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Volumetric MRI analysis of the pineal gland and brain ventricles in patients with migraine

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MAIN POINTS

- Individuals with migraine have significantly smaller pineal gland and cerebral ventricle volumes compared to healthy controls.
- A smaller pineal gland volume may indicate reduced melatonin production capacity, potentially contributing to migraine pathophysiology.
- The reduction in third ventricle volume may be associated with increased intracranial pressure and decreased CSF-mediated melatonin transport.
- The study demonstrates that migraine is associated not only with functional but also with microstructural brain alterations.

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ABSTRACT

Aim: Previous studies have reported reduced melatonin levels and elevated cerebrospinal fluid (CSF) pressure in patients with migraine. However, the volumetric characteristics of the pineal gland, which is the primary source of melatonin, and the brain ventricles, which serve as CSF reservoirs, have not been sufficiently investigated. This study analyzed the volumes of the pineal gland and brain ventricles in migraine patients.

Materials and Methods: The study included 21 migraine patients and 22 age- and sex-matched healthy controls. Brain volumetric analyses were performed using high-resolution magnetic resonance imaging (MRI). Pineal gland volumes were manually segmented and measured using ITK-SNAP software, while ventricular volumes were automatically computed using volBrain software. All volumetric measurements were expressed in cubic centimeters (cm^3).

Results: The groups were comparable in terms of age ($p=0.730$), gender ($p=0.420$), and body mass index ($p=0.082$). Pineal gland volume was significantly reduced in the migraine group. An ANCOVA controlling for total intracranial volume confirmed this significant reduction ($F(1, 39) = 34.95$, $p<0.001$, partial $\eta^2 = 0.473$). Likewise, ventricular volumes were significantly smaller in migraine patients ($p<0.001$).

Conclusion: These findings indicate that the reduction in pineal gland volume in migraine patients occurs independently of overall brain size, pointing to a specific structural change relevant to the underlying pathology of the disease.

Keywords: Pineal gland, Cerebral ventricles, Migraine, Headache

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INTRODUCTION

Migraine is a neurological disorder that affects approximately 15% of the global population and may occur at any age [1]. It is more prevalent among women and individuals under the age of 50, tends to follow a chronic course, and typically lasts between 4 hours and 3 days [2,3]. Migraine manifests primarily as a headache and is frequently accompanied by symptoms such as photophobia, phonophobia, nausea, or vomiting [1].

Despite the considerable individual and societal burden of migraine, its pathophysiology remains incompletely understood. While various theories have been proposed, neuroimaging studies have consistently revealed both structural and functional alterations in the brains of individuals with migraine [4,5,6]. Among these findings, the observation of reduced melatonin levels and elevated cerebrospinal fluid (CSF) pressure in migraine patients has drawn increasing attention.

The pineal gland, located above the thalamus, is responsible for the secretion of several hormones, most notably mela-

tonin [7]. Melatonin, one of the most potent natural antioxidants, can readily cross cellular membranes to neutralize reactive oxygen and nitrogen species, thereby reducing oxidative stress [8]. Emerging evidence suggests that melatonin plays a role in the pathophysiology of both primary and secondary headache disorders [9,10,11], and studies have consistently reported lower melatonin levels in individuals with migraine [8].

Melatonin secretion has been shown to be positively correlated with the volume of the pineal gland, and inter-individual differences in this volume may influence circulating melatonin levels [12,13]. Additionally, the cerebral ventricles—cavities within the central nervous system—are responsible for the production and circulation of CSF [14]. Several studies have suggested a potential link between ventricular system morphology and migraine pathophysiology, particularly regarding CSF dynamics [15,16]. Furthermore, it has been demonstrated that a large portion of melatonin secreted by the pineal gland enters the third ventricle directly through the pineal recess, suggesting that the ventricular system may be indirectly influenced by melatonin levels [17,18].

Although various theories exist regarding migraine pathogenesis, volumetric studies focusing on the pineal gland and cerebral ventricles remain limited. Given the evidence of low melatonin levels and increased CSF pressure in individuals with migraine, investigating the structural characteristics of these regions is warranted. Therefore, the aim of this study was to examine possible volumetric differences in the pineal gland and cerebral ventricles between migraine patients and healthy controls using magnetic resonance imaging (MRI).

MATERIALS AND METHODS

Study design and ethical considerations

This a cross-sectional cohort study conducted in a single center and adhered to the Declaration of Helsinki for scientific and ethical conduct in scientific research. Written informed consent was obtained from the participants. The study was approved by the institutional review board on February 28, 2024 (Institutional Review Board of Hitit University, Decision No. 2024-04).

Study groups

The study included a Migraine Group of 21 patients (15 females, 6 males) and a Control Group of 22 healthy, asymptomatic individuals (18 females, 4 males).

Inclusion and exclusion criteria

Migraine patients were selected based on the International Headache Society diagnostic criteria for migraine without aura. These criteria included: (I) headache attacks lasting 4–72 hours (untreated or unsuccessfully treated); (II) unilateral, pulsating pain of moderate to severe intensity; (III) aggravation by routine physical activity; (IV) associated nausea/vomiting or photophobia/phonophobia; and (V) the absence of other underlying diseases.

General inclusion criteria for all participants required that they be between 18 and 65 years of age, have a normal neurological examination, and show no lesions or anomalies on brain MRI. Participants were required to have no systemic diseases affecting the autonomic nervous system, no history of alcohol or substance abuse in the last five years, and no regular medication use for at least one month prior to the study. Individuals with neurodegenerative diseases, congenital brain anomalies, or a history of head trauma were excluded.

Image acquisition

Radiological evaluation of brain structures and the pineal gland was performed using a 3-Tesla MRI scanner (Magnetom Skyra, Siemens). The pineal gland was localized by identifying the corpus callosum, superior colliculus, third ventricle (ventriculus tertius), and quadrigeminal cistern. A T1-weighted MPRAGE sequence was acquired with the following parameters: sagittal plane, slice thickness = 1 mm, flip angle = 9°, voxel size = 1 × 1 × 1 mm, repetition time (TR) = 2300 ms, field of view (FOV) = 250 × 250 mm^2, echo time (TE) = 3.4 ms, and matrix = 256 × 256.

Pineal gland volumetry

Pineal gland volumes were measured using ITK-SNAP software (Insight Segmentation and Registration Tool Kit). Manual segmentation was performed to ensure accuracy. Brain MRI data in DICOM format were imported into ITK-SNAP, and the boundaries of the pineal gland were delineated in the coronal, sagittal, and axial planes. Using the 'Active Label' and 'Interpolate Labels' tools, the gland boundaries were traced across all relevant slices. Upon completion of the segmentation, the software automatically calculated the pineal gland volume in cubic centimeters (cm^3) (Figure 1).

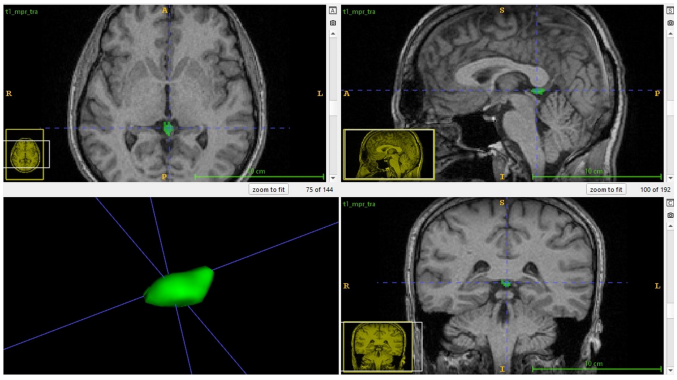

Figure 1. Pineal gland image reconstructed in ITK-SNAP program.

Brain ventricular volumetry

Brain ventricular volumes were calculated using the automated cloud-based volumetry system, volBrain (https://volbrain.upv.es). T1-weighted images were first converted from

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DICOM to NIfTI format using dcm2niigui software and compressed into .zip archives. The data were then uploaded to the volBrain server. The 'vol2Brain' pipeline was selected, and participant demographic data (age and sex) were entered into the system. The server processed the data and generated a report detailing the volumetric information of the brain ventricles (Figure 2).

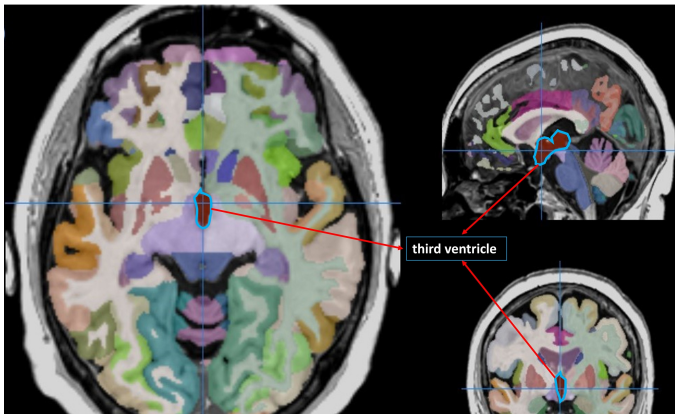

Figure 2. Brain ventricle images reconstructed in volBrain program.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics (Version 22.0; IBM Corp., Armonk, NY, USA), R (Version 4.4.3), and JASP (Version 0.19.3). Continuous variables were expressed as mean and standard deviation (Mean ± SD), while categorical data were presented as frequencies (n) and percentages (%). Group comparisons for baseline characteristics were performed using the independent samples t-test for continuous variables and the Pearson chi-squared test for categorical variables.

To assess differences in pineal gland volume between migraine patients and healthy controls while accounting for variations in overall brain size, Analysis of Covariance (ANCOVA) was employed. Total intracranial cavity volume was included as a covariate to isolate the effect of group status. Model assumptions were rigorously verified: linearity was assessed via scatterplots; homogeneity of regression slopes was confirmed by the non-significant interaction between Group and Intracranial Cavity; normality of residuals was checked using Q-Q plots and the Shapiro-Wilk test; and homogeneity of variance was assessed using Levene's test.

A post-hoc power analysis was conducted using G*Power (version 3.1.9.7) to evaluate sample size adequacy. The analysis indicated a high statistical power ($1-\beta = 0.99$) to detect the observed effect size [$f = 0.94$] at $\alpha = 0.05$. Statistical significance was defined as $p<0.05$.

RESULTS

Demographics and initial comparisons

Table 1 summarizes the demographic characteristics and initial volumetric measurements. There were no statistically significant differences between the groups regarding gender distribution (p=.420), mean age (t(41) = -0.35, p=.730), or Body Mass Index (t(41) = -1.78, p=.082), confirming the comparability of the two cohorts.

Volumetric analysis

Volumetric comparisons, summarized in Table 2, revealed distinct structural differences. The migraine group exhibited a significantly smaller pineal gland volume, which was approximately 23% smaller than that of the control group (p<.001). A consistent reduction was also observed across the ventricular system; volumes of the lateral ventricle (p<.001), third ventricle (p<.001), and fourth ventricle (p=.005) were all significantly smaller in migraine patients. Conversely, while the total volumes of Grey Matter, White Matter, and the overall Intracranial Cavity were slightly smaller in the migraine group, these differences were not statistically significant (p=.961 and p=.791, respectively). This indicates that the observed volumetric reductions are specific to the pineal-ventricular system rather than a consequence of global differences in brain or head size.

Results of ANCOVA

As detailed in Table 3, Analysis of Covariance (ANCOVA) was performed to determine if the difference in pineal gland volume persisted after accounting for intracranial cavity volume (ICV). Prior to analysis, all assumptions were verified. The assumption of homogeneity of regression slopes was met, as the interaction between group status and ICV was not statistically significant ($F(1, 39) = 0.237$, p=.629, partial η^2 =.006), confirming that the relationship between ICV and pineal volume was consistent across groups. Levene's test for homogeneity of error variances was also non-significant ($F(1, 41) = 0.351$, p=.557). Additionally, standardized residuals were normally distributed with no significant outliers.

After adjusting for ICV, the ANCOVA revealed a significant main effect of group status ($F(1, 39) = 34.95$, p<.001). The effect size was large (partial $\eta^2 = .473$), indicating that 47.3% of the variance in pineal gland volume was attributable to group differences after controlling for brain size.

Analysis of means

Unadjusted descriptive statistics showed a mean pineal gland volume of 0.20 cm^3 (SD=0.03) for the migraine group and 0.26 cm^3 (SD=0.04) for the control group. After controlling for ICV, the adjusted means (estimated marginal means) remained 0.20 cm^3 and 0.26 cm^3, respectively. Pairwise comparisons confirmed that the control group had a significantly larger pineal gland volume, with a mean difference of 0.058 cm^3 (95% CI: 0.038 to 0.078, p<.001). The minimal difference between unadjusted and adjusted means suggests that the reduction in pineal volume in migraine patients is a robust finding, independent of intracranial cavity volume.

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Table 1. Descriptive statistics of the participants.

	Migraine group (n=21) (Mean±SD)	Control group (n=22) (Mean±SD)	Sig. (p)
Gender F/M (F% / M%)	15/6 (71.43% / 28.57%)	18/4 (81.2582% / 18.18%)	0.420
Age (years)	37.86±6.75	38.55±6.22	0.730[a]
BMI	26.42±1.64	27.48±2.25	0.082[b]

SD: Standard deviation, BMI: Body mass index, [a]: t-test, [b]: Welch t-test.

Table 2. Comparison of pineal gland and brain ventricle volume data between groups.

	Migraine group (n=21) (Mean±SD)	Control group (n=22) (Mean±SD)	Sig. (p)
Pineal gland volume (cm^3)	0.20±0.018	0.26±0.036	**p<0.001[a]**
Lateral ventricle volume (cm^3)	7.65±2.39	15.63±6.80	**p<0.001[b]**
Third ventricle volume (cm^3)	0.76±0.33	1.32±0.55	**p<0.001[b]**
Fourth ventricle volume (cm^3)	1.12±0.511	1.52±0.37	**0.005[a]**
Grey and White Matter (cm^3)	1135.98±96.07	1136.55±100.54	0.961[b]
Intracranial Cavity (cm^3)	1306.99±86.26	1313.27±96.99	0.791[a]

SD: Standard deviation, [a]: t-test, [b]: Welch t-test.

Table 3. Analysis of Covariance (ANCOVA) for the effects of group and intracranial cavity volume on pineal gland volume.

Source	SS	df	MS	F	Sig. (p)[c]	η^2
ANCOVA Model						
Group (Main Effect)	0.036	1	0.036	34.951	**<0.001**	0.473
Intracranial Cavity (Covariate)	0.001	1	0.001	0.750	0.392	0.019
Assumption Test						
Group x Intracranial Cavity	0.00025	1	0.00025	0.237	0.629	0.006
Error	0.040	39	0.001			

SS: Sum of Squares, MS: Mean Square, Model R Squared = 0,478 (Adjusted R Squared = 0.438), [c]: Analysis of covariance test. Note. The main effect of Group is interpreted as the interaction term was not significant.

DISCUSSION

This study demonstrated that individuals with migraine have significantly smaller pineal gland and cerebral ventricle volumes compared to healthy controls. These findings may be associated with the reduced melatonin levels and increased intracranial pressure frequently observed in migraine patients. Although multiple theories have been proposed regarding the pathophysiology of migraine, the role of reduced melatonin levels has recently attracted significant attention [19,6].

Located above the thalamus, the pineal gland plays a key role in regulating the body's physiological and circadian rhythms [8]. In addition to glial cells, the pineal gland contains endocrine cells known as pinealocytes, which are of photoreceptor origin and are responsible for synthesizing hormones, particularly melatonin [20]. Melatonin is one of the most potent natural antioxidants, capable of easily diffusing across cell membranes to neutralize reactive oxygen and nitrogen species [8].

The pineal gland's involvement in migraine is supported by studies demonstrating that melatonin supplementation reduces headache frequency and intensity [9,10,11]. In an experimental study, Tanuri et al. (2009) showed that rats subjected to pinealectomy exhibited increased c-fos positive cells associated with pain, and that melatonin administration significantly reduced the number of these cells [21]. Other animal studies have reported that melatonin modulates pain by reducing neuroinflammation [22,23].

Previous research has consistently shown that individuals with migraine tend to have lower melatonin levels [8,9,10,11]. These biochemical differences may be linked to the structural characteristics of the pineal gland, as melatonin secretion has been found to correlate with pineal volume [12,24]. Studies suggest that in healthy adults aged 25–65, the average pineal volume ranges between 0.22–0.24 cm^3 [25,26]. In the present study, the average pineal volume was 0.24 cm^3 in the control group compared to 0.19 cm^3 in the migraine group. This reduction in volume may reflect a diminished capacity for melatonin production, potentially contributing to the low melatonin levels reported in this population.

The cerebral ventricles—cavities within the central nervous system—play a crucial role in the production and circulation of cerebrospinal fluid (CSF) [14]. Beyond providing mecha-

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nical protection, the ventricles help maintain brain homeostasis by clearing metabolic waste and regulating CSF composition. Several studies suggest a potential link between CSF dynamics and migraine pathophysiology [15,16]. For instance, Chen et al. found a reduction in fourth ventricle volume in individuals with episodic migraine. Although we did not directly measure CSF pressure, alterations in ventricular volume may indirectly reflect changes in intracranial pressure [27].

While some studies have reported that longer migraine duration is associated with increased CSF volumes in the lateral and third ventricles, hinting at intracranial hypertension, our findings differ. Notably, although migraine and idiopathic intracranial hypertension share common risk factors, their pathophysiological mechanisms are distinct [15,16].

In our study, the reduced ventricular volumes observed in migraine patients may indicate restricted physical space for CSF, potentially leading to increased CSF pressure despite the smaller volume. The third ventricle is particularly significant in this context. The pineal gland, situated just above the roof of the third ventricle, secretes melatonin directly into the CSF via the pineal recess [28,29]. Consequently, melatonin concentrations in the ventricular system may be higher than in peripheral blood. CSF-delivered melatonin may suppress the activity of the trigeminovascular system, a key pathway in migraine pathogenesis [30,31]. Trigeminal neurons, similar to visceral sensory neurons, innervate the meninges and are directly involved in pain transmission [12,29,32]. In this study, the third ventricle volume in migraine patients was approximately 44% smaller than in controls. This reduction, combined with decreased pineal volume, may result in lower local melatonin concentrations and subsequent disinhibition of the trigeminovascular system, contributing to headache severity.

The cross-sectional design of the present study precludes establishing a causal relationship between reduced pineal gland volume and migraine. It remains uncertain whether the observed volumetric reduction represents a predisposing structural vulnerability contributing to migraine onset or a secondary adaptation resulting from the chronic course of the disorder. Previous neuroimaging studies have shown that prolonged pain exposure and recurrent nociceptive activation can induce microstructural and volumetric alterations in brain regions associated with pain modulation and circadian regulation [33,34]. Similarly, long-term alterations in melatonin secretion secondary to repeated attacks could lead to pineal gland remodeling or atrophy over time [8,28]. Therefore, the reduced pineal volume observed here likely reflects a complex interaction between predisposing neuroendocrine dysregulation and chronic disease-related neuroplasticity. Longitudinal studies integrating volumetric, biochemical, and clinical data are required to disentangle this bidirectional relationship.

Neuroimaging has previously revealed functional and microstructural alterations in migraine patients, particularly in pain processing regions such as the brainstem, hypothalamus, basal ganglia, and cerebral cortex [27,33,34]. The present study suggests that the pineal gland and cerebral ventricles should be added to the list of structures undergoing microstructural changes in the migraine brain.

Limitations

This study has several limitations. First, only patients with migraine without aura were included; future studies should examine different migraine subtypes. Second, the sample size was relatively small; however, a post-hoc analysis indicated sufficient statistical power for the main outcome. Third, although we attempted to control for confounding variables, factors such as lifestyle, medication use, and genetic predisposition were not comprehensively analyzed. Lastly, the study relied solely on volumetric MRI data; integrating functional imaging and biochemical markers would provide a more comprehensive understanding of structural-functional correlations. Addressing these limitations in future research will strengthen the clinical implications of these findings.

CONCLUSION

These findings demonstrate that individuals with migraine have significantly smaller pineal gland and cerebral ventricle volumes compared to healthy controls. Notably, the reduction in pineal gland volume appears to be independent of overall brain size, suggesting a specific structural alteration in the migraine brain that may contribute to the underlying pathophysiology of the disorder.

Ethics Committee Approval: Ethical approval was obtained from the Institutional Review Board of Hitit University, Çorum, Turkey (Date: February 28, 2024; Decision No: 2024-04).

Informed Consent: Written informed consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors have no conflict of interest to declare.

Author Contributions: AP: Conception, Design, Supervision, Fundings, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing, Critical Review. HA: Fundings, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review. ŞG: Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review. YG: Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review. HY: Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing. HK: Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Literature Review, Writing, Critical Review.

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