

ORIGINAL STUDY**Volumetric analysis of pons, middle brain and thalamus by MRI in migraine patients; and evaluation of vertebral artery diameter****Mehmet Hamdi Sahan¹**, **Nuray Bayar Muluk²**, **Fatih Kocturk³**, **Melih Aksamoglu¹**¹Radiology Department, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey²ENT Department, Kırıkkale University, Faculty of Medicine, Kırıkkale, Turkey³Neurology Department, Gaziantep University, Faculty of Medicine, Gaziantep, Turkey**ABSTRACT**

OBJECTIVES. We investigated whether there were atrophic changes in grey matter (pons, midbrain, and thalamus) in migraine patients. Vertebral artery diameters were also evaluated.

MATERIAL AND METHODS. The cranial MRI images of 49 adult migraine-diagnosed patients and 49 adult subjects with normal cranial MRI results were included in the study. In both groups, pons, midbrain, and thalamus volumes, as well as vertebral artery diameters were measured.

RESULTS. There were no significant differences between pons, midbrain, bilateral thalamus volumes and vertebral artery diameters of the migraine and control groups ($p > 0.05$). In the right-sided migraine group, the right thalamus volume was significantly lower than the contralateral side ($p < 0.05$). In the left-sided migraine group, the left thalamus volume was non-significantly lower than the contralateral side ($p > 0.05$). In the right-sided and left-sided migraine groups, left vertebral artery diameters were significantly higher than those on the right side ($p < 0.05$). In older migraine patients, pons and midbrain volumes decreased ($p < 0.05$). In longer migraine duration, pons volume decreased ($p < 0.05$). In aura-present migraine patients, right vertebral artery diameters decreased ($p < 0.05$).

CONCLUSION. We concluded that migraine is related to grey matter atrophy in terms of thalamus atrophy on the migraine side. Pons atrophy in longer migraine, and pons and midbrain atrophy in older migraine patients were also detected. Therefore, during the follow-up of the migraine patients, grey matter atrophy should be examined by MRI, and treatment to prevent migraine attacks should be planned.

KEYWORDS: migraine, pons volume, midbrain volume, thalamus volume, vertebral artery diameter.

INTRODUCTION

Migraine is characterized by recurrent headaches with the intensity of moderate to severe. It affects 18% of females and 6% of males in the general population^{1,2}. Migraine is a neurovascular disorder defined by recurrent unilateral headaches with nausea, vomiting, photophobia, and phonophobia. This may in turn lead to a wave of cortical spreading depression (CSD) at the onset of an attack. Early PET studies have suggested the involvement of an active migraine region in the brainstem³.

Other mechanisms recommended for pathogenesis are "extracranial arterial vasodilatation, extracranial neurogenic inflammation, and decreased inhibition of central pain transmission"⁴. The artery which is predominantly

located in the mechanism of migrainous vasodilatation is the superficial temporal artery's frontal branch, leading to pain in the temple, which is very characteristic of migraine¹. This artery's amplitude of the systolic pulse wave was studied by Tunisia and Wolff⁴ in migraine patients. They reported that arterial caliber increased between headaches compared to the control group, and there was a further increase during headaches⁴. It was also reported that about a third of patients have an aura before a migraine headache^{1,5}.

Aura is due to cerebral vasoconstriction causing localized hypoxia in the brain; and arterial caliber increased between headaches. Vascular changes were reported in migraine^{6,7}.

During migraine headaches, the artery expands on the

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side of the pain. Expansion is relative since generalized vasoconstriction occurs due to the activation of the sympathetic nervous system, which is secondary to migraine headache pain. There is paleness of the face and hands and feet get cold related to vasoconstriction during migraine headaches¹. For paleness of the face, it was explained as the opening of arteriovenous anastomosis resulting in arterial dilatation⁸.

Olesen et al.⁹ reported that aura symptoms occur when blood flow is still decreasing in the opposite hemisphere's posterior region. The headache begins while decreasing in the blood flow and after that, a gradual increase is detected in blood flow¹. Moreover, in the contralateral side of the migrainous pain, activation in the brainstem is detected, which plays a role in migraine generator¹⁰.

Decreasing blood flow may change gray matter. According to brain morphology studies, variations in gray matter may result from repeated ischemia in the interictal phase. In migraine, there is also neuronal hyperexcitability that is associated with pain processing, which is "pre-frontal, cingulate and insular cortices, and brain stem"¹¹⁻¹⁴. Cortical volume/thickness increased in the "primary somatosensory cortex, hippocampus and caudate nucleus" and decreased volume in "precentral gyrus, cingulate and insular cortices"^{11,13,15-18}.

Villella et al.¹⁹ reported that headaches and migraines are common initial symptoms in a significant portion of carotid artery dissections (57-92%) and vertebral artery dissections (69-72%). The location of the pain does not necessarily indicate which artery is affected; however, frontal pain is more often associated with carotid dissections, while pain in the back of the head or neck is more frequently linked to vertebral artery dissections. Pain in the eye, ear, or face may suggest an involvement of the carotid artery¹⁹. Therefore, the vertebral artery is important in patients with migraine and headaches.

The pathogenesis of migraines remains unclear. The posterior system and brain stem may play an important role in the pathophysiology of migraines. In our study, we evaluated whether there were atrophic changes in grey matter (pons, midbrain, and thalamus) in migraine patients. Volumetric analysis of the pons, midbrain, and thalamus was performed by MRI. We also measured the vertebral artery diameter and investigated if the vertebral artery diameter changes affected grey matter volumes. In migraine patients, the detection of volumetric and anatomical changes will contribute to the literature on the pathophysiology of migraine.

MATERIAL AND METHODS

This retrospective study was conducted at the Radiology and Neurology Departments, Gaziantep University, Medical Faculty, and the Department of Otolaryngology,

Kırıkkale University, Medical Faculty. This study was approved by Gaziantep University Clinical Research Ethics Committee (Decision Number: 2022/79, Date:23.02.2022) and conducted according to the Declaration of Helsinki.

Subjects

The cranial MRI images of 49 adult migraine-diagnosed patients (11 males and 38 females) were retrieved from the hospital PACS system of the Radiology Department, Gaziantep University, Medical Faculty, between March 16, 2020, to March 16, 2022. The migraine diagnosis was confirmed by the Neurology Department according to the International Classification of Headache Disorders (ICHD) criteria²⁰. The mean age of the migraine group (Group 1) was 42.57±9.99 years (ranging from 21 to 66).

A control group was formed of 49 adult subjects (11 males and 38 females) with normal cranial MRI results and no findings of migraine. The age-matched control subjects were selected from the hospital PACS system screening from March 16, 2020, to March 16, 2022. The mean age of the control group (Group 2) was 40.41±10.33 years (ranging from 21 to 63).

Patients were selected according to the similar studies²⁵. Gpower 3.1 program was used for the Power analysis. In each group, the minimum patient number was found as 37 ($\alpha=0.20$, $1-\beta=0.80$). Therefore, the total number was 74 (Cohen $d=0.5$).

In migraine patients, the side of the headache (right, left, or no-sided), duration of the migraine (years), aura before the migraine attacks (present or absent), and frequency of the migraine attacks were evaluated from the Hospital files.

Inclusion criteria:

1. Patients over the age of 18,
2. Patients diagnosed with migraine in accordance with the ICHD criteria,
3. Patients with complete cranial MRI images.

Exclusion criteria:

1. Patients who have previous cranial trauma and surgery,
2. Patients with intracranial mass,
3. Patients with diabetes mellitus and any metabolic diseases,
4. Patients with demyelinating and degenerative diseases affecting cerebral structures,
5. Patients with cerebrovascular and cardiovascular diseases,
6. Patients with hypertension (blood pressure >160/95 mmHg),
7. Patients with congenital and anatomical variations in the brain.

MRI technique

All MRI examinations were performed using cranial coil by 3.0 Tesla (T) MRI systems (Ingenia, Philips Healthcare, Best, the Netherlands). The routine cranial MRI protocol for the 3.0-T MR machine at Gaziantep University Hospital was as follows: T1-FFE (Fast Field

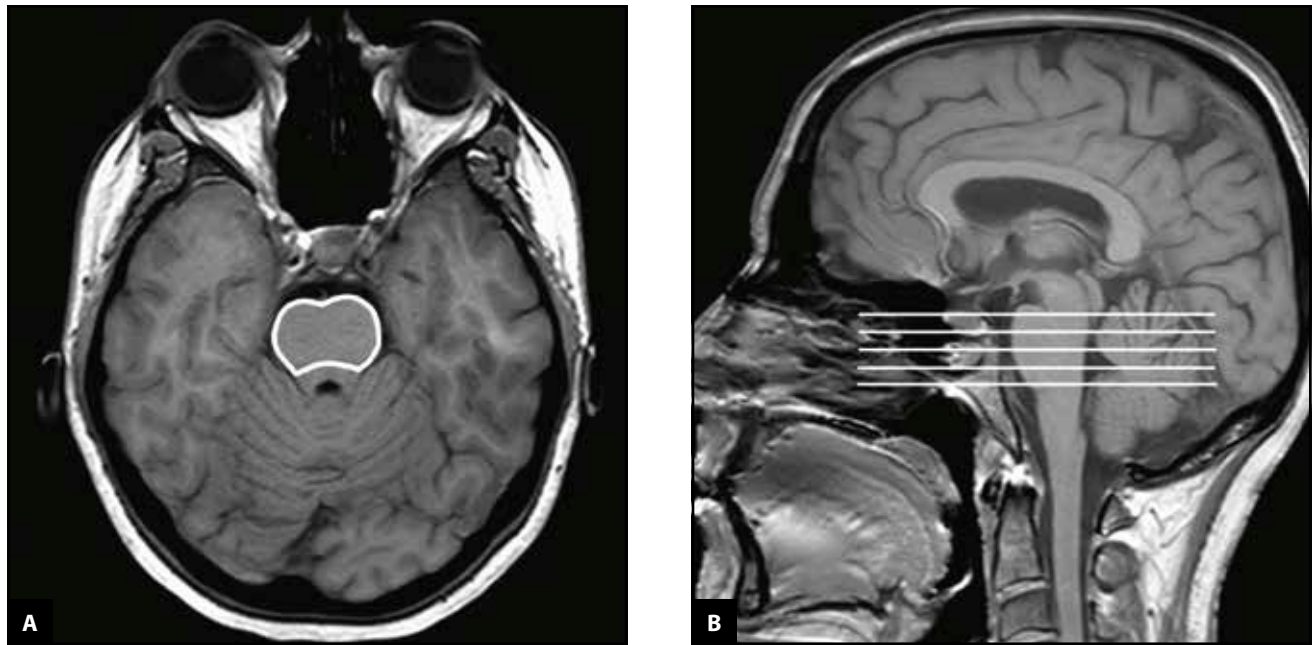


Figure 1. Cranial MRI: **A** - Measurement of the pons area in axial T1W images; **B** - Sections passing through the pons in sagittal T1W images.

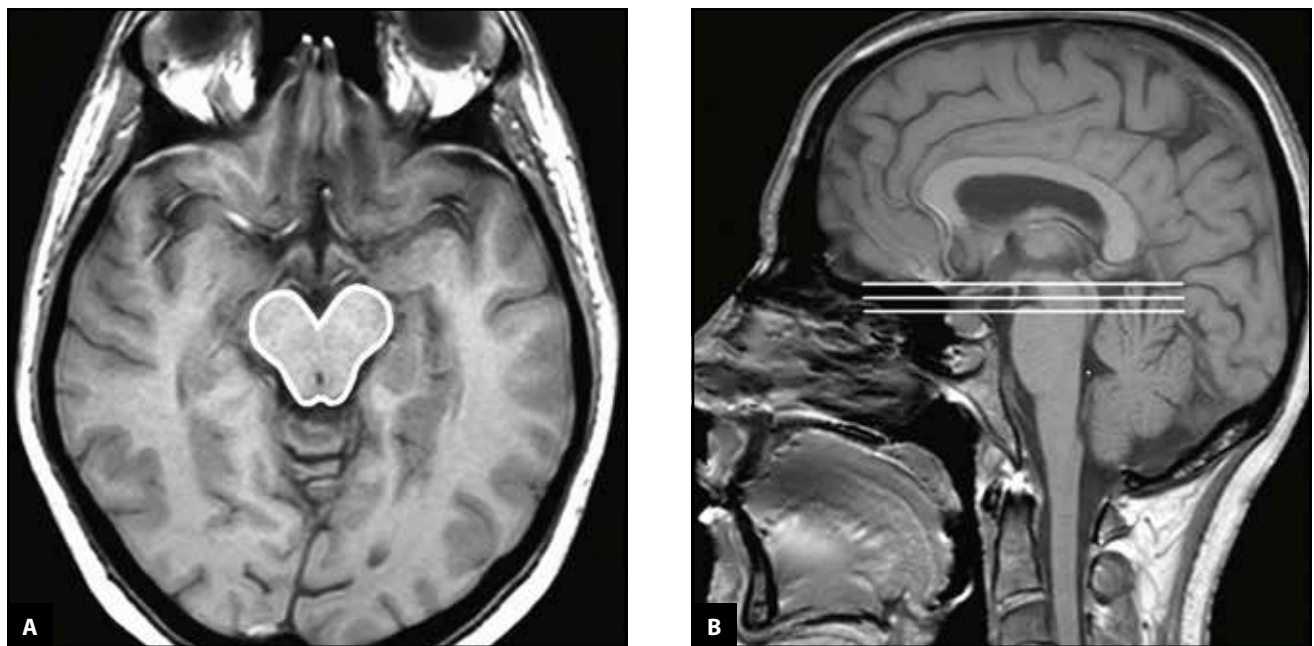


Figure 2. Cranial MRI: **A** - Measurement of the midbrain area in axial T1W images; **B** - Sections passing through the midbrain in sagittal T1W images.

Echo) weighted sequences in the sagittal and the axial plane (TR ms/TE ms; 330/20, FOV 230 x 130 mm and matrix 256 x 139 mm) were obtained using a 4 mm slice thickness and 0.5 mm intersection gap; and 30-32 sagittal and axial sections were obtained. T2-TSE (Turbo Spin Eko) weighted sequences in the coronal plane (TR ms/TE ms; 4040/80, FOV 200 x 152 mm and, matrix 288 x 163 mm) were obtained using a 4-mm slice

thickness and 0.5-mm intersection gap; and 34 coronal sections were obtained.

Measurements

After the MRI images were processed at the workstation with the consensus of two radiologists (MHŞ, MA), measurements were performed by one radiologist (MHŞ).

Pons volume (cm³): After measuring the pons area in each section from the axial T1W images, the sum of the

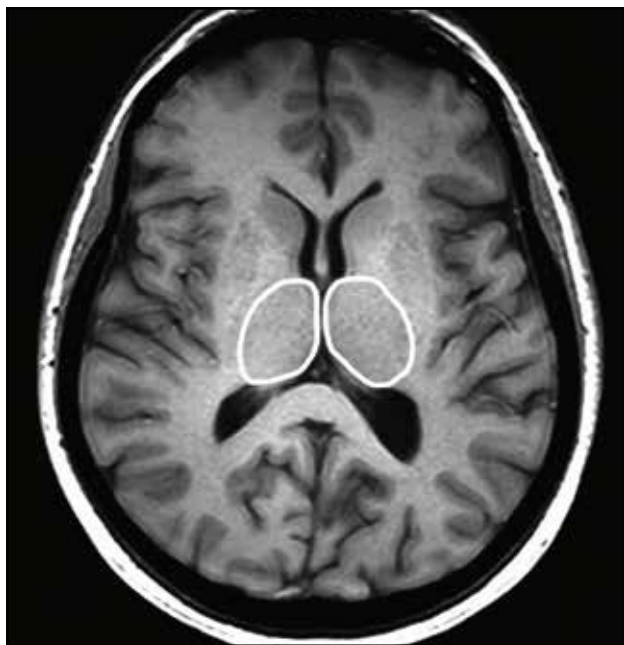


Figure 3. Measurement of bilateral thalamus area in axial T1W images (cranial MRI).

areas was calculated. The volume was obtained by multiplying this calculated value by the sum of the section thickness with intersection gap^{18,21-24} (Figure 1A, B).

Midbrain volume (cm³): After measuring the midbrain area in each section from the axial T1W images, the sum of the areas was calculated. The volume was obtained by multiplying this calculated value by the sum of the section thickness with the intersection gap^{18,21-24} (Figure 2A, B).

Bithalamic volume (cm³): After measuring the bithalamic area in each section from the axial T1W images, the sum of the areas was calculated. The volume was obtained by multiplying this calculated value by the sum of the section thickness with the intersection gap^{18,21-24} (Figure 3).

Diameter of vertebral artery (mm): In coronal T2W images, the vertebral artery was measured from a distance of approximately 2 mm after the intradural (V4) segment entered the dura (to exclude variable collateral and anatomical variations). Right and left side measurements were performed^{25,26} (Figure 4).

Statistical analyses

Power Analyses were performed by the Gpower 3.1 program.

Version 21.0 of the Statistical Package for the Social Sciences (SPSS) software was used for the analysis. A chi-square test, independent samples t-test, paired samples t-test, Mann Whitney U test, Wilcoxon signed rank test, Kruskal Wallis Variance analysis, Pearson correlation test, and Spearman's correlation rho efficient test were used.

A p-value < 0.05 was considered as statistical significance.



Figure 4. The appearance of both vertebral arteries in coronal T2W images (white arrows), measurement technique in magnified images.

RESULTS

There were 11 males (22.4%) and 38 females (77.6%) in the migraine group; and 11 males (22.4%) and 38 females (77.6%) in the control group ($p=0.000$, $\chi^2=0.000$). There were no significant differences between the ages of the groups ($p<0.05$) (Table 1).

Features of the migraine

In the migraine group, migraine duration was 9.24 ± 6.52 years (ranging from 1 to 25 years). Aura was present in 4 patients (8.2%) and absent in 45 patients (91.8%). The migraine was right-sided in 10 patients (20.41%), left-sided in 11 patients (22.45%) and no-sided in 28 patients (57.14%). The frequency of migraine attacks was 8.78 ± 6.31 attacks per month (ranging from 1 to 30 attacks per month).

Measurement results in migraine and control groups are shown in Table 1.

There were no significant differences between pons ($p=0.782$), midbrain ($p=0.127$), and bithalamic volumes ($p=0.081$ on the right and $p=0.095$ on the left) of the migraine (9.47 ± 1.71 cm³, 6.04 ± 1.33 cm³, 5.98 ± 1.31 cm³ (Right thalamus (R)) and 6.05 ± 1.28 cm³ (Left thalamus (L)) respectively) and control groups (9.56 ± 1.33 cm³, 6.48 ± 1.45 cm³, 6.39 ± 0.94 cm³ (R) and 6.43 ± 0.88 cm³ (L) respectively) ($p<0.05$). In each of the migraine (5.98 ± 1.31 cm³ on the right and 6.05 ± 1.28 cm³ on the left) and control groups (6.39 ± 0.94 cm³ on the right and 6.43 ± 0.88 cm³ on the left) separately, thalamic volumes were not different on the right and left sides (for the migraine group, $p=0.128$; for the control group, $p=0.296$) ($p>0.05$) (Table 1).

Table 1. Measurement results in migraine and control groups.

	Group 1 (Migraine) (n=49)			Group 2 (Control group) (n=49)			p*	
	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.		
Age	42.57	42.00	9.998	40.41	41.00	10.334	0.095	
Measurement results								
Pons volume (cm ³)	9.47	9.20	1.71	9.56	9.40	1.33	0.782	
Midbrain volume (cm ³)	6.04	5.99	1.33	6.48	6.38	1.45	0.127	
Thalamus volume (cm ³)	R	5.98	5.82	1.31	6.39	6.39	0.94	0.081
	L	6.05	5.98	1.28	6.43	6.40	0.88	0.095
	p**	0.128		0.296				
Diameter of Vertebral artery (mm)	R***	2.09	2.00	0.42	2.13	2.10	0.41	0.387
	L	2.41	2.26	0.54	2.49	2.40	0.51	0.499
	p****	0.007		0.002				

R – right; L – left; *p value shows the results of independent samples t-test; **p value shows the results of paired samples t-test; ***p value shows the results of Mann Whitney U test; ****p value shows the results of Wilcoxon signed ranks test

There were no significant differences between vertebral artery diameters of the migraine (2.09±0.42 mm on the right and 2.41±0.54 mm on the left) and control groups (2.13±0.41 mm on the right and 2.49±0.51 mm on the left) (p=0.387 on the right and p=0.499 on the left) (p<0.05). In each of the migraine (p=0.007) and control groups (p=0.002) separately, left vertebral artery diameters were significantly higher than those on the right side (p<0.05) (Table 1).

Measurement results according to the migraine side in the migraine group are shown in Table 2.

There were no significant differences between pons (p=0.860), midbrain (p=0.359), and bithalamic volumes (p=0.860 on the right thalamus and p=0.725 on the left thalamus) and between the right-sided (9.34±1.65 cm³, 5.72±1.23 cm³, 5.78±1.08 cm³ (R) and 6.14±0.96 cm³ (L) respectively), left-sided (9.35±2.02

cm³, 6.25±1.56 cm³, 6.00±1.46 cm³ (R) and 5.97±1.44 cm³ (L) respectively), and no-sided migraine groups (9.57±1.66 cm³, 6.08±1.29 cm³, 6.05±1.36 cm³ (R) and 6.06±1.36 cm³ (L) respectively) (p<0.05). In the right-sided migraine group, the right thalamus volume (5.78±1.08 cm³) was significantly lower than those on the left side (6.14±0.96 cm³) (p=0.05) (Table 2). In the left-sided and no-sided migraine groups, thalamic volumes were not different on the right and left sides (p>0.05) (Table 2). However, in the left-sided migraine group, the left thalamus volume (5.97±1.44 cm³) was non-significantly lower than in the right-side group (6.00±1.46 cm³) (p=0.266).

There were no significant differences between vertebral artery diameters of the right-sided (1.98±0.53 mm on the right and 2.53±0.55 mm on the left), left-sided (1.95±0.26 mm on the right and 2.62±0.51 mm on the

Table 2. Measurement results according to the migraine side in the migraine group.

Measurement results	Group 1 (Right-sided migraine) (n=10)			Group 2 (Left-sided migraine) (n=11)			Group 3 (No-sided migraine) (n=28)			p*	
	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.		
Pons volume (cm ³)	9.34	8.95	1.65	9.35	9.71	2.02	9.57	9.30	1.66	0.860	
Midbrain volume (cm ³)	5.72	5.23	1.23	6.25	6.00	1.56	6.08	6.11	1.29	0.359	
Thalamus volume (cm ³)	R	5.78	5.40	1.08	6.00	5.82	1.46	6.05	5.90	1.36	0.860
	L	6.14	6.10	0.96	5.97	5.98	1.44	6.06	5.96	1.36	0.725
	p**	0.05		0.266		0.564					
Diameter of vertebral artery (mm)	R	1.98	1.85	0.53	1.95	2.00	0.26	2.19	2.10	0.42	0.943
	L	2.53	2.35	0.55	2.62	2.40	0.51	2.30	2.20	0.54	0.572
	p**	0.034		0.016		0.427					

R – right; L – left; *p value shows the results of Kruskal Wallis Variance analysis; **p value shows the results of Wilcoxon signed rank test.

left), and no-sided (2.19 ± 0.42 mm on the right and 2.30 ± 0.54 mm on the left) migraine groups ($p=0.043$ on the right and $p=0.572$ on the left) ($p<0.05$). In the right-sided ($p=0.034$) and left-sided migraine groups ($p=0.016$), left vertebral artery diameters were significantly higher than those on the right side ($p<0.05$) (Table 2). In the no-sided migraine group, vertebral artery diameters were not different on the right and left sides ($p>0.05$) (Table 2).

Correlation test results in the migraine group are shown in Table 3.

There were positive correlations between the pons and midbrain volumes, midbrain and bithalamic volumes, right and left thalamus volumes ($p<0.05$) (Table 3). These results showed that these measurement values increased or decreased altogether.

In older migrainous patients, pons and midbrain volumes decreased ($p<0.05$) (Table 3). It shows that, in older migraine patients, these volumes reduced.

In longer migraine duration, pons volume decreased ($p<0.05$) (Table 3). It shows that in longer migraine patients, pons volumes were found as reduced.

In aura-present migraine patients, right vertebral artery

diameters decreased ($p<0.05$) (Table 3).

There were no significant correlations between gender and pons, midbrain and bithalamic volumes and bilateral vertebral artery diameters ($p>0.05$) (Table 3).

DISCUSSIONS

During neurogenic inflammation, chemicals of “substance P, calcitonin gene-related peptide, and neurokinin A” were released from sensory nerve fibers which are present in the nociception. In migraines, the activation of nerve fibers results in extracranial arterial dilatation. Nerve fibers are coiled and stretched around the arteries; at the end, depolarization occurs and dilatation of blood vessels develops²⁷.

The thalamus is placed in the diencephalon, which is the central deep brain structure and is located between the cortex and midbrain. Thalamic nuclei are located in the dorsal thalamus, epithalamus, hypothalamus, and ventral thalamus²⁰. The dorsal thalamus and hypothalamus are important structures in migraines. Thalamus is a relay center for nociceptive information through the

Table 3. Correlation test results in the migraine group.

		Pons volume (cm ³)	Midbrain volume (cm ³)	Thalamus volume (cm ³)		Diameter of vertebral artery (mm)		
				R	L	R**	L	
Pons volume (cm ³)	r		0.335	0.157	0.115	-0.047	0.110	
	p*		0.018	0.282	0.432	0.748	0.451	
Midbrain volume (cm ³)	r	0.335		0.304	0.322	0.153	0.052	
	p*	0.018		0.033	0.024	0.293	0.721	
Thalamus volume (cm ³)	R	r	0.157	0.304		0.972	-0.062	0.223
		p*	0.282	0.033		0.000	0.674	0.123
	L	r	0.115	0.322	0.972		-0.045	0.171
		p*	0.432	0.024	0.000		0.759	0.239
Frontal sinus level (mm)	R	r	-0.047	0.153	-0.062	-0.045		-0.237
		p**	0.748	0.293	0.674	0.759		0.102
	L	r	0.110	0.052	0.223	0.171	-0.237	
		p*	0.451	0.721	0.123	0.239	0.102	
Age	r	-0.417	-0.634	-0.210	-0.223	-0.123	-0.079	
	p*	0.003	0.000	0.148	0.124	0.400	0.589	
Gender (Code 1: Male, Code 2: Female)	r	-0.211	-0.159	-0.272	-0.268	-0.171	-0.246	
	p**	0.145	0.275	0.059	0.063	0.241	0.088	
Migraine duration	r	-0.392	-0.061	-0.133	-0.109	0.134	-0.119	
	p*	0.005	0.677	0.364	0.457	0.359	0.414	
Aura (Code 1: Present, Code 2: Absent)	r	0.040	0.026	-0.214	-0.206	0.353	-0.190	
	p**	0.787	0.857	0.141	0.156	0.013	0.190	
Frequency of migraine attacks/month	r	-0.020	-0.179	-0.107	-0.148	-0.225	0.094	
	p*	0.890	0.219	0.466	0.309	0.120	0.520	

R- right; L- left; * p value shows the results of Pearson correlation test; ** p value shows the results of Spearman's correlation rho efficient

trigeminovascular pain pathway, between lower brain areas to the cortex²⁸.

The thalamus transmits and modulates sensory and motor information, including pain regulation between the peripheral nervous system and cortical regions, and plays a role in sleep-wake cycle regulation, cognitive behaviors (i.e. memory), awareness, decision-making, attention and, visual information modulation²⁹⁻³¹. It also has a role in cortico-cortical communication between cortical areas through trans-thalamic information transfer³².

It has been suggested that the dysregulation of subcortical regions, such as the hypothalamus and midbrain, may allow changes in brain activity that initiate and sustain migraine attacks; that is, migraine can cause dysfunction of subcortical regions below diencephalon level and lead to an "abnormal perception of the basal level of primary traffic"³³.

In the present study, we investigated the grey matter volume changes in migraine patients. Measurements were performed on pons, midbrain volume, and bilateral thalamus volume in cranial MRI. We also measured the vertebral artery dimension and its relationship with the grey matter volumes. In the migraine group, migraine duration was 9.24 ± 6.52 years. Aura was present in 8.2% and absent in 91.8% of the patients. Most of the patients were no-sided migraine (57.14%); right-sided (20.41%) and left-sided (22.45%) migraine was also detected. The frequency of migraine attacks was 8.78 ± 6.31 attacks per month. There were no significant differences between pons, midbrain, bilateral thalamus volumes, and vertebral artery diameters of the migraine and control groups. The same observation was made in migraine groups of the side definitions (right-sided, left-sided, and no-sided). In both groups, left vertebral artery diameters were significantly higher than those on the right side.

In the literature, it was reported that the overall volume of the thalamus was found as no change between migraine patients and controls³⁴. However, it was reported that the central nuclear complex, lateral dorsal, and anterior nucleus volume of the thalamus reduce in migraine patients. All these structures are connected to the limbic system and show abnormal processing of pain in terms of cognitive and affective components³⁵.

In the present study, in the right-sided migraine group, the right thalamus volume was significantly lower than on the contralateral side. In the left-sided migraine group, the left thalamus volume was non-significantly lower than on the contralateral side. In the no-sided migraine groups, thalamic volumes were not different on the right and left sides. In our study, in the right-sided and left-sided migraine groups, the left vertebral artery diameters were significantly higher than those on the right side. In the no-sided migraine group, vertebral artery diameters were not different on the right and left sides. In our study, the reduction of the thalamus volume in migraine patients was similar to the literature report³⁵.

In brain stem nuclei, activity increase is detected during the migraine attacks. These nuclei are dorsal pons, hypothalamus, midbrain periaqueductal gray matter, thalamus, spinal trigeminal nucleus, cingulate and insular cortices³⁶⁻³⁸. However, some studies did not find strong evidence of specific brain anatomical alterations reliably associated with migraine³⁹. Yilmaz-Kusbeci et al.⁴⁰ reported that there is no significant difference in the cerebellar and cerebral volumes, or in the ratio of cerebellar to cerebral volume, between individuals with migraine with aura and those without migraine. Husøy et al.⁴¹ reported that individuals with migraine without aura had a lower number of perivascular spaces in the basal ganglia compared to those without headache ($p=0.003$), and in both the basal ganglia and hemispheric white matter together ($p=0.046$). However, there was no difference in the number of perivascular spaces between those with and without long-term headaches.

For nociceptive and somatosensory processing, there is a strong connection between the brain areas and midbrain in migraine patients having frequent attacks⁴². Brainstem subregions' volumes were smaller in migraine patients having allodynia and lower heat pain thresholds⁴³. Additionally, gray matter volume decreased in the pons-dorsomedial part and spinal trigeminal nucleus⁴⁴. Periaqueductal gray matter volume was also larger in episodic migraine⁴⁵. In the pons, the locus ceruleus can be activated by nociceptive trigeminal activation. Via this mechanism, a migraine is triggered⁴⁶.

Petrusic et al.⁴⁷ investigated total brain stem volume changes in "pons, medulla, midbrain and superior cerebellar peduncles" in migraines with aura (MwA) and healthy controls (HC). MwA patients had a larger brain stem volume than HC's as well as midbrain ($6155.98 \pm 565.7 \text{ mm}^3$ vs $5964.22 \pm 457.0 \text{ mm}^3$) and pons ($15.105.13 \pm 1765.5 \text{ mm}^3$ vs $14.539.89 \pm 1408.4 \text{ mm}^3$). Total brain stem volume and volumes of brain stem sub-regions were not associated with MwA properties. They concluded that MwA is related to a larger volume in the brain stem and a certain involvement of the midbrain and pons.

Marciszewski et al.⁴⁴ investigated the brainstem anatomy in migraine patients. They reported a decrease in the grey matter volume of dorsomedial pons and spinal trigeminal nucleus. Moreover, in "midbrain periaqueductal gray matter, dorsolateral pons, and medullary raphe", free water diffusivity increased. These findings were not related to the migraine's severity, duration, frequency of the attacks, or time to the following attack. They concluded that these anatomical results may result in ascending trigeminal pathway activation and headache perception during the attacks.

A recent study reported a decrease in overall brain stem volume in migraine sufferers. They found that migraines were associated with significant "overall brain stem volume reduction" consistent with "regional gray matter reductions" reported in this study⁴⁸. It is important to investigate

the anatomy of higher brain centers. Brain stem regions transmit information from meninges and cranial vessels. They also have potential role for input modulation and even migraine generation^{44,48}.

In our study, in the migraine group, there were positive correlations between the pons and midbrain volumes, midbrain and bithalamic volumes, right and left thalamus volumes. In older migraine patients, pons and midbrain volumes decreased. In longer migraine duration, pons volume decreased. In aura-present migraine patients, right vertebral artery diameters decreased.

Decreased gray matter volume can be caused by neuronal loss, but also by atrophy or shrinkage of neurons or glia, or synaptic loss⁴⁹. In addition, in migraine patients, increases are an indicator of subtler changes in tissue microstructure caused by tissue shrinkage or gliosis⁵⁰.

The midbrain plays a role in connecting the components of the motor system (cerebral hemisphere, basal ganglia, and cerebellum). In the midbrain, periaqueductal gray matter is thought to be related to headaches in various studies⁵¹. Chen et al.⁴⁵ reported that chronic migraine sufferers had the largest periaqueductal grey matter compared to the control group.

In migraine, the thalamus has an important role in photophobia, central sensitization, and allodynia. In these patients, there is an abnormal functional link between various cortical regions and the thalamus, indicating altered pain processing. In addition, the thalamus plays a role in the modulation and processing of dysfunctional pain in migraines²⁸.

Limitations of our study are written as follows: first, inter and intraobserver variability was not evaluated in the measurements; second, there may be misconceptions at the millimeter level, especially in field measurements in axial images. Moreover, the handedness of the participants was not documented, which is another limitation of our study. Nevertheless, we believe that this study is meaningful. Additional comprehensive studies are required to correct the limitations.

CONCLUSIONS

Our study showed that in right and left-sided migraine, thalamus volume decreased as compared to the contralateral side. In these migraine sub-groups, left vertebral artery diameters were higher than on the right side. In longer migraine duration, pons volume decreased and in older migraine patients, pons and midbrain volumes decreased. In aura-present migraine patients, right vertebral artery diameters decreased.

We can conclude that migraine is related to gray matter atrophy in terms of thalamus atrophy on the migraine side. Pons atrophy in longer migraine, pons and midbrain atrophy in older migraine patients were also detected. Therefore, during the follow-up of migraine patients, grey

matter atrophy should be examined by MRI, and treatment to prevent migraine attacks should be planned.

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