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ORIGINAL ARTICLE

# Changes in the hippocampal volume in chronic migraine, episodic migraine, and medication overuse headache patients

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**Background and purpose** – Hippocampi are the structures located in the medial depths of both temporal lobes, mainly responsible for memory, navigation and regulation of emotions, and activated during the processing of pain and the modification of nociceptive stimuli. Chronic pain is thought to have stress-like detrimental modulatory effects on the hippocampal neurogenesis, and adults with chronic pain have been showed to have lower hippocampal volumes. The present study aims to show the relationship between headaches and hippocampal volume by comparing the right, left and total hippocampal volumes of patients with Episodic Migraine (EM), Chronic Migraine (CM) and Medication Overuse Headache (MOH) to those of the healthy control group using the Magnetic Resonance Imaging (MRI) technique, also by looking into the correlation between the number of painful days and attacks and the current hippocampal volumes.

**Methods** – A total of 30 patients (10 EM, 10 CM, 10 MOH) from 18 to 45 years of age diagnosed with migraine and also followed up by the neurology outpatient clinic from February to May 2022 and 30 healthy volunteers of similar ages and sexes to the patient group were included in the study. In addition to the routine cranial MRI protocols of all the participants, further cranial images were taken with the addition of the T1W 3D FSPGR sequence adjusted to the hippocampal body in the coronal plane and covering the whole brain. Hippocampal volumes were measured manually.

**A hippocampus-térfogat változásai krónikus migrénben, epizodikus migrénben és gyógyszer-túlhasználat miatti fejfájásban**

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**Háttér és cél** – A hippocampusok a két halántéklebeny medialis mélyén elhelyezkedő struktúrák, amelyek elsősorban a memóriáért, a navigációért és az érzelmek szabályozásáért felelősek, és a fájdalom feldolgozása, valamint a nociceptiv ingerületek módosítása során aktiválódnak. A krónikus fájdalomról úgy gondolják, hogy stressz-szerű káros moduláló hatással van a hippocampalis neurogenezisre, és a krónikus fájdalomban szenvedő felnőtteknél kimutatták, hogy kisebb a hippocampalis térfogatuk. Jelen tanulmány célja, hogy bemutassa a fejfájás és a hippocampus térfogata közötti összefüggést az epizodikus migrénben (EM), krónikus migrénben (CM) és gyógyszer-túlhasználat okozta fejfájásban (MOH) szenvedő betegek jobb, bal és teljes hippocampalis térfogatának az egészséges kontrollcsoport hippocampalis térfogatainak összehasonlítása révén mágneses rezonancia képalkotó (MRI) technika segítségével, továbbá a fájdalmas napok, valamint a rohamok száma és az aktuális hippocampalis térfogat közötti összefüggés vizsgálatával.

**Módszerek** – A vizsgálatba összesen 30, 18 és 45 éves kor közötti, migrénnel diagnosztizált és a neurológiai ambulancián 2022 februárjától májusáig követett beteget (10 EM, 10 CM, 10 MOH), valamint 30, a betegcsoporthoz hasonló korú és nemű egészséges önkéntest vontunk be. Az összes résztvevő rutin koponya-MRI-protokolljain kívül további koponyafelvételeket készítettünk a hippocampus testéhez igazított T1W 3D FSPGR szekvenciával kiegészítve a coronalis síkban, az egész agyat lefedve. A hippocampus térfogatát manuálisan mértük.

**Results** – There were 27 females and 3 males in the patient group versus 28 females and 2 males in the control group, and no statistically significant differences in age and sex were found between the groups. The control group had higher average right, left and total hippocampal volumes than the whole patient group, but only the total hippocampal volume was significantly different between the groups. There was a negative correlation between the number of painful days and the measured right hippocampal and total hippocampal volumes; however, the measured values were not statistically significant.
**Conclusion** – It was concluded that the changes in the hippocampal volume in migraine might be associated with the pain characteristics of the disorder.

**Keywords:** episodic migraine, chronic migraine, medication overuse headache, hippocampus

**Eredmények** – A betegcsoportban 27 nő és három férfi volt, míg a kontrollcsoportban 28 nő és két férfi. A csoportok között nem volt statisztikailag szignifikáns különbség sem az életkor, sem a nem tekintetében. A kontrollcsoportban az átlagos jobb, bal és teljes hippocampus-térfogatok nagyobbak voltak, mint a teljes betegcsoporté, de csak a teljes hippocampus-térfogat különbözött szignifikánsan a kontroll- és a betegcsoport között. Negatív korreláció volt a fájdalmas napok száma és a jobb, valamint a teljes hippocampus-térfogatok között; a mért értékek azonban statisztikailag nem voltak szignifikánsak.
**Következtetés** – Arra a következtetésre jutottunk, hogy a hippocampus térfogatának változása migrénben összefügghet a betegség fájdalomjellemzőivel.

**Kulcsszavak:** epizodikus migrén, krónikus migrén, gyógyszer-túlhasználat okozta fejfájás, hippocampus

Hippocampi are the structures located in the medial depths of both temporal lobes and are mainly responsible for memory, navigation, and regulation of emotions. Hippocampus, together with the amygdala, the prefrontal cortex and the cingulate gyrus, makes up the limbic system. Furthermore, by keeping the cortisol at a certain level, the hippocampus controls the stress response triggered by the amygdala through negative feedback mechanism on the hypothalamic-pituitary-adrenal axis[1].

Animal studies have found some changes which are thought to cause post-stress loss of hippocampal volume, i.e. extensive cell shrinkage, apoptosis, loss of astrocytes, changes in the cerebrospinal fluid balance, reduced gliogenesis, and loss of neurogenesis capacity in the dentate gyrus, with dendritic debranching being the most common of them all[2].

Hippocampus is also one of the brain regions playing a key role in the modulation of pain signals; it is activated during the pain processing and the modification of nociceptive stimuli. Chronic pain affects the plasticity of the hippocampal mossy fiber-CA3 synapses and the neurogenesis in the dentate gyrus[3]. It has been shown that elderly adults having severe acute pain or chronic pain have lower hippocampal volumes and lower hippocampal N-acetylaspartate-to-creatine (NAA/Cr) ratio, which is an indicator of the loss of neuronal integrity and neurons[4]. These hippocampal changes suggest that chronic pain has stress-like detrimental modulatory effects on hippocampal neurogenesis[5]. Furthermore, it has been found that TNF-α, a proinflammatory cytokine, plays a role in neuropathic pain and is associated with the dysfunctions of the hippocampal neurogenesis. Neuropathic pain has been found to cause the development of symptoms of depression over time, and to be associated with impaired neurogenesis and also with the reduction in the expression of the neuroplasticity markers and myelin basic proteins[6].

Based on all the above data, the present study aims to show the relationship between headaches and hippocampal volume by comparing the right, left and total hippocampal volumes of the patients with Episodic Migraine (EM), Chronic Migraine (CM) and Medication Overuse Headache (MOH) to those of the healthy control group using the MRI technique, also by looking into the correlation between the number of painful days and attacks and the current hippocampal volumes.

## Methods

### Selection of patients

A total of 30 patients from 18 to 45 years of age diagnosed with no other neurological disorders than migraine by headache specialist and also followed up by the neu-

rology outpatient clinic from February to May 2022 were prospectively included in the study. The International Classification of Headache Disorders-3 (ICHD-3) was used for diagnoses[7]. The other group included in the study, i.e. the healthy control group, comprised 30 volunteers who presented to the neurology outpatient clinic with complaints like hypoesthesia in hands (carpal tunnel syndrome) or dizziness, had normal results from their neurological examinations with no known neurological disorders, were given cranial MRI scans, and were of similar ages to the migraine patient group. All the participants gave their informed consent for the present study.

Both for the patient and the healthy volunteer groups, individuals who were diagnosed with depression, had a history of chronic diseases such as diabetes and hypertension, chronic pain, or had malignancies, could not tolerate MRI scanning or had suboptimal MRI results due to artifacts, or could not undergo volumetric MRI were excluded from the study.

### MRI protocol

The MRI scans for all the study participants were performed using General Electric's Optima™ MR450w 1.5T system. In addition to the routine cranial MRI protocols, further cranial images were taken with the addition of the T1W 3D FSPGR sequence adjusted to the hippocampal body in the coronal plane and covering the whole brain (TR/TE: 5412/1.94, flip angle: 15°, matrix: 192x256, FOV: 250 mm, number of sagittal slices: 284, slice thickness: 1 mm). Axial and sagittal multiplanar reconstructed images were acquired through coronal T1W 3D FSPGR sequence images.

The acquired MR images were evaluated using the software Volume Viewer, version 13.0 and the hippocampus was identified from the anatomical reference points[8]. The present study used 3D modelling for volumetric calculations and the hippocampal volume was measured manually by neurologist. The alveus for anterior and superior borders, the atrium of the lateral ventricle for posterior border, the white matter of the parahippocampal gyrus below the subiculum for inferior border, the cerebrospinal fluid (CSF) of the lateral ventricle for lateral border, the CSF of the cisterna ambiens for superior medial and the straight line that tracing with an angle of 45° from the most inferior part of the hippocampal body to the cisterna ambiens for inferior medial border were taken as reference points[9]. The hippocampal volume measurement unit was $cm^3$.

### Statistical method

The software IBM SPSS™ (Version 22, New York/USA) was used for statistical analyses. Independent t-test was used to compare the migraine and non-migraine groups in terms of age, and sex. Due to the small number of subjects in the groups, the volume comparison of the right hippocampus, left hippocampus and total hippocampus was made with the One-Way ANOVA test and Bonferroni correction was applied. Within the migraine group, Spearman's correlation test was used to determine the correlation between the number of painful days in a month and the right hippocampal volume, left hippocampal volume, and total hippocampal volume. The value $p \leq 0.05$ was accepted as the measure of statistical significance.

As a result of power analysis, it was planned to work with at least 27 individuals in each group and a total of 54 people as a result of minimum 80% power and maximum 5% type error.

## Results

The study group comprised 60 individuals. It was divided into the sub-groups of 30 healthy controls (50%), 10 EM patients (16.7%), 10 CM patients (16.7%), and 10 MOH patients (16.7%). The patient group consisted of 27 females and 3 males while the control group comprised 28 females and 2 males. Mean ages were 30,27±5.98 years in the control group and 33.47±7.75 years in the patient group, and there were no statistically significant differences in sex and age between the groups.

The average numbers of painful days in a month were 3.3±2.21, 16.3±1.77, and 18±2.31 for the EM, CM, and MOH groups, respectively, and the total average number of painful days in a month for 30 patients was 12.53±6.98. Across the whole patient group, the average right hippocampal volume was 2.51±0.33 $cm^3$, the average left hippocampal volume was 2.43±0.38 $cm^3$, and the total hippocampal volume was 4.93±0.67 $cm^3$. In the control group these volumes were 2.59±0.36, 2.51±0.36, and 5.1±0.67 $cm^3$, respectively, which showed that all the volumetric values of the control group were higher compared to those of both the whole patient group comprising 30 patients and the sub-groups **(Table 1)**.

The correlation analysis performed to determine the correlation between the number of painful days and the measured right, left and total hippocampal volumes revealed that there was a negative correlation between the number of painful days and the measured right hippocampal and total hippocampal volumes, which meant that the hippocampal volume decreased as the number of painful days increased; however, the measured values were not statistically significant (p=0.847, 0.496, 0.842, respectively).

When only the patient group and the control group were considered without any sub-group analysis, the control group had higher average right, left and total hip-

**Table 1.** *Descriptive statistics of the patient and control groups*

| | Control | Episodic migraine | Chronic migraine | Medication overuse headache | Total (Patient) |
|---|---|---|---|---|---|
| | Avg. ± Std. | Avg. ± Std. | Avg. ± Std. | Avg. ± Std. | Avg. ± Std. |
| Number of painful days (days/month) | | 3.3±2.21 | 16.3±1.77 | 18±2.31 | 12.53±6.98 |
| Right hippocampal volume ($cm^3$) | 2.59±0.36 | 2.41±0.31 | 2.52±0.37 | 2.35±0.2 | 2.43±0.30 |
| Left hippocampal volume ($cm^3$) | 2.51±0.36 | 2.23±0.46 | 2.5±0.35 | 2.29±0.29 | 2.34±0.38 |
| Total hippocampal volume ($cm^3$) | 5.1±0.67 | 4.64±0.72 | 5.02±0.67 | 4.64±0.44 | 4.77±0.63 |

pocampal volumes than the whole patient group, and the average total hippocampal volume was found to be significantly different between the control and patient groups (p=0.05) **(Table 2)**.

The sub-group analyses further showed that there was no statistically significant difference in the right, left and total hippocampal volumes between the EM, CM, and MOH sub-groups **(Table 3)**.

**Table 2.** *Comparison of right, left and total hippocampal volumes of the groups*

| | Control | Patient | t | p |
|---|---|---|---|---|
| Right hippocampal volume ($cm^3$) | 2.59±0.356 | 2.43±0.297 | 1.876 | 0.066 |
| Left hippocampal volume ($cm^3$) | 2.51±0.359 | 2.34±0.377 | 1.803 | 0.077 |
| Total hippocampal volume ($cm^3$) | 5.10±0.672 | 4.77±0.63 | 1.964 | *0.05* |

**Table 3.** *Comparison of right. left and total hippocampal volumes of the sub-groups with One-Way ANOVA. bonferroni correction*

| | | N | Mean | Std. Deviation | F | p |
|---|---|---|---|---|---|---|
| Right hippocampal volume ($cm^3$) | Control | 30 | 2.59 | .36 | 1.628 | .193 |
| | EM | 10 | 2.41 | .31 | | |
| | CM | 10 | 2.52 | .37 | | |
| | MOH | 10 | 2.35 | .20 | | |
| Left hippocampal volume ($cm^3$) | Control | 30 | 2.51 | .36 | 2.090 | .112 |
| | EM | 10 | 2.23 | .46 | | |
| | CM | 10 | 2.50 | .35 | | |
| | MOH | 10 | 2.29 | .29 | | |
| Total hippocampal volume ($cm^3$) | Control | 30 | 5.10 | .67 | 2.063 | .115 |
| | EM | 10 | 4.64 | .72 | | |
| | CM | 10 | 5.02 | .67 | | |
| | MOH | 10 | 4.64 | .44 | | |

## Discussion

Migraine is known to be a common neurological disorder and characterized by the attacks of throbbing headaches accompanied by phonophobia, photophobia, and nausea[10]. It has conventionally been reported to be a disorder with no long-term effects on the brain. However, the recent data show that migraine increases the risk of the development of silent brain findings in the patients such as white matter lesions, ischemic lesions and volumetric changes in both gray and white matter seen in MRI. These changes have been found to progress together with an increased number of migraine attacks which represent a form of the anatomical progression of the disorder[11, 12].

Studies using the structural and functional imaging of CM have found changes in the cortex, basal ganglia, brain stem and the hypothalamus involved in pain modulation. While these changes may be associated with the severity and/or duration of headaches, it has also been suggested that they might be linked with the cognitive status, sleep pattern and/or mood of the person[13]. *Gudmundsson* et al. found that patients with migraine and depression had reduced total brain volumes, white matter and gray matter volumes compared to healthy controls and also to migraine alone or depression alone groups[14]. While the detected changes indicated the neural plasticity occurring in migraine, it could not be determined whether these changes represented the etiology or the result of the chronicity. A study by *Naguib* et al. showed that chronic migraine patients had significantly lower total brain

volumes, and thickness of gray matter, cerebellum and frontal lobe compared to episodic migraine patients[15]. On the other hand, the same study could not determine the mechanism of the reshaping of the brain in migraine; it suggested that the mechanism might be associated with the variations related to the number, size and synapses of neurons and glial cells, various interstitial fluids or blood flow, and caused by neuroinflammation, vasoconstriction or vasodilation, and neuronal degeneration.

The accumulated evidence suggests the role of a maladaptive stress response in the migraine mechanism especially in chronic migraine[16]. Although previous studies have detected the changing volume of the hippocampus time and time again, the aspects of this change are not entirely consistent. Patients experiencing 1-2 painful days a month have been shown to have higher hippocampal volumes on both right and left sides compared to patients experiencing 8-14 painful days a month and to healthy controls, and it has been determined that there is a negative correlation between the hippocampal volume and the estimated number of attacks. Another study categorizing patients into 8 different sub-groups based on the number of painful days from 1 to 30 a month found the highest hippocampal volume in the patients having 5-7 painful days[17] . These two studies suggested that the hippocampus showed an adaptive plasticity in lower frequencies of headaches and higher frequencies caused a maladaptive reduction in the hippocampal volume[16, 17]. Our study, as well, highlighted a negative correlation between the number of painful days and the right and total hippocampal volumetric values investigated without any sub-group analyses; however, the values were not statistically significant. On the other hand, our study did not find any correlation with the left hippocampal volume.

While *Hubbard* et al. found increased left hippocampal volumes in migraine patients compared to healthy controls, Chong et al. reported the opposite and could not associate the hippocampal volumes with the duration of disorder or frequency of headaches[18, 19]. Another study showed that hippocampal volumes of the healthy controls were lower than those of the EM group while higher than those of the CM group. This finding was found to be consistent with the findings of the two aforementioned cross-sectional studies suggesting an adaptive increased volume in low frequencies of headache and a maladaptive reduced volume in higher frequencies, and it also proved the necessity of comparing the migraine patients having different frequencies of headache while investigating the changes in brain circuits related to the hippocampus[20]. While our study did not find any statistically significant results from the comparison of the right, left and total hippocampal volumes of the EM and CM patients with those of the healthy controls, the volumetric values for both sub-groups were lower compared to the healthy controls with the EM subgroup having the lowest values.

The pathogenesis of MOH, which is still difficult to understand, involves central sensitization and the dysfunction of the endogenous serotonin system[21, 22]. Considering neuroimaging studies, the study by *Lai* et al. comparing the MOH patients with healthy controls showed gray matter atrophy in the gyrus rectus, inferior frontal gyrus, medial frontal gyrus, and precuneus[23]. Supporting the findings of our study, *Mehnert* et al. discovered the MOH-related gray matter atrophy in the medial orbital gyrus, hippocampus, inferior frontal gyrus, and precuneus[24]. On the other hand, several studies reported they could not find any gray matter changes in the MOH group compared to the control group[25]. In conclusion, there have been only few volumetric brain imaging studies related to the MOH so far. Our study compared the hippocampal volumes of the MOH patients with those of the healthy controls and found that the volumetric values for MOH were lower compared to the control group's values but there were no statistically significant differences.

It was though that the hippocampal volume changes in migraine might be associated with the pain characteristics of the disorder and the amount of medication used, however it was found that factors such as migraine subtype, frequency of attacks, cumulative number of migraine attacks, anxiety, and depression affected the hippocampal volume and there were inconsistent findings in the literature. Further studies would ensure a clearer determination of the relationship between the hippocampus and migraine by way of careful selection of sub-groups and eliminating the influencing factors.

## Limitations

Disease duration was not included in the study because patients declared a wide range of disease duration. The number of patients in the subgroups were underpowered compared to the control group; we couldn't separate the subgroups according the type of medications like triptans or non-steroidal anti-inflammatory drugs. We also could not evaluate whether the presence or absence of aura had an effect on hippocampal volume. This study was cross-sectional; we could not comment on the effects of the preventive drugs that the patients used before or after the diagnosis, on hippocampal volume.

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