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Original Article

Choroid Plexus Enlargement in Patients with Chronic Migraine: Implications for Glymphatic System Dysfunction

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ABSTRACT: ***Objectives:*** The choroid plexus produces cerebrospinal fluid, which is crucial for glymphatic system function. Evidence suggests that changes in the volume of the choroid plexus may be associated with glymphatic system function. Therefore, this study aimed to investigate alterations in choroid plexus volume in patients with migraines compared with healthy controls. ***Methods:*** We enrolled 59 patients with migraines (39 and 20 with episodic and chronic migraines, respectively) and 61 healthy controls. All participants underwent brain magnetic resonance imaging, including three-dimensional T1-weighted imaging. We analyzed and compared choroid plexus volumes between patients with episodic migraines, those with chronic migraines and healthy controls. Additionally, we evaluated the association between choroid plexus volume and the clinical characteristics of patients with migraine. ***Results:*** The choroid plexus volume in patients with chronic migraines was higher than that in healthy controls (2.018 vs. 1.698%, $p = 0.002$) and patients with episodic migraines (2.018 vs. 1.680%, $p = 0.010$). However, no differences were observed in choroid plexus volumes between patients with episodic migraine and healthy controls. Choroid plexus volume was positively correlated with age in patients with migraines ($r = 0.301$, $p = 0.020$) and in healthy controls ($r = 0.382$, $p = 0.002$). ***Conclusion:*** We demonstrated significant enlargement of the choroid plexus in patients with chronic migraine compared with healthy controls and those with episodic migraine. This finding suggests that chronic migraine may be associated with glymphatic system dysfunction.

Résumé: L'influence de l'hypertrophie des plexus choroïdes sur le dysfonctionnement du systéme glymphatique chez les patients atteints de migraine chronique. ***Objectif :*** Les plexus choroïdes produisent le liquide céphalorachidien, formations qui jouent un rôle très important dans le fonctionnement du système glymphatique. D'après des données scientifiques, les changements de volume des plexus choroïdes pourraient être associés au fonctionnement du système glymphatique. Aussi l'étude visait-elle à examiner et à comparer les changements de volume des plexus choroïdes chez les personnes atteintes de migraine et chez des témoins en bonne santé. ***Méthode :*** Au total, 59 patients atteints de migraine (39 et 20 atteints de migraine épisodique et de migraine chronique, respectivement) et 61 témoins en bonne santé ont participé à l'étude. Tous les sujets ont subi des examens d'imagerie du cerveau par résonance magnétique, dont l'un par imagerie en trois dimensions et pondérée en T1. Ensuite, il y a eu analyse du volume des plexus choroïdes, puis comparaison des données entre les patients atteints de migraine épisodique, ceux atteints de migraine chronique et les témoins en bonne santé. En outre, l'équipe a évalué l'association du volume des plexus choroïdes avec les caractéristiques cliniques des migraines. ***Résultats :*** Le volume des plexus choroïdes chez les patients atteints de migraine chronique était plus gros que celui observé chez les témoins en bonne santé (2,018 contre [c.] 1,698 %; $p = 0{,}002$) et chez les patients atteints de migraine épisodique (2,018 c. 1,680 %; $p = 0{,}010$). Par contre, aucune différence n'a été relevée quant au volume des plexus choroïdes entre les patients atteints de migraine épisodique et les témoins en bonne santé. Enfin, une corrélation positive a été établie entre le volume des plexus choroïdes et l'âge chez les patients atteints de migraine ($r = 0{,}301$; $p = 0{,}020$) et chez les témoins en bonne santé ($r = 0{,}382$; $p = 0{,}002$). ***Conclusion :*** Les résultats de l'étude ont permis de démontrer l'existence d'une augmentation importante du volume des plexus choroïdes chez les patients atteints de migraine chronique comparativement aux témoins en bonne santé et aux patients atteints de migraine épisodique. Cette constatation donne à penser que la migraine chronique pourrait être associée au dysfonctionnement du système glymphatique.

Keywords: choroid plexus; glymphatic system; neuroimaging; MRI; migraine

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Highlights

- Choroid plexus volume was significantly larger in patients with chronic migraines compared to healthy controls and episodic migraine patients, suggesting glymphatic dysfunction.
- No significant differences were found between episodic migraine patients and healthy controls.
- Choroid plexus volume positively correlated with age in migraine patients, indicating potential age-related changes.

Introduction

Migraine is a recurring condition characterized by intense headaches, often accompanied by nausea or vomiting and sensitivity to light and sound.[1] It is a common neurological disease that reduces a patient's quality of life.[2] Numerous studies conducted to understand the pathophysiological mechanism of migraine have suggested several key mechanisms and pathways. These mechanisms include genetic predisposition, cortical spreading depression, trigeminovascular system activation, central sensitization, neurotransmitter abnormalities, brain network changes and the role of calcitonin gene-related peptide (CGRP).[3–6] However, the exact pathophysiological mechanism remains unclear.

Research has increasingly focused on the association between glymphatic system dysfunction and neurological disorders.[7] The glymphatic system is a waste clearance pathway in the brain that helps remove metabolic waste products and proteins, including amyloid-beta, from the brain.[7] A growing research body highlights the importance of the glymphatic system in maintaining brain health and its potential role in the pathogenesis and progression of various neurological disorders such as Alzheimer's dementia, Parkinson's disease, epilepsy, obstructive sleep apnea, restless legs syndrome and cluster headache.[8–13]

Several imaging techniques can evaluate glymphatic system function. Two-photon microscopy allows real-time observation of glymphatic flow at the microscopic level and is used in animal models owing to its invasiveness. Magnetic resonance imaging (MRI) is primarily used to study the glymphatic system in humans, with various methods, including intrathecal contrast-enhanced MRI, enlarged perivascular space counting, diffusion tensor image analysis along the perivascular space (DTI-ALPS) index and phase contrast method.[14] Another accessible method is to measure choroid plexus volumes. The choroid plexus produces cerebrospinal fluid (CSF), which is crucial for the function of the glymphatic system. Evidence suggests that changes in choroid plexus volume may be associated with glymphatic system dysfunction.[15,16] This method does not require a contrast agent, is noninvasive and can be analyzed using only three-dimensional T1-weighted images.

Recently, a few studies have reported an association between migraines and glymphatic system dysfunction, although these findings have been contradictory. One study explored this relationship using the nitroglycerin migraine model in C57/BL6 mice and found a reduced glymphatic influx of CSF tracer in the migraine model.[17] Another human study utilized the DTI-ALPS index and dynamic contrast-enhanced MRI to demonstrate glymphatic system dysfunction in patients with migraine, especially those with chronic migraine.[16] However, a study using the DTI-ALPS index showed no difference in glymphatic system function between patients with episodic migraine and healthy controls.[18] Additionally, a large population-based study observed no increase in MRI-visible enlarged perivascular space in patients with migraine compared with headache-free participants.[19] Therefore, further research on glymphatic system function in patients with migraine is needed.

In this study, we aimed to evaluate the alterations of choroid plexus volume in patients with migraine compared with healthy controls. Given our hypothesis that glymphatic system function varies with headache frequency, we categorized patients with migraine into episodic and chronic migraine groups for analysis.

Methods

Participants

This study received approval from the Institutional Review Board of our hospital and was prospectively conducted at a single institution. It enrolled 59 newly diagnosed patients with migraines without migraine aura following the International Classification of Headache Disorders, 3rd edition.[1] These patients had no history of neurological or psychiatric disorders at enrollment, and no structural brain lesions were detected on MRI scans. All of the patients had no prior history of prophylactic use of antimigraine medication and were not taking any medications at the time of enrollment. Clinical characteristics, including age, age at onset of migraine, headache frequency per month, duration of migraine and headache intensity (measured using a visual analog scale), were recorded. The duration of migraine was defined as the period from the onset of the first migraine headache to the time of MRI acquisition. Based on headache frequency, patients with migraine were categorized into two groups: 39 with episodic migraine (headache < 15 days per month) and 20 with chronic migraine (headache ≥ 15 days per month). Additionally, a control group of 61 healthy participants, matched for age and sex with patients with migraines, was enrolled. Control participants had no medical, neurological or psychiatric history and showed no structural brain lesions on MRI scans.

MRI acquisition

Patients with migraines and healthy controls underwent brain MRI using the same sequence on a 3T-MRI scanner equipped with a 32-channel head coil from Achieva (Philips Healthcare, Best, Netherlands). Three-dimensional T1-weighted images were acquired using a turbo-field echo sequence with the following parameters: inversion time = 1300ms, repetition time/echo time = 8.6/3.96 ms, flip angle = 8° and voxel size of 1 mm^3 isotropic. There were no migraine attacks during MRI scans.

Choroid plexus volume analysis

The choroid plexus segmentation in the bilateral lateral ventricle was semi-automatically performed using a Gaussian mixture model-based segmentation with slight modifications to a previously reported method.[20] Briefly, T1-weighted images were corrected for bias field using the Sequence Adaptive Multimodal Segmentation pipeline.[21] Subsequently, the volumes of the right and left lateral ventricle masks and the segmentation-based total intracranial volume were acquired using SynthSeg with the bias-corrected images as input.[22] The Gaussian mixture model was then applied to the bias-corrected T1-weighted images to differentiate the choroid plexus from the CSF and ventricular walls, identifying distinct clusters of voxel intensities within the lateral ventricle masks. A board-certified neuroradiologist with 10 years' experience examined and refined the choroid plexus masks resulting from the automated

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Table 1. Demographic and clinical characteristics of patients with migraine and healthy controls

	Patients with migraine (N = 59)	Healthy controls (N = 61)	SMD	*p*-value
Age, years (±SD)	37.7 (±10.9)	38.0 (±8.1)	0.003	0.870
Men, n (%)	9 (15.3)	7 (11.5)	0.111	0.544
Age of onset, years (interquartile range)	28.5 (18.5–35.0)			
Disease duration, months (interquartile range)	120 (60–240)			
Attack frequency per month, n (interquartile range)	3.5 (2.0–17.0)			
Headache intensity, visual analog scale (interquartile range)	7.0 (6.0–8.0)			
	Patients with chronic migraine (N = 20)	**Patients with episodic migraine (N = 39)**	**SMD**	***p*-value**
Age, years (±SD)	38.2 (±9.9)	37.4 (±11.6)	0.073	0.796
Men, n (%)	4 (20.0)	5 (12.8)	0.195	0.471
Age of onset, years (interquartile range)	27.0 (17.0–35.0)	29.0 (20.0–36.0)	0.224	0.454
Disease duration, months (interquartile range)	120 (36–246)	120 (60–240)	0.083	0.940
Attack frequency per month, n (interquartile range)	19.5 (16.5–26.5)	2.0 (1.0–3.0)	4.162	<0.001
Headache intensity, visual analog scale (interquartile range)	6.0 (5.0–8.0)	7.0 (6.0–8.0)	0.230	0.341

SMD = standardized mean difference; SD = standard deviation.

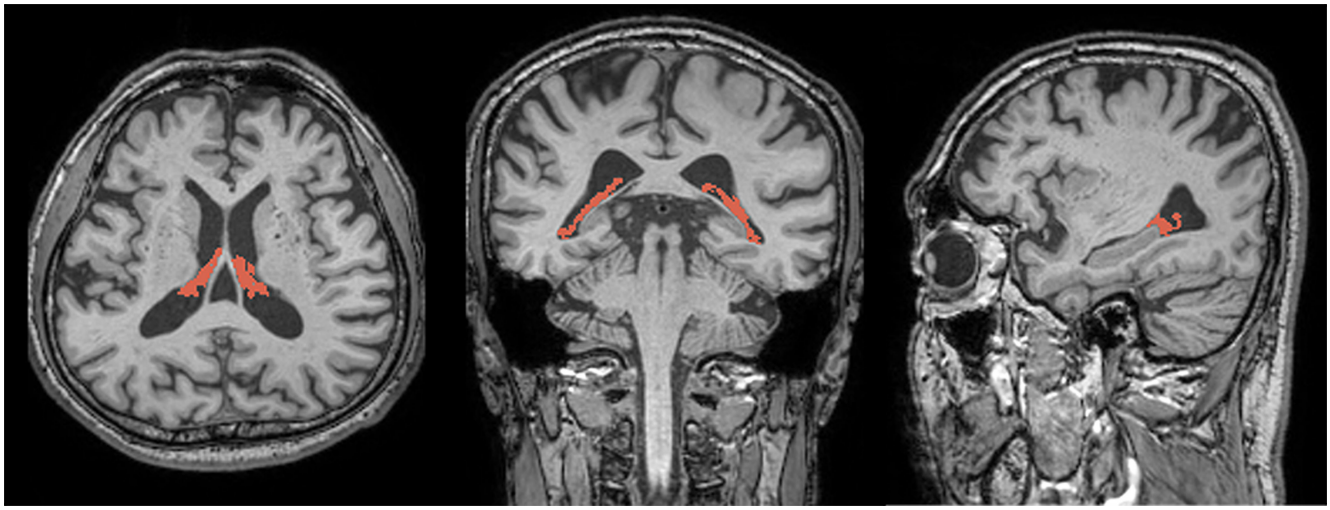


Figure 1. Representative images showing choroid plexus segmentation (red) overlaid on three-dimensional T1-weighted magnetic resonance images in the axial (left), coronal (center) and sagittal (right) planes.

pipeline to remove any non-choroid plexus areas, such as septum pellucidum, ventricular walls, flow artifacts or noise within the CSF. The volumes of the final masks (Figure 1) were calculated and normalized using the segmentation-based total intracranial volume. Thus, the calculated choroid plexus volume was divided by the total intracranial volume and multiplied by 100 to obtain the final result.

Statistical analysis

Categorical variables were compared using the chi-square test, and continuous variables were compared using the independent *t*-test. Pearson's correlation test was used to quantify the association between the choroid plexus volume and clinical characteristics in participants. We also investigated the differences in choroid plexus volumes between groups using an analysis of covariance, with age as a covariate. Statistical significance was set at a *p*-value of < 0.05 for all calculations. A *p*-value of 0.0166 or less (0.05 divided by 3) was judged to be significant because differences in choroid plexus volumes were a comparison of three groups (patients with episodic migraine, those with chronic migraine and healthy controls). In addition, standardized mean difference (SMD) was used to assess the magnitude of differences between groups, with an SMD < 0.1 indicating negligible differences, and SMD < 0.25 considered an acceptable level of balance for adjusted variables. Statistical analyses were conducted using R studio version 4.4.1 (RStudio Inc.; https://www.r-project.org) and MedCalc® Statistical Software version 22.016 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2023).

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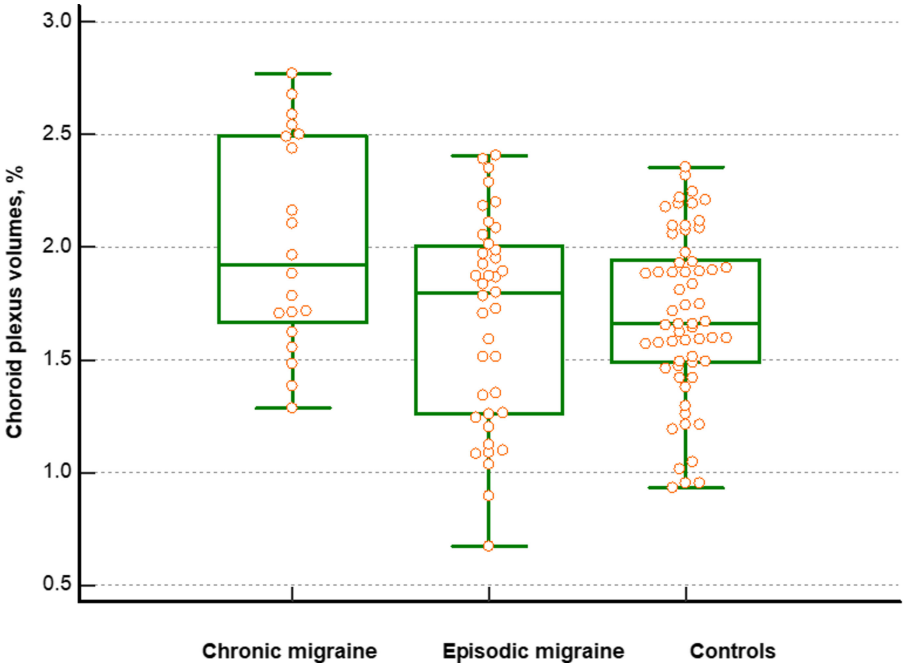


Figure 2. Differences in choroid plexus volumes between patients with migraine and healthy controls. The figure shows that choroid plexus volumes in patients with chronic migraines were higher than those in healthy controls (2.018 vs. 1.698%, $p = 0.002$) and patients with episodic migraines (2.018 vs. 1.680%, $p = 0.010$).

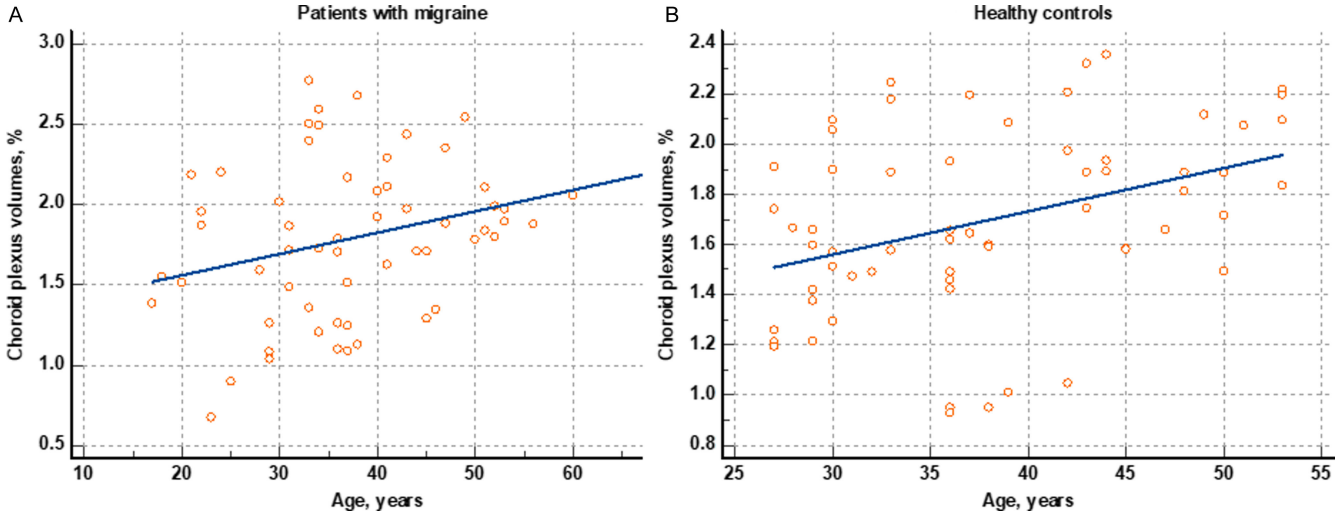


Figure 3. Correlation between choroid plexus volumes and age in participants. Choroid plexus volume was positively correlated with age in patients with migraines ($r = 0.301$, $p = 0.020$) (A) and healthy controls ($r = 0.382$, $p = 0.002$) (B).

Results

Demographic and clinical characteristics of participants

Table 1 presents the demographic and clinical characteristics of the participants. Age and sex did not differ between patients with migraines and healthy controls (age, 37.7 vs. 38.0 years, $p = 0.870$; men, 9/59 (15.3%) vs. 7/61 (11.5%), $p = 0.544$). Additionally, no differences in age or sex were observed between patients with chronic migraine and those with episodic migraine (age, 38.2 vs. 37.4 years, $p = 0.796$; men, 4/20 (20.0%) vs. 5/39 (12.8%), $p = 0.471$).

Choroid plexus volumes

The choroid plexus volumes were higher in patients with chronic migraines than in healthy controls (2.018 vs. 1.698%, $p = 0.002$; adjusting for age, $p = 0.007$) and patients with episodic migraines (2.018 vs. 1.680%, $p = 0.010$; adjusting for age, $p = 0.009$)

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(Figure 2). However, no differences in choroid plexus volumes were observed between patients with episodic migraine and healthy controls.

There were no differences in the lateral ventricular volumes between patients with chronic migraines and healthy controls (5.224 vs. 5.954%, $p = 0.213$), and between patients with chronic migraine and those with episodic migraine (5.224 vs. 4.896%, $p = 0.502$).

Correlation between choroid plexus volumes and clinical characteristics in patients with migraine

Choroid plexus volumes were positively correlated with age in patients with migraines ($r = 0.301$, $p = 0.020$) (Figure 3A). However, choroid plexus volumes were not associated with other clinical characteristics in patients with migraine, such as age of onset ($r = 0.145$, $p = 0.304$), headache frequency per month ($r = 0.210$, $p = 0.120$), migraine duration ($r = 0.084$, $p = 0.566$) and headache intensity ($r = -0.187$, $p = 0.198$).

In addition, choroid plexus volumes were positively correlated with age in healthy controls ($r = 0.382$, $p = 0.002$) (Figure 3B).

Discussion

Choroid plexus volumes were higher in patients with chronic migraine than in healthy controls and patients with episodic migraine, suggesting glymphatic system dysfunction may be related to chronic migraine. However, no differences in choroid plexus volumes were observed between patients with episodic migraine and healthy controls. Additionally, choroid plexus volume was positively correlated with age in patients with migraines.

The choroid plexus is a vascular tissue located within the four ventricles of the brain and plays a crucial role in the blood-CSF barrier. Its primary function is to produce the majority of CSF.[16,23–25] Additionally, the choroid plexus mediates brain clearance pathways, contributing to maintaining brain homeostasis, and is considered part of the glymphatic system. Changes in choroid plexus volume can influence CSF pressure and flow, affecting the waste clearance capacity of the glymphatic system. Enlargement of the choroid plexus could be a compensatory mechanism for glymphatic system dysfunction or excessive CSF production, disrupting fluid dynamics and waste removal efficacy.[16,23–25] The choroid plexus is also involved in inflammatory processes and immune responses. Chronic inflammation can alter its structure and functions, potentially disrupting CSF production and glymphatic clearance. Enlargement of the choroid plexus is associated with several MRI measures of inflammation.[16,23–25] Therefore, functional and anatomical changes in the choroid plexus can lead to glymphatic system dysfunction, evidenced by a slower glymphatic clearance rate.[16] Studies have demonstrated choroid plexus enlargement in various neurological disorders, such as multiple sclerosis, Alzheimer's disease, Parkinson's disease and moyamoya vasculopathy.[15,26–28] In this study, we first investigated choroid plexus volumes in patients with migraine to evaluate glymphatic system function. We observed choroid plexus enlargement in patients with chronic migraines compared with healthy controls. This finding is consistent with those of previous studies. In a mouse model of migraine with aura, a single wave of cortical spreading depression induced a rapid and nearly complete closure of the perivascular space around cortical arteries and veins, which lasted several minutes and gradually recovered over 30 min, as visualized by two-photon microscopy.[29] Another study showed a higher prevalence of high-grade enlarged perivascular spaces, a marker for glymphatic system dysfunction, in the centrum semiovale and midbrain levels in patients with migraine compared with healthy controls.[30] Recently, Wu et al. demonstrated a decrease in the DTI-ALPS index, which is positively correlated with glymphatic flow, in patients with chronic migraine compared with healthy controls.[16] These studies provide evidence that glymphatic system dysfunction may play a role in migraine pathophysiology. Three main assumptions about how glymphatic system dysfunction can cause migraines have been highlighted.[31] The first assumption is related to inflammation.[31,32] Glymphatic system dysfunction results in the accumulation of proinflammatory cytokines, such as tumor necrotic factor-α and interleukin-1β, which can exacerbate inflammation. The pathophysiology of migraines is heavily influenced by inflammation. Proinflammatory cytokines can amplify nociceptive signals, overexcite neurons and activate nociceptors, thereby triggering migraines.[31,32] The second hypothesis involves elevated CGRP levels.[31,33] Plasma CGRP levels increase during migraine attacks, and CSF CGRP concentrations are five times higher than those in plasma. Glymphatic system dysfunction may contribute to CGRP accumulation in the perivascular space, promoting migraine development.[31,33] The third assumption involves sleep disturbance.[31,34] Among patients with migraine, 57.47% experience sleep disturbances, and 48%–74% report poor sleep quality as a common migraine trigger. The glymphatic system is highly active during deep sleep; hence, sleep disorders can trigger migraines and glymphatic dysfunction.[31,34] In this study, we discovered that the choroid plexus volumes of patients with episodic migraines did not differ from those of patients with chronic migraines. Two previous studies also demonstrated no differences in the DTI-ALPS index between patients with episodic migraine and healthy controls, indicating no glymphatic system dysfunction in patients with episodic migraine.[16,18] This finding supports the fact that chronic and episodic migraines, while part of the same spectrum, are distinct clinical entities.[35,36] Episodic migraine is defined as having 0–14 headache days per month, whereas chronic migraine is described as having 15 or more headache days per month. Patients with chronic migraine experience longer and more severe headache attacks and have a less robust response to triptans than those with episodic migraine.[36] Chronic disruption of glymphatic system function may impede proinflammatory cytokines and CGRP clearance, contributing to chronic migraine. Additionally, patients with chronic migraines have poorer sleep quality than those with episodic migraines.[31] Further research is required to confirm these assumptions.

We also found that choroid plexus volume was positively correlated with age in patients with migraines. Glymphatic system function declines with age, leading to an increase in choroid plexus volume. Aging is associated with decreased pulsatility of hardened arteries, reduced CSF production and reduced aquaporin 4 polarization, all of which contribute to decreased glymphatic system function.[7,37]

There was only one report investigating the choroid plexus volume in patients with migraine. Müller et al.'s study included patients with migraine as a control group for comparison with those with multiple sclerosis or neuromyelitis optica spectrum disorder, and reported no differences in choroid plexus volume between neuromyelitis optica spectrum disorder, migraine and healthy controls.[38] However, this study did not provide detailed information regarding whether the migraine cases were episodic or chronic.

The strength of this study is that to increase homogeneity, we included only patients with migraine without aura and excluded

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the effects of chronic anti-migraine medication use by enrolling newly diagnosed patients. However, this study has some limitations. First, it was conducted at a single tertiary hospital, which may limit the generalizability of our findings to all patients with migraine. Second, being a cross-sectional design study, we could not establish a causal relationship between migraine and glymphatic system dysfunction. Therefore, whether glymphatic system dysfunction precedes migraine or vice versa remains unclear. Third, while choroid plexus volume is associated with glymphatic system function, it can be influenced by various factors such as age, sex, inflammation, infections, medications, trauma and genetic predispositions.[39–41] Fourth, we only segmented the choroid plexus in the lateral ventricles and did not include choroid plexus in the 3rd and 4th ventricles because it is often challenging to reliably distinguish them on non-contrast T1-weighted images at resolution widely used clinically, as in previous studies.[42–44] The infratentorial portion accounts for approximately 35% of the total choroid plexus and may influence the findings. However, in a study that compared choroid plexus volumes of patients with multiple sclerosis and neuromyelitis optica spectrum disorder, the inclusion of infratentorial parts did not alter the overall results. Lastly, we did not evaluate sleep quality in patients with migraine and healthy controls, which is closely associated with the glymphatic system and could not be adjusted for in this study. Additionally, differences in sleep quality likely exist between patients with episodic migraine and those with chronic migraine. Other clinical characteristics, such as obesity, depression or anxiety, may also differ significantly, but these factors were not comprehensively investigated, representing a limitation of this study.

Conclusion

We demonstrated significant enlargement of the choroid plexus in patients with chronic migraine compared with healthy controls and patients with episodic migraine. This finding suggests that chronic migraine may be associated with glymphatic system dysfunction.

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Author contributions. All authors participated in study conception and design and interpretation of results. All the coauthors contributed to the project implementation and data collection. The first author analyzed data and drafted the first version of the manuscript. The last author supervised the whole process. All authors revised and approved the manuscript before submission and take responsibility for the contents of the article.

Competing interests. The authors declare no conflict of interest.

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