen in the posterior midbody of corpus callosum. According to Witelson subdivions deformation in in the rostral body was less prominent. There was no global or regional shape difference between patients with migraine and controls for cerebellum. No significant correlation was recognized between the size and disease duration or frequency of migraine attacks, both for corpus callosum and cerebellum. **Conclusion:** The data suggest that migraine sufferers have global structural changes in corpus callosum but not in cerebellum, and that deformations did not vary with the disease progress.

Key Words: Cerebellum; corpus callosum; geometric morphometrics; migraine; statistical shape analysis

ÖZET Amaç: Bu çalışmanın amacı, kontrollerle karşılaştırıldığında migren hastalarının korpus kallozum ve serebellumundaki şekil farklılıklarını araştırmak ve migren atak frekansı ile hastalık süresinin migren hastalarında beyin anormalliklerini etkileyip etkilemediğini değerlendirmektir. **Gereç ve Yöntemler:** Çalışma, 25 kontrol ve 38 migren hastasından elde edilen manyetik rezonans görüntüleri kullanılarak gerçekleştirilmiştir. Mirengi noktası koordinatlarından elde edilen veriler, istatistiksel şekil analizi ile incelenmiştir. Şekil farklılıklarını değerlendirmede genelleştirilmiş Procrustes analizi kullanılmıştır. Korpus kallozumdaki bölgesel şekil farklılıklarını daha iyi değerlendirebilmek için Witelson alt bölgelendirme analizi dikkate alınmıştır. **Bulgular:** Korpus kallozumun şekli açısından kontrol olguları ve migren hastaları arasında anlamlı bir fark bulunmuştur. Korpus kallozum için, migren hastalarında kontrollere oranla deformasyonlar olduğu gözlenmiştir. En belirgin deformasyonlar korpus kallozumun posterior orta gövdesinde gözlenmiştir. Witelson alt bölgelendirme analizine göre, korpus kallozumun rostral gövdesinde çok daha az miktarda deformasyon gözlenmiştir. Diğer taraftan, serebellum açısından, migren hastaları ve kontroller arasında genel ya da bölgesel bir şekil farklılığı gözlenmemiştir. Ayrıca, hem korpus kallozum hem de serebellum için, büyüklük ile hastalık süresi ve büyüklük ile atak frekansı arasında anlamlı bir ilişki bulunmamıştır. **Sonuç:** Bu veri seti, migren hastalarında korpus kallozumda bölgesel yapısal değişiklikler olduğunu, fakat serebellumda farklılık bulunmadığını ve hastalık süreciyle deformasyonların değişmediğini göstermektedir.

Anahtar Kelimeler: Serebellum; korpus kallozum; geometrik morfometri; migren; istatistiksel şekil analizi

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Migraine is a common and multifactorial neurovascular brain disorder, characterized by recurrent attacks of disabling headache with associated symptoms and with autonomic nervous system dysfunction. It is a common problem that affects 5-20% of the general population. Adult women are 3 times more affected than men.[1] Up to one-third of migraineurs also experience an aura, neurological transient symptoms.[2,3] Many factors have been accused in its etiology but the most favored mechanism is the vasoconstriction in the extra and intracranial vessels at the beginning causing relative cerebral ischemia. Decreased cerebral blood flow during aura and early phases of headache has been shown in many.[4] Migraine has traditionally been considered a benign disorder without any long-term consequences for the brain parenchyma. However, recent data have showed that migraine may be related to brain lesions, detected on magnetic resonance imaging (MRI). Based on advances in neuroimaging, migraine has been transformed from a vascular to a neurovascular disorder and most recently, to a central nervous system disorder.[5]

Many previous studies in the migraineurs have showed structural differences in different regions of the brain.[1,6-9] Schmitz et al. reported that, predilection sites (sites with a higher likelihood) of damage to the brains of migraineurs were identified in the frontal lobe, limbic system, parietal lobes, brainstem and cerebellum.[1] While Schmitz et al. suggested that the frontal lobe was one of the most prominent areas of brain abnormalities in migraineurs, they also detected abnormalities in the superior frontal gyrus and limbic lobe (parahippocampal gyrus).[6] Also Rocca et al. stated that changes observed in migraine patients were mainly located in the cortex of frontal and temporal lobes.[7] Furthermore, Valfré et al. reported gray matter abnormalities in migraine patients in different brain regions such as the right superior temporal gyrus, right inferior frontal gyrus and left precentral gyrus.[8] Other structural brain abnormalities in migraineurs have been reported for the brainstem, the cerebellar and posterior white matter, temporal cortex and periaqueductal gray matter. These studies, in which abnormalities of different brain regions have been shown, reported both white and gray matter abnormalities.[9]

Corpus callosum (CC), which is known to be damaged in the course of central nervous system disorders, is the largest compact white matter fiber bundle. A number of studies reported the role of CC in central nervous system diseases like autism, Behcet's disease, schizophrenia and multiple sclerosis using different methods. Involvement of CC in migraineurs has been shown in a few studies, especially as case reports.[5,10] Sub-clinic periventricular and deep white matter, and callosal lesions were reported to be found in the cranial magnetic resonance (MR) images of migraineurs.[2]

In addition to the involvement of CC, cerebellar dysfunction in migraine, especially associated with specific forms of migraine has been recognized for for many years.[11] Clinical and pathophysiological evidences pointed to a connection between migraine and the cerebellum. Data documenting cerebellar abnormalities in migraine, however, is relatively scarse. All these have added to many speculations about the pathophysiology of migraine with unclear etiology. Different brain region involvements in migraine led us to study the structural differences in two brain regions.

Many different methods have been used to measure changes caused by neurovascular diseases on anatomical brain structures, which are often based on global volume and area measurements. However, the structural changes that occur at specific locations are not sufficiently reflected in those measurements. Statistical shape analysis involves methods for studying the geometrical properties of random objects where location, rotation and scale information can be removed.[12] Landmark-based shape analysis has been popular in neuroanatomical research because of its convenience and effectiveness in obtaining shape information. Landmarks are usually determined by anatomical prominences of the biological structure of interest.[13] In recent years it has been widely used in the biomedical field to study various structures of interest, to identify morphometric abnormalities associated with a particular condition or disease assisting with diagnosis and treatment.[14-20]

The aim of this study was to investigate the shape differences in the CC and cerebellum of migraine patients compared with healthy controls and to assess whether migraine attack frequency and disease duration are indicators for brain abnormalities in migraineurs. We analyzed the CC shape based on a clinically relevant CC subdivision scheme. A configuration of the landmarks was identified in the brain magnetic resonance imaging (MRI) mid-sagittal sections, performing statistical shape analysis.

MATERIAL AND METHODS

SUBJECTS

This study was conducted using the MRI scans of 38 migraine patients (5 male, 33 female) with a median age of 34 (22-53) years [median (min-max)], 14 (22.22 %) with migraine with aura, and 24 (38.10 %) with migraine without aura, and 25 control subjects (4 male, 21 female) with a median age of 34 (24-61) years [median (min–max)]. The median duration of the disease was 11.5 (1-30) years, median frequency of migraine attacks was 15 (1-25) days/month and median visual analog scale (VAS) score was 7 (5-9) for the migraine patients (Table 1).

The MRI scans of the migraine patients and controls referred to the Department of Radiology, Faculty of Medicine, Uludağ University between April 2009 and September 2011, were retrospectively included. All migraine patients fulfilled the diagnostic criteria defined by the International Headache Society (IHS).[21] The diagnosis of the migraine patients were confirmed by two trained neurologists in the outpatient clinic of the Department of Neurology, Faculty of Medicine, Uludağ University. All patients were migraine-free for at least 72 hours at the time of MRI, had no medical or psychiatric condition other than migraine, had no history of medication overuse, and were without any prophylactic or chronic medication for at least 1 year prior to study entry. All migraineurs included in the study had a normal neurological examination.

The local ethics committee of our institution approved this retrospective study.

MRI EXAMINATIONS

MRIs were performed in a 1.5-Tesla Magnet (Magnetom Vision Plus, Siemens Medical Solutions, Erlangen, Germany) with a standard head coil. The images were acquired using a three-dimensional magnetization prepared-rapid acquisition gradient echo (3D MP-RAGE) sequences with the following parameters: TR/TE/TI/flip angle=10/4/300/10°, 250 FOV, 1.25 mm slice, 192x256 matrix, 1 Nex. Furthermore, the sequences were chosen to provide good gray- and white matter contrast. The scanner alignment tool and immobilization of the head helped to ensure the patient's standardized position.

CC SEGMENTATION AND LANDMARK COLLECTION

The mid-sagittal section that most clearly displayed the cerebral aqueduct, CC and superior colliculus

TABLE 1: Demographic and clinical details of migraine patients and controls.

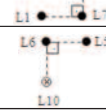
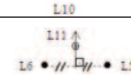
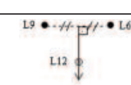
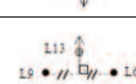
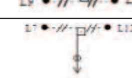
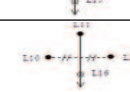
		Controls (n=25)	Cases (n=38)	p-value
Age, years [median (min-max)}		34 (24-61)	34 (22-53)	0.789
Sex	male	4 (16)	5 (13.16)	1.000
	female	21 (84) (86.84)	33 (86.84)	
Disease duration, years (median (min-max))		-	11.5 (1–30)	-
Frequency of migraine attacks, days/month [median (min-max)]		-	15 (1-25)	-
VAS score [median (min-max)]		-	7 (5-9)	-
Aura (n, %)	present	-	14 (22.22)	
	absent	-	24 (38.10)	-

VAS: Visual analog scale.

was manually selected from each of the sagittal planes. The anterior to posterior commissure line and interhemispheric fissure were identified and were used to align the brains of all subjects at a standard position. We implemented a statistical shape analysis by using homologous anatomical landmarks, which were selected as the most relevant. Sixteen anatomical landmarks were defiend on the CC.[22] Eight of those were constructed by referencing anatomical landmarks defined by Özdemir et al.[23] A descriptive list of the 16 chosen landmarks for the CC was shown in Table 2.[22] Landmarks used for CC, were demonstrated on MRI image of a control subject (Figure 1). Each CC was divided into seven subdivisions to better describe the shape. This division was based on the established Witelson framework, which divides the CC into seven subdivisions according to specific geometric constructs.[24] The subdivisions of a sample CC were also shown in Figure 1.

Eight midline cerebellar landmarks were selected from the image corresponding to the midsagittal plane. The landmarks were chosen on the basis of reliability, maximizing anatomical coverage, and cerebellar morphological descriptions.[22] The cerebellum has traditionally been recognized as having three anterior-posterior divisions: the anterior lobe is separated from the posterior lobe by the primary fissure, and the posterior lobe is separated from the flocculonodular lobe by the posterolateral fissure.[25] In another study, Pierson et al. have divided the cerebellar cortex into three sections as anterior lobe, superior-posterior lobe and inferior posterior lobe.[26] In our study, only anterior lobe (covered by the landmark 1, 2, 3 and 8) and posterior lobe (cov-

TABLE 2: A descriptive list of the landmarks used for the corpus callosum.

Landmark	Landmark definition	
1	Anterior-most point of the CC	
2	Interior notch of the splenium	
3	Inferior tip of the splenium	
4	Posterior-most point of the CC	
5	Top most point of the splenium	
6	Top most point of the CC	
7	Posterior angle of the genu	
8	Posterior tip of the genu	
9	The point at which the line that passes through landmark 7 is perpendicular to the segment, which was drawn from landmark 1 to landmark 7, and cuts the upper bound of the CC.	
10	The point at which the line that passes through landmark 6 is perpendicular to the segment, which was drawn fro landmark 5 to landmark 6, and cuts the lower bound of the CC.	
11	The point at which the line that passes through the midpoint of the segment, which was drawn from landmark 5 to landmark 6, is perpendicular to this segment, and cuts the upper bound of the CC.	
12	The point at which the line that passes through the midpoint oft he segment, which was drawn from landmark 6 to landmark 9, is perpendicular to this segment, and cuts the lower bound of the CC.	
13	The point at which the line that passes through the midpoint of the segment, which was drawn from landmark 6 to landmark 9, is perpendicular to this segment, and cuts the upper bound of the CC.	
14	The point at which the line that passes through the midpoint of the segment, which was drawn from landmark 7 to landmark 12, is perpendicular to this segment, and cuts the lower bound of the CC.	
15	The point at which the line that passes through landmark 7 and the midpoint of the segment, which was drawn from landmark 1 to landmark 8, and cuts the left boundary of the CC.	
16	The point at which the line that passes through landmark 11 and the midpoint of the segment, which was drawn from landmark 2 to landmark 10, and cuts the lower bound of the CC.	

CC: Corpus callosum.

ered by landmark 3, 4, 5, 6, 7 and 8), which are separated by the primary fissure, were evaluated in the midsagittal MRI images.[22] A descriptive list of these anatomical landmarks was shown in Table 3. Landmarks used for cerebellum were demonstrated on MRI image of a control subject (Figure 2).

The selected landmarks were marked on the digital images by using the TPSDIG 2.16 software.[27] All of the points of these landmarks fell within the criteria outlined by Bookstein and included extreme points, terminals and maxima of curvature, as well as other local shape processes.[28]

STATISTICAL ANALYSIS

A generalized Procrustes analysis was used to evaluate the shapes. The homogeneity of the variance–covariance matrices was examined using the Box-M test.[12] The variance-covariance matrices were homogeneous (p=0.521) for the cerebellum. So the Hotelling T^2 test was used to compare the shapes of the cerebellum between the controls and migraine patients. Since the variance-covariance matrices were not homogeneous (p=0.002) for the CC, James F_J test was used to compare the shapes of the CC between the control and migraine patients.

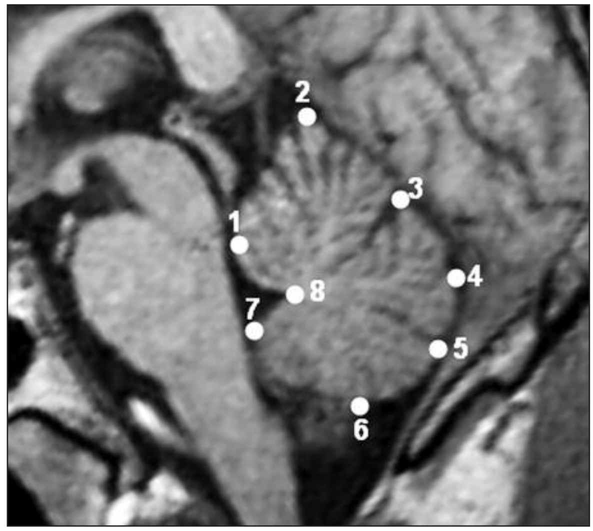


FIGURE 2: T1-weighted mid-sagittal slice demonstrating the cerebellar landmarks.

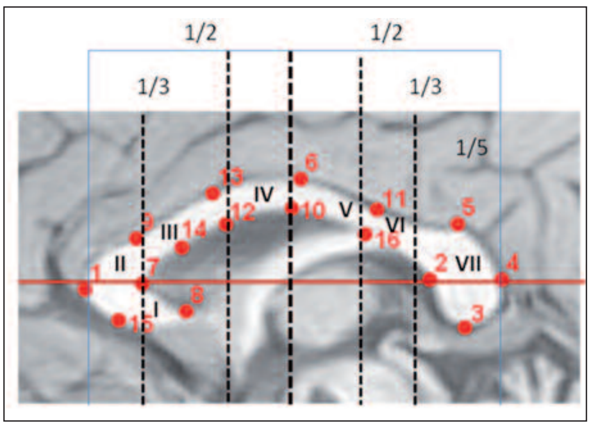


FIGURE 1: T1-weighted mid-sagittal slice demonstrating the corpus callosum landmarks and Witelson subdivisions (I: rostrum; II: genu; III: rostral body; IV: anterior midbody of corpus callosum; V: posterior midbody of corpus callosum; VI: isthmus; VII: splenium).
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

TABLE 3: A descriptive list of the landmarks used for the cerebellum

Landmark	Landmark definition
1	Velum medullare superius angulation-cerebellar outline junction
2	Superior cerebellum
3	Primary fissure- cerebellar outline junction
4	Posterior cerebellum
5	Prepyramidal fissure- cerebellar outline junction
6	Inferior cerebellum
7	Velum medullare inferius angulation-cerebellar outline junction
8	Fastigium cerebelli

Mean landmark configurations of migraine patients and control subjects were calculated by Procrustes analysis using landmark coordinate data. The differences between shapes were also visualized using the thin-plate spline function and deformation grids, to show the actual spatial changes.[28] The thin-plate spline interpolating function compares geometries according to the minimum energy required to bend a hypothetical surface transforming one shape into another. The energy required to bend the grids is proportional to the intensity of localized deformation. In accordance with the thin-plate spline (TPS) analysis, the points exhibiting the greatest enlargements or reductions were labeled as deformations.[28]

Centroid size, which can be computed as the square root of the sum of squared distances of a set of landmarks from their centroid is the one measure of size that is mathematically independent of shape.[12] The relationships between the centroid sizes and the durations of disease in migraine patients were examined by the growth curve models of Richards, Logistic, Gompertz, Michaelis–Menten, Bleasdale-Nelder, Monomolecular and Holliday.[29]

Since the data were not normally distributed, Mann-Whitney U test was used to compare continuous variables and the median, minimum and maximum values were expressed as descriptive statistics. Fisher's Exact Chi-square test was performed to compare the categorical variables between the groups.

Shapes 1.1-3 package from the R 2.12.1 software with an open-source code was used for the statistical shape analysis. PAST version 2.04 was used for TPS analysis.[30] NCSS version 7.1.1 was used for growth curve analysis. SPSS version 16.0 for Windows was used for basic statistical tests.

LANDMARK RELIABILITY

We calculated the intrarater reliability coefficient for a two-facet crossed design (landmark pairs-by-rater-by subject) based on the generalizability theory (GT).[31] In the GT, the reliability for the relative (norm referenced) interpretations is referred to as the generalizability coefficient.[32] In this study, a single rater marked the anatomical landmarks. The reliability of the rater was judged using repeated landmarks on groups. Landmarks on CC and cerebellum were collected by a single investigator, and after a month, the same investigator re-marked the same landmarks on all images again. The analysis indicated good repeatability for CC and cerebellum (G=0.998 and G=0.995 respectively).

RESULTS

The two groups were homogenous in terms of age and sex (Table 1).

CORPUS CALLOSUM

The CC shape of the controls was significantly different from the CC shape of the migraine patients ($p<0.001$) (Figure 3). Shape deformations in CC were observed in migraine patients compared to control cases defined according to Witelson subdivisions. The most prominent deformations were seen in the region V (posterior midbody of CC) with a much less prominent deformation in the region III (rostral body), which were in the form of shrinkage. A second type of deformation in the form of expansion was seen in region VI (isthmus)and a similar one to a much lesser extent in region VII (splenium) (Figure 4). In the growth curve analysis, there was no significant growth in the CC size with regard to disease duration or attack frequency in the growth curve analysis.

CEREBELLUM

There was no statistically significant difference between the controls and migraine patients in terms of cerebellar shape (p=0.164) (Figure 5). According to TPS graphs, although cerebellar deformations were present in the cerebellum of migraine patients compared to controls, they were not notable enough to influence general shape. Fewer deformations were

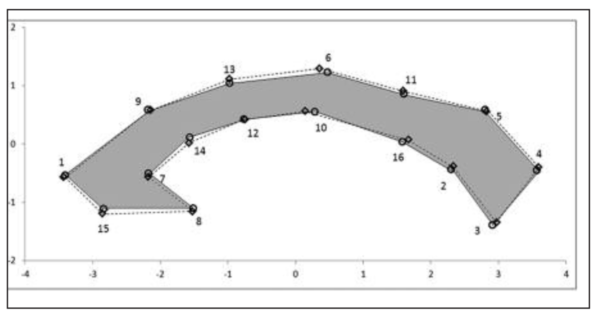


FIGURE 3: Procrustes mean shapes for the corpus callosum images of migraine patients and controls (Cases: o, Controls: ◊)

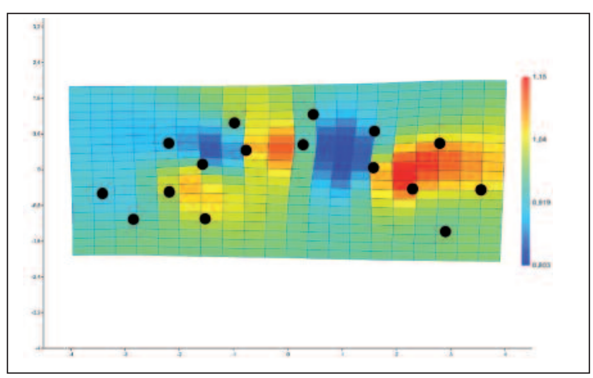


FIGURE 4: A thin-plate spline demonstrating the average corpus callosum shape deformation from controls to migraine patients.
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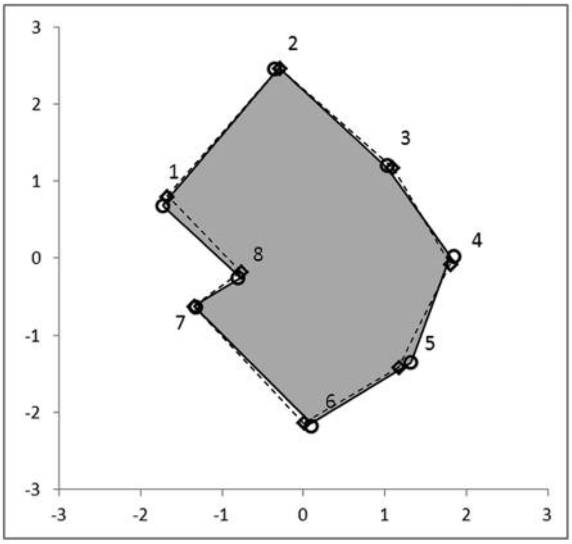

FIGURE 5: The Procrustes mean shapes for cerebellar images of migraine patients and controls (Cases: o, Controls: ◊).

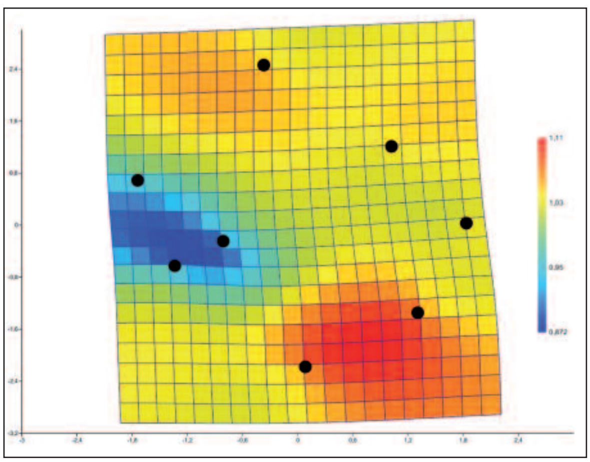

FIGURE 6: A thin-plate spline demonstrating the average cerebellar shape deformation from controls to migraine patients.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

observed in the posterior lobe especially in the regions, which were identified by landmark 7-8 and landmark 5-6 (Figure 6). There was no significant growth in the cerebellum size with regard to disease duration or attack frequency.

DISCUSSION

In present study, we aimed to determine the association, if any, between migraine and structural brain changes. We used landmark-based geometrical morphometric method to measure those changes. Our study showed that CC shape of controls was significantly different from the CC shape of the migraineurs. The most prominent deformation was seen in the posterior body and in the isthmus according to Witelson subdivision. In terms of cerebellar shape, there was no statistically significant difference between the controls and migraine patients.

Migraine is associated with an increased risk of deep white matter lesions and subclinical posterior circulation infarcts. A significant association between deep white matter hyperintensities and cerebral atrophy is true for various neurological diseases; however, this was not specifically proven for migraine. Over the past decades, several reports have suggested a possible correlation between migraine and structural brain damage (white and gray matter). While the data in the present study were comparable to those in other studies, that have suggested structural changes in migraine, they conflict with those of Matharu et al., where no structural changes in brain structures was found in migraine patients compared to controls.[1,6,8,9,33] These different findings may be attributed to the different methods used in different studies. Voxel-based morphometry method was used in many of these studies while landmark-based geometric morphometric method was used in our study.

CC is the largest compact white matter fiber bundle of the brain, which connects cortical and subcortical regions of the two hemispheres, thus allowing interhemispheric transfer of auditory, sensory, and motor information that is central for maintaining normal cognitive performance.[34] Possible changes that should occur in the CC have been studied for different disease groups. It is important to determine possible changes on the CC related to migraine, which was initially considered a vascular disease but has been suggested to be a neurovascular condition in recent years. CC atrophy, which is observed in different disease groups such as multiple sclerosis (MS), schizophrenia, Alzheimer's disease, autism and Behcet's disease, is frequently presented in global volume studies using different methods. However, few studies have been performed on the regional differences in the CC using the shape analysis method in several neurologic diseases.[13,35,36] The lack of work on the shape of CC in migraine may be related to its designation as a vascular disease. To our knowledge, this is the first study that incestigated CC shape in migraine with the shape analysis method.

Limited studies that investigated CC in migraine suggested that, the most frequent altered signal on MRI in patients affected by migraine was due to white matter lesions. A recent study by Li et al. suggested that fractional anisotropy values of the corpus callosum (genu, body, and splenium) in migraine patients with depressive/anxious disorders were significantly lower compared to the values of the control group and the migraine group without depressive/anxious disorders.[10] In the same study, the authors reported that there might be an integrity change or damage of neurofibrotic microstructure existing in the CC of migraine patients with depressive/anxious disorder.[10] Furthermore, Agarwal et al. described a patient suffering from migraine with aura associated with a transient abnormality in the midline of the splenium of the corpus callosum, showed by magnetic resonance imaging.[37] Our study showed that CC shape in migraine patients was significantly different from that of the controls. In present study, the most prominent deformations were in the posterior midbody of the CC. A second deformation was detedcted in the isthmus. Deformation to a much lesser extent was seen in the rostral body. Thus, we concluded that the posterior part of the CC was more influenced in migraine. In addition, there was no correlation between the CC size and disease duration or attack frequency in our study.

Clinical and pathophysiological evidences suggested another region that could be influenced in migraine as the cerebellum.[1,11,38-40] Cerebellar abnormalities are thought to be the underlying cause for functional and metabolic disturbances in migraine. Brain balance changes have been recognized in migraine, but cerebellar function between or during attacks have been assessed only in a few studies. Besides, few studies have specifically addressed cerebellar structural morphological changes in migraine. Autopsy studies have shown pathological abnormalities in spinal cerebellar ataxia including mild atrophy of the cerebellar folia, reduced number of Purkinje cells especially in the vermis, swelling of the Purkinje cell axons, decrease in granular cells, reduced number of dendrites in the molecular layers of Purkinje cells, and cerebellar cortical degeneration with reduced thickness of the molecular layer.[12] Takahashi et al. reported chronic degenerative changes in the anterior lobe of the cerebellar vermis.[38] Nicole Smith et al., in their study where they have identified predilection sites of possible brain damage in migraine, emphasized cerebellum as one of the predilection sites of brain abnormalities in migraineurs.[1] They indicated that, their data provided the first step of a whole brain quantitative investigation of brain abnormalities in migraine. Göçmen et al. aimed to investigate the hemicerebellar volume changes of patients with migraine without aura (MWoA). Volumetric changes of cerebellar hemispheres were evaluated in terms of asymmetry using stereological methods on MRIs retrospectively. There was no significant cerebellar atrophy or hemicerebellar asymmetry in MWoA compared to control subjects.[40] Yılmaz et al. aimed to examine whether migraine with aura caused cerebellar and cerebral atrophy and reported that there were no significant differences between the volumes of cerebrum, cerebellum, and the ratio of cerebellum to cerebrum for males and for females. Their results suggest that patients with migraine with aura do not have a significant difference in cerebellar and cerebral volumes and cerebellar/cerebral volume ratios compared to the non-migraine group.[39] We concluded in our study based on shape analysis method that the cerebellum shape was not influenced in migraine. Although general shape differences were not found in cerebellum, there were some regional changes in migraine patients. Minimal deformations were observed in the posterior lobe. Takahashi et al. reported severe cortical cerebellar degeneration in the anterior lobe of the vermis in light microscope examination.[38] We found deformation more in the posterior lobe while they observed atrophy especially in the anterior lobe.

In the present study, we studied two brain structures in migraine, which has transformed from a vascular disease to a neurovascular disease with the recent findings. We used landmark-based geometric morphometric method, which provides additional information by detecting regional changes as well as global changes. The results of this study suggest that migraine sufferers have global structural changes in CC but not in cerebellum, and that deformations do not vary with the disease progress. We hope that our findings would contribute to the understanding of migraine etiology for further clinical studies.

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