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Research Article

Retrospective Investigation of Brainstem Volume and Craniovertebral Junction Morphometry in Migraine Patients

Gulru Esen[1], Rabia Ruya Gurler[1], Erman Altunisik[2], Mehmet Sirik[3], Davut Ozbag[1]

[1]Adıyaman University, Faculty of Medicine, Department of Anatomy, Adıyaman, Türkiye
[2]Adıyaman University, Faculty of Medicine, Department of Neurology, Adıyaman, Türkiye
[3]Adıyaman University, Faculty of Medicine, Department of Radiology, Adıyaman, Türkiye

Abstract

Aim: Migraine, a complex, multifactorial neurovascular brain disorder, might cause several functional and morphometric changes in the brain. Despite many studies, a consensus has not emerged on its pathophysiology, and it is not fully elucidated so far. Recently, changing brain structures in migraine with aura has been attracting the attention of the scientific periphery. The brainstem is a critical region in the pathogenesis of migraine. Another transition point is the craniovertebral junction. Regional pathologies might trigger off the pathogenesis of neurodegenerative and neurological diseases by affecting hydrodynamics. Moreover, there is insufficient data on the relationship between migraine and the craniovertebral junction. The present study aimed to make the volumetric analysis of brainstem volume in migraine with and without aura, perform some angular and linear measurements of the craniovertebral junction, and evaluate the effects of these parameters in migraine patients.

Material and Methods: The study retrospectively analyzed the brain Magnetic Resonance Images of 108 migraine patients (aged 18 to 65). Their brainstem volumes were measured using volBrain (online brain MRI volumetry system). Also, the angular and linear parameters of craniovertebral junctions were derived from the images. The obtained data were transferred to the SPSS 22 package program and analyzed.

Results: The mean brainstem volume was 17.21±2.79 cm^3 in the migraine with aura group, 17.33±2.48 cm^3 in the migraine without aura, and 19.27±2.76 cm^3 in the control group. There was no statistically significant difference between migraine with and without aura groups ($p>0.05$). There was a statistically significant difference between the control and both migraine groups ($p<0.05$). Furthermore, the clivus-canal angle was significantly different between the control and patient groups.

Conclusion: The study found that the brainstem volume was lower in the migraine groups (with and without aura) than in the control group. Also, the different clivus-canal angles between the control and patient groups show that this issue should be more comprehensively studied.

Keywords: Migraine, brainstem volume, craniovertebral junction

INTRODUCTION

Pain sense experienced by human beings–at least once in their life–significantly affects the quality of daily life but protects the body against possible dangers. Headache is a crucial protective mechanism for our brains. Migraine, in which autonomic, neurological, gastrointestinal, cognitive, vestibular, and emotional symptoms induced by genetic and environmental factors can accompany recurrent headache attacks, is a neurovascular headache that develops from excessive trigeminovascular system activations. The International Headache Society (IHS) classified migraine as a primary headache. The worldwide prevalence of migraine is 15%, with a higher prevalence in women, which might depend on fluctuations in female sex hormone levels (1). Although there are many subgroups according to the complications it accompanies, there are two main types: with and without aura. Auras are transient neurological deficits that occur in 20% of the cases, usually before (sometimes after) a headache, and gradually increase in severity within five minutes. Harold G Wolff suggests aura symptoms relate to cerebral vasoconstriction and headaches to cerebral vasodilation (2). In addition to positive visual symptoms, such as zig-zag patterns and photopsia, and negative visual symptoms, such as hemianopsia and quadrantopsia, unilateral

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Corresponding Author: Gulru Esen, Adıyaman University, Faculty of Medicine, Department of Anatomy, Adıyaman, Türkiye
E-mail: gbakay@adiyaman.edu.tr

positive or negative somatosensory pictures and less common speech/language disorders can appear as the aura. There are many subtypes according to the symptoms seen. Despite many studies on migraine pathophysiology, there is still no consensus (1-7). Research on the aura mechanism has focused on cortical spreading depression and changes in brain structures (2). In the past, researchers considered no morphological change in brain structures in neurological imaging and examination of chronic migraine. However, as a result of increasing human studies over time, morphometric changes in the brain structures of migraine patients have been reported (6,8-11). It has been emphasized that there might be volumetric changes in gray and white matter structures. Despite many functional neuroimaging studies in the literature to understand the pathophysiology of migraine, very few studies have investigated structural changes in the brain. Besides, these studies could not reach a consensus. While some studies reported a statistically significant difference in the gray and white matter, cerebellum, and brainstem volumes (BV) in the migraine patient group, others documented no statistically significant difference in the control and migraine groups (7,10-12). Some studies report that vertigo, vomiting, and autonomic dysfunctions prevalent in migraine originate from the brain stem (2), a transition region that contains the main structures in the pathogenesis of migraine (10). Another critical neurovascular transition is the craniovertebral junction (CVJ), also known as the skull base. Being the most mobile region of the axial skeleton and containing important neural and vascular structures explains the region's importance (13). CVJ is a potential bottleneck for craniospinal hydrodynamics. Malformations or deformations in the region cause obstruction in the cerebrospinal fluid (CSF) and blood flow. Reportedly, this may be the cause or a contributing factor in the pathogenesis and progression of neurodegenerative and neurological diseases (14,15). Therefore, changes in some angular and linear parameters might indicate migraine pain triggers. Migraine and other headache diseases make up 20% of the patients who visited the neurology outpatient clinic (6). The fact that migraine affects most of the population and that there is still no consensus in the studies reveals that more studies are necessary on the macro anatomy and morphometry of the brain. Therefore, the current study aimed to conduct a volumetric analysis of the brainstem volume in migraine with and without aura and contribute to the literature by researching the relationship between migraine and some angular and linear parameters in CVJ, a crucial transition point and potential bottleneck between the cranium and spinal canal.

MATERIAL AND METHOD

Related University Non-Interventional Clinical Research Ethics Committee granted necessary permissions (Nr: 2021/02-16) for the current study, carried out between 01.01.2012 and 31.12.2020 in Related University Training and Research Hospital Neurology Headache Outpatient Clinic. This research covering 108 individuals (female: 80, male: 28), aged 18-65 years (mean 34.78±10.83), diagnosed with migraine according to the International Classification of Headache Disorders (ICHD)-3 beta criteria, retrospectively analyzed participants' brain Magnetic Resonance Images (MRI) and divided migraine patients into two groups: migraine with aura and migraine without aura. Those with neurological diseases such as multiple sclerosis, cerebrovascular disease, Parkinson's disease, Alzheimer's disease, epilepsy, and systemic diseases such as chronic liver disease, chronic renal failure, diabetes, hypertension, and the ones with head trauma, intracranial surgery, and malignancy were excluded from the study. Besides these, the control group had to meet additional criteria, such as not having a migraine or having a different primary headache diagnosis, and so forth. The control group had a brain MRI for other reasons (somatization, benign positional paroxysmal vertigo, etc.) Brain T1-weighted MRI of the with-aura, without-aura, and control groups that met the criteria were taken in DICOM format. Then, DICOM files were converted to nifti format with a converter named dcm2niigui. Images of each individual converted to nifti were uploaded to the online brain MRI volumetry system (volBrain) by entering age and gender information. VolBrain reports brainstem volume measurements in cm3.

The following parameters on Sagittal T1 weighted MRI were measured using the program in the radiology department:

1. McGregor Line Length (MGL): The line drawn from the posterior edge of the hard palate to the lowest point of the os occipitale (Figure 1) (16).

2. McRae Line Length (MRL): The line drawn from basion to opisthion. (Figure 1) (17).

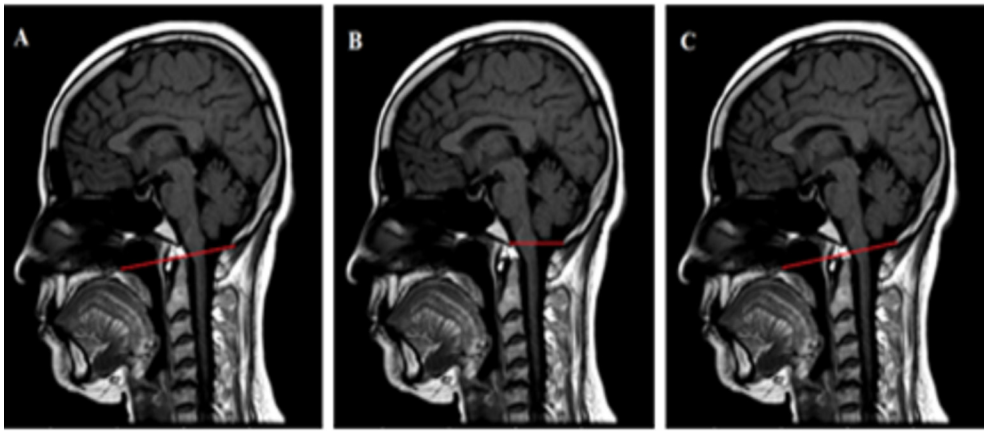

Figure 1. Demonstration of linear parameters. A: McGregor line (MGL), B: McRae line (MRL), C: Chamberlain line (CL)

3. Chamberlain Line Length (CL): The line drawn from the posterior edge of the hard palate to the opisthion (Figure 1) (17).

4. Craniocervical Tilt Angle (CTA): The angle between the line drawn upwards from the anterior face of the dens of axis and the line drawn from the anterior aspect of the clivus (Figure 2) (18).

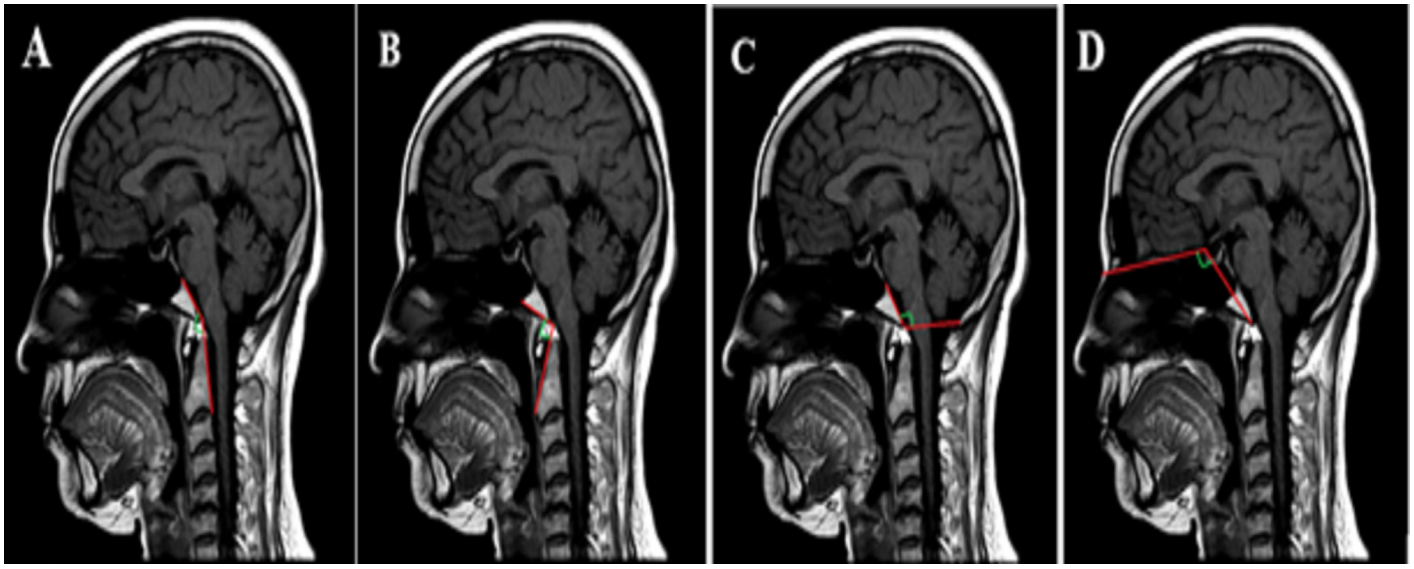

Figure 2. Demonstration of angular parameters. A: Clivus canal angle (CCA), B: Craniocervical tilt angle (CCT), C: Boogard angle (BA), D: Welcher basal angle (WBA)

5. Clivus Canal Angle (CCA): The angle between the line extending from the posterior of the dens of axis on the upper surface of the clivus to the vertebral canal (Figure 2) (16).

6. Boogard Angle (BA): The angle between a line drawn from the upper face of the clivus and the opisthion (Figure 2) (19).

7. Welcher Basal Angle (WBA): The angle between a line extending "from the nasion to the tuberculum sella" and a line extending "from the basion to the tuberculum sella" (Figure 2) (16).

The obtained data were transferred to the SPSS 22 package program. The normal distribution of the data was checked with skewness and kurtosis values. Values between -2 and +2 were accepted in a normal distribution and used in parametric tests (20). Descriptive statistical analyzes were performed using the mean and standard deviation. One Way ANOVA test, one of the parametric tests, was used for comparisons between groups. Among the post hoc tests, the Tukey test served for homogeneous variances, and the Games-Howell test for non-homogeneous variances. Pearson correlation analysis was performed to determine the relationship between all parameters. In the study, $P<0.05$ was statistically significant.

RESULTS

The study was carried out on the brain MRI images of 108 participants (aged 18-65) in the Control and Patient groups, consisting of 80 females (mean age: 34.25±10.13) and 28 males (mean age: 36.29±12.72). In the study, the patient group was divided into two subgroups: migraine with- and without-aura. Table 1 shows the distribution of participants by group and gender.

Table 1. The distribution of participants by group and gender

	Gender		
Groups	**(F)**	**(M)**	**Sum**
MA	21	7	28
MO	38	11	49
C	21	10	31
Sum	80	28	108

MA: Migraine with aura, MO: Migraine without aura, C: Control, F: Female, M: Male

In the study, of the participants, 74.1% were female (n=80), and 25.9% were male (n=28). Despite the retrospective analysis of brain MRI across the entire data range in the current study, due to the less prevalence of migraine with aura in the community and failure to convert some files to a proper format, only the images of 28 individuals (male:7, female:21) have been possible to convert into the volBrain-compliant file format. The number of male participants in the control and migraine without aura groups was kept low to balance the difference between the groups' sample numbers. Therefore, the study could not examine the inter-gender variations in the parameters. Table 2 shows the mean and standard deviation values of the angular, linear and volumetric parameters of the data obtained from 80 women and 28 men by gender. The mean BV of the control group was higher than the other two patient groups. According to Pearson correlation analysis, no relationship existed between BV and age ($r=-0.006$, $p=0.954$).

Table 2. Findings of the parameters of the patient and control groups

Para meters	Groups	N	Total Mean±SD	N	Female Mean±SD	N	Male Mean±SD
MGL (mm)	MA	28	81.28±5.44	21	81.24±5.67	7	81.41±5.11
	MO	49	82.18±4.97	38	82.56±5.28	11	80.88±3.57
	C	31	83.44±3.92	21	82.59±3.66	10	85.23±4.02
MRL (mm)	MA	28	36.92±3.46	21	36.89±3.71	7	37.02±2.82
	MO	49	37.44±3.57	38	37.44±3.65	11	37.44±3.45
	C	31	41.51±9.92	21	38.49±4.20	10	39.40±4.18
CL (mm)	MA	28	78.04±6.13	21	78.00±6.40	7	78.18±5.73
	MO	49	78.50±5.38	38	79.09±5.74	11	76.44±3.32
	C	31	77.88±12.67	21	79.47±4.57	10	83.02±3.80
CCA (°)	MA	28	149.00±10.05	21	149.66±9.18	7	147.04±12.95
	MO	49	149.72±8.07	38	150.27±8.52	11	147.79±6.18
	C	31	154.77±10.15	21	152.23±9.66	10	160.11±9.47
CTA (°)	MA	28	118.35±9.86	21	117.15±8.55	7	121.94±13.18
	MO	49	115.86±8.16	38	115.61±7.81	11	116.71±9.63
	C	31	121.57±12.30	21	119.45±12.12	10	126.02±12.06
BA (°)	MA	28	130.44±9.34	21	129.94±9.25	7	131.94±10.16
	MO	49	126.77±8.32	38	127.39±8.00	11	124.63±9.45
	C	31	125.68±8.34	21	125.24±8.19	10	126.62±9.01
WBA (°)	MA	28	129.58±6.90	21	129.94±6.72	7	128.50±7.86
	MO	49	131.11±5.51	38	131.72±5.70	11	128.97±4.37
	C	31	131.84±5.29	21	133.16±3.31	10	129.66±2.58
BV (cm^3)	MA	28	17.27±2.79	21	16.84±2.99	7	18.58±1.58
	MO	49	17.33±2.48	38	16.83±2.06	11	19.05±3.13
	C	31	19.27±2.63	21	18.15±1.72	10	21.61±2.76

MA: Migraine with aura, MO: Migraine without aura, C: Control, SD: Standard deviation, MGL: McGregor Line Length, MRL: McRae Line Length, CL: Chamberlain Line Lenght, CCA: Clivus-canal angle, CTA: Craniocervical tilt angle, BA: Boogard angle, WBA: Welcher basal angle, BV: Brainstem volume

Table 3. Comparison of brainstem volume according to patient (1,2) and control (3) groups

Groups	N	Mean±SD(cm^3)	Sources of variance	SS	df	MS	F	p	Significance
MA (1)	28	17.27±2.79	Between group	84.663	2	42.332	6.201		
MO (2)	49	17.33±2.48	Within group	716.777	105	6.826		0.003*	3 to 1.2
C (3)	31	19.27±2.63	Total	801.440	107				

MA: Migraine with aura, MO: Migraine without aura, C: Control, SS: Sum of squares, df: Degree of freedom, MS: Mean squares, SD: Standart deviation, *signifcant difference ($p<0.05$)

Table 4. Correlation values between all parameters investigated in the MA group

	1) Age	2) BV	3)MGL	4) MRL	5) CL	6) CCA	7) CTA	8) BA	9)WBA
2	-0.320								
3	0.054	-0.171							
4	-0.217	0.111	0.308						
5	0.001	0.000	0.950**	0.335					
6	0.389*	0.049	-0.221	-0.153	-0.216				
7	0.223	-0.208	-0.359	-0.351	-0.414*	0.375*			
8	-0.318	0.334	-0.248	0.017	-0.186	-0.415*	-0.030		
9	-0.181	0.304	0.206	0.317	0.237	-0.304	-0.363	0.388*	1

*p<0.05 ve **p<0.01

Table 5. Correlation values between all parameters investigated in the MO group

	1) Age	2) BV	3)MGL	4) MRL	5) CL	6) CCA	7) CTA	8) BA	9)WBA
2	0.126								
3	0.112	0.136							
4	0.092	0.281	0.337*						
5	0.054	0.109	0.948**	0.357*					
6	0.039	0.037	-0.167	0.086	-0.194				
7	0.049	0.272	-0.062	0.246	-0.062	0.395**			
8	0.123	-0.090	-0.129	-0.218	-0.073	-0.108	-0.169		
9	-0.157	-0.170	0.061	0.018	0.072	-0.319*	-0.192	-0.309*	1

*p<0.05 ve **p<0.01

Table 6. Correlation values between all parameters investigated in the control group

	1) Age	2) BV	3)MGL	4) MRL	5) CL	6) CCA	7) CTA	8) BA	9)WBA
2	0.097								
3	-0.057	-0.136							
4	-0.241	-0.046	-0.046						
5	0.150	0.041	-0.521*	-0.812*					
6	0.236	0.430*	0.099	-0.095	0.262				
7	0.077	0.453*	0.314	0.225	0.102	0.646**			
8	-0.073	0.296	-0.351	0.217	-0.380	-0.139	-0.187		
9	0.214	-0.337	-0.93	-0.104	0.016	-0.393*	-0.593**	0.308	1

*p<0.05 ve **p<0.01

Post Hoc analyses revealed that, among angular and linear parameters, only CCA showed a statistically significant difference between control and migraine with aura (p=0.048) and migraine without aura (p=0.049) groups (p<0.005). While there was a moderate negative correlation between CCA and BA in migraine with aura, no correlation was found in migraine without aura (table 4-5). Correlations of all parameters according to the groups are given in tables 4,5, and 6.

DISCUSSION

In migraine, volumetric changes can appear in many brain structures, especially in the cerebellum and brain stem (10,21). Techniques such as positron emission tomography (PET) and functional MRI can detect which brain parts show higher activation during migraine attacks. In migraine that develops from the excessive activation of the trigeminovascular system, a high

activation is evident in the brainstem structures such as the nucleus spinalis nervi trigemini, the tegmentum pontis and the substantia grisea centralis in the mesencephalon, especially during attack periods (21,22). Gray matter amounts can decrease, especially in active areas during migraine pain attacks. Some researchers thought that one of the underlying causes of migraine pathophysiology might be the volumetric changes in some structures in the brain stem (21). However, more morphometric studies are necessary on this subject because the studies are scant in the literature, and no consensus has been reached (1-4,6,8,21). There is no specific laboratory or radiological evaluation method for the diagnosis of migraine. Therefore, morphometric studies that provide objective data in addition to the patient's history will guide physicians for "normal" and "early" diagnosis. The current study found brainstem volume lower in the migraine patient 3 groups with- and without-aura than in the control group but no statistically significant difference between them. In a study consisting of a patient group with chronic migraine (n=24) and a control group (n=24), Bilgiç et al.(10), found that the brainstem volume was statistically lower in the migraine patient group than in the control group, similar to our study. In the current study too, the brainstem volume of the migraine groups with aura (17.27±2.79 cm^3) and without aura (17.33±2.48 cm^3) differed statistically significantly from the control group (19.27±2.63 cm^3) ($p<0.05$). Both studies have revealed that brainstem volumes decrease in migraine. In their work, Bilgiç et al. (10) did not divide the migraine patients into groups as with- and without-aura. Chong et al. (23) calculated the brainstem volumes of the migraine (n=55) and control (n=58) groups–as a whole and part by part. They reported no statistically significant difference between the total brainstem volume of the migraine patient group and the control group. In another study consisting of the patient (n=25) and control groups (n=25), researchers reported that the brainstem volume was statistically significantly lower in the patient group ($p<0.005$) (11). The literature shows that research on migraine and volumetric changes in brain structures is generally on the brain's total volume, gray or white matter, cerebellum, and brain lobe volumes (7,9,11,12,24). However, very few studies investigate the relationship of brainstem volume with migraine with-aura and without-aura. In the neutral position, the clivo-axial angle varies between 145° and 160°. An angle of less than 150° causes deformations in the upper cervical vertebrae and creates pressure on the brain stem. In addition to neurological problems, this pressure also deteriorates regional craniospinal hydrodynamics due to obstruction (25). The clivo-axial angle refers to the CCA angle in this research. In the current study, the CCAs of patients with aura and without aura were less than 150°, but no statistically significant difference emerged between the control and patient groups (Table 2). The clivo-axial angle has recently appeared as a prominent angular parameter in evaluating CVJ instability and deciding on stabilization surgeries (25). Asal et al. reported that the clivo-axial angle exhibited a statistically significant difference between migraine (142.65±8.73) and control (153.66±6.35) groups and that skull base angles changed in migraine disease (14). MGL, MRL, and CL are linear parameters used for evaluating basilar invagination. Odontoid protrusion above this line is always pathological and indicates basilar invagination. MRL also refers to the anterior-posterior diameter of the foramen magnum and should be greater than 19 mm (13,19). The current study found the control group's MRL value as 41.51±9.92 mm. Yüksel et al., in their research examining Chiari Malformation Type-1 and CL and MRL values of the control group, reported the CL and MRL values of the control group as 74 mm and 38.2 mm, respectively (26). The current study found the CL and MRL values as 79.47 mm and 38.49 mm, respectively. In their research, Chandra et al. measured the CTA angle from BT images of 70 patients diagnosed with atlantoaxial dislocation and basilar invagination. They documented the value of CTA in the control group as 119.8°±9.2° (27). The current study revealed the value of CTA in the control group as 121.57±12.30. These results suggest that different results might stem from separate studies with various exclusion criteria and patient groups.

WBA is an important angular parameter in the evaluation of the platybasia and should be less than 140° (13, 16). It was less than 140° in the current study, and no statistically significant difference emerged between the groups (Table 2). Nascimento et al. measured the WBA, CCA, and BA of the control group and patients with basilar invagination and reported statistically significant differences between the groups (28). As stated above, despite retrospectively scanning MRI across the entire data range in this research, the sample size of this group could not increase further due to the low prevalence of migraine with aura. Therefore, the sample size of migraine without aura and control groups remained the same to balance the sample size difference in all groups. A review of the literature did not demonstrate any other studies investigating the angular and linear parameters–considered by this study–which are significant in evaluating CVJ anatomy in patients with migraine. Since migraine is affected by several factors, such as its phase, attack frequencies, and disease duration, abnormalities in the brain are dynamic (24). Therefore, measurements and evaluations performed on MR, PET, or fMRI images taken instantly in volumetric and functional changes during an attack will produce more accurate results. However, the current study could not perform a dynamic measurement because of its retrospective nature. Studies have shown that migraine is not a simple trigeminovascular but a complex neurovascular disease affecting many neural structures, such as cortical, subcortical, and brainstem (24). Knowing both functional and morphometric changes of the brain stem in migraine is likely to provide important clues in understanding the pathophysiology of migraine and in early diagnosis.

CONCLUSION

The present study found that the brainstem volume of migraine patient groups was statistically significantly

lower than the control group (p<0.05). Based on these data, we have concluded that migraine affects the brainstem morphometry, where our crucial vital functions are managed. However, the scant number of relevant studies and the lack of a consensus reveal that more studies are necessary. Volumetric MRI examinations in further studies will guide clinicians in migraine diagnosis, treatment, and complication follow-up.

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