

ORIGINAL ARTICLE

Glymphatic system dysfunction in patients with cluster headache

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Abstract

Introduction: The aim of this study was to investigate alterations of the glymphatic system function in patients with cluster headache.

Methods: We enrolled patients with cluster headache and healthy controls, and they underwent brain magnetic resonance imaging (MRI), including diffusion tensor imaging (DTI). We used the MRICron and DSI studio programs for DTI preprocessing and DTI analysis with perivascular space (DTI-ALPS) index calculation.

Results: Fourteen patients with cluster headache and 23 healthy controls were enrolled. The DTI-ALPS indexes of the groups were significantly different. The DTI-ALPS index for the patients with cluster headache was lower than that for the healthy controls (1.586 vs. 1.786, $p = 0.044$). There was a significant negative correlation between the DTI-ALPS index and age in the patients with cluster headache ($r = -0.549$, $p = 0.042$). However, the DTI-ALPS index was not associated with other clinical characteristics, including disease duration and headache intensity ($r = -0.405$, $p = 0.150$; $r = -0.048$, $p = 0.869$, respectively).

Conclusion: Patients with cluster headache had a lower DTI-ALPS index than the healthy controls; this might indicate glymphatic system dysfunction in the patients with cluster headache. Further research is required to determine whether glymphatic system dysfunction is related to the pathophysiology of cluster headache.

KEYWORDS

cluster headache, diffusion tensor imaging, glymphatic system

1 | INTRODUCTION

Until the glymphatic system theory was published in 2012, it was assumed that the brain, like any other organ, recycled all of its protein waste (Rubinsztein, 2006). However, the concept has changed since the introduction of the glymphatic system. The glymphatic system is now thought to be a brain-wide perivascular pathway for the exchange

of cerebrospinal fluid (CSF) and interstitial fluid (ISF) in the central nervous system, promoting effective elimination of solutes and waste products from the brain (Iliff et al., 2013). Alzheimer's dementia, aging, traumatic brain injury, brain hemorrhage, cerebrovascular disease, Parkinson's disease, and normal pressure hydrocephalus (NPH) are all known to be linked to glymphatic system dysfunction (Gaberel et al., 2014; Goulay et al., 2017; Iliff et al., 2014; Jiang et al., 2017; Kress

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et al., 2014; Mestre et al., 2018; Peng et al., 2016; Plog et al., 2015; Wang et al., 2017).

The use of magnetic resonance imaging (MRI) to visualize glymphatic system function is critical for understanding the pathophysiology of various neurodegenerative disorders, and it can be a therapeutic target or be used to determine therapeutic efficacy. MRI has been used to visualize glymphatic system function in several ways, and the use of intrathecal gadolinium-based contrast agents (GBCAs) is the most representative. There have been reports of studies using MRI and patients with NPH, and the intracranial kinetics of GBCAs significantly differ between patients with NPH and controls (Edeklev et al., 2019; Ringstad et al., 2018). However, the method involving the use of intrathecal GBCAs is invasive, and the degree and speed of penetration vary from person to person (Ringstad et al., 2018). As a result, the application of intrathecal GBCAs to investigating glymphatic system function has been challenging and wrought with several limitations.

Diffusion tensor imaging (DTI) has been recently utilized to assess glymphatic system function in several studies (Debaker et al., 2020; Yokota et al., 2019). DTI analysis with the perivascular space (DTI-ALPS) calculation method is based on the idea that perivascular ISF movement in the white matter near the lateral ventricles is prominent along the parallel medullary veins (Yokota et al., 2019). The DTI-ALPS method requires no GBCAs, uses clinically common DTI data, and can be performed retrospectively with the use of previous imaging data; therefore, it is highly useful for research.

Cluster headache is the most severe types of headaches, and they are characterized by ipsilateral pain localized to the orbital, supraorbital, and/or temporal areas, as well as associated autonomic processes. Lacrimation (tearing), conjunctiva injection (sclera redness), rhinorrhea, nasal congestion, hyperhidrosis (excessive sweating), and eyelid edema occur ipsilateral to the pain, with only 3% of individuals showing no autonomic symptoms (Sjaastad, 1992). They last for 15–80 min and occur up to eight times a day (Society, 2013). Sleep has been identified as a common trigger for cluster headache. A previous questionnaire-based study involving 275 patients with cluster headache showed that 80% of patients reported that sleep is a trigger for their headache episodes (Barloese, Lund et al., 2015). Patients with cluster headache scored higher on the Pittsburgh Sleep Quality Index than healthy people, indicating a low self-perception of sleep quality. In addition, patients who report that sleep is a trigger for their headache attacks scored higher than those who report sleep is not a trigger factor (Barloese, Lund et al., 2015). Furthermore, the majority of headaches occur at night during sleep, and the greatest issue for patients with cluster headache is sleep inefficiency (Jensen et al., 2007). Cognitive dysfunction does not last beyond headaches, but patients with cluster headache usually experience repeated cognitive deterioration (Favoni et al., 2018). Patients with Alzheimer's dementia also have glymphatic system dysfunction (Nedergaard & Goldman, 2020; Taoka et al., 2017). Considering all these, and the evidence that the glymphatic system is activated especially during sleep, patients with cluster headache may have decreased glymphatic system function.

This study aimed to investigate alterations of the glymphatic system function in patients with cluster headache. The glymphatic system and

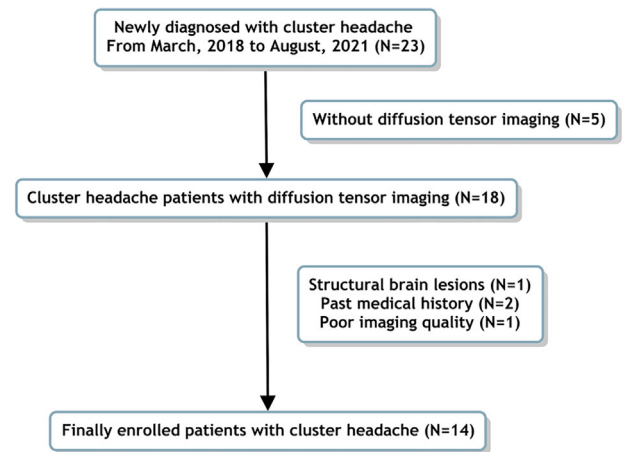


FIGURE 1 Selection process for the patients with cluster headache in this study

cluster headache are both linked to sleep, and our research is based on the hypothesis that patients with cluster headache have glymphatic system dysfunction. To our knowledge, there have not been studies on this.

2 | METHODS

2.1 | Participant: Patients with cluster headache and healthy controls

This study was conducted retrospectively in a single hospital and approved by the institutional review board at Haeundae Paik Hospital. We enrolled patients with cluster headache based on the third edition of the International Classification of Headache Disorders and the following criteria (Headache Classification Committee of the International Headache Society [IHS], 2018): (1) newly diagnosed episodic cluster headache at our hospital between March 2018 and August 2021, who were not taking any preventive medications for cluster headache. (2) Brain MRI including DTI. We excluded patients with the following: (1) previous history of any medical or neurological disease, except cluster headache, (2) structural lesion on brain MRI, or (3) having poor quality DTI for analysis. Figure 1 shows the selection process for patients with cluster headache in this study. We reviewed the medical records to obtain demographic and clinical characteristics, such as age, sex, disease duration (time interval from headache onset to MRI taken), headache intensity, and headache laterality (side with most headaches) for the patients with cluster headache.

We also enrolled age- and sex-matched healthy controls who had no previous history of any medical or neurological disease. All healthy controls underwent brain MRI including DTI, and they had no structural lesions on brain MRI. They had been already recruited from our previous study, which had enrolled a total of 150 healthy participants (Jang et al., 2017). Of the 150 patients, those who did not consent to the use of their data in this study were excluded. Finally, we included

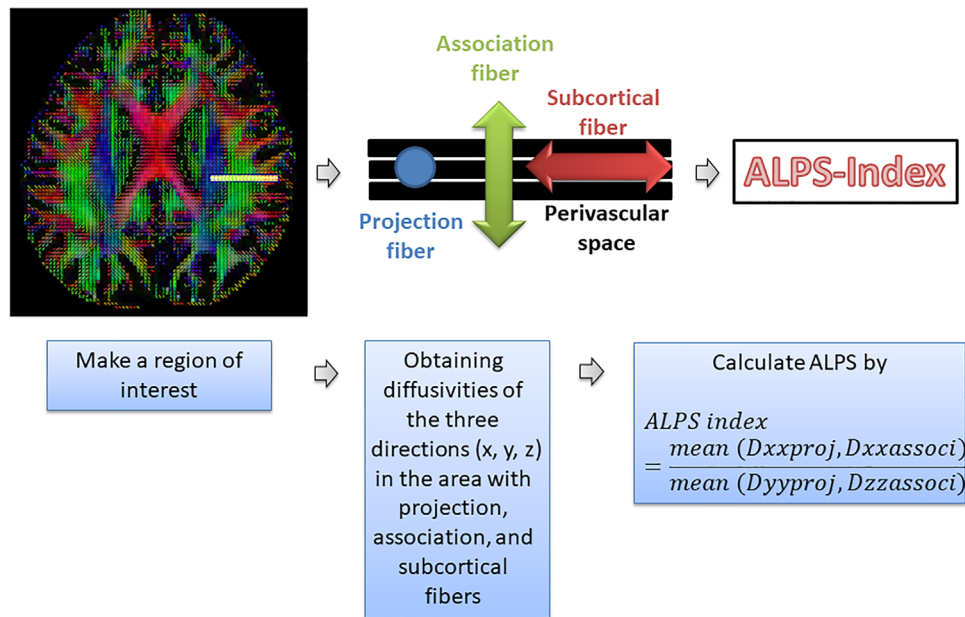


FIGURE 2 Diffusion tensor image analysis with the perivascular space (DTI-ALPS) index calculation. The figure was generated from our previous study (Lee et al., 2021)

the remained healthy participants in the control group with similar age and sex as the patients with cluster headache.

2.2 | Diffusion tensor imaging acquisition

All MRI scans of the participants were obtained using the same MRI scanner, which was a 3 tesla with a 32-channel head coil (AchievaTx; Phillips Healthcare). From March 2018, routine brain MRI protocols at our hospital for patients with cluster headache included DTI. All of the MRI scanning was conducted during out-of-out phase of headache attacks in patients with cluster headache, and MRI scans were performed during the daytime in all participants (before 5 pm). The participants underwent the same brain MRI protocol, which included three-dimensional (3D) FLAIR imaging, coronal T2-weighted imaging, 3D T1-weighted imaging, and DTI. FLAIR and T2-weighted imaging were used to evaluate the structural abnormalities of the brain. The detailed MR parameters for DTI with 32 different diffusion directions have been described in our previous studies (Lee et al., 2021)

2.3 | Diffusion tensor imaging preprocessing and diffusion tensor image analysis along with the perivascular index calculation

We used the MRIcron and DSI studio programs for DTI preprocessing and DTI-ALPS index calculations. The steps for DTI preprocessing and DTI-ALPS index calculation were described in our previous study (Lee et al., 2021). The preprocessing for DTI included setting up a mask, reconstruction with the DTI method, and fiber tracking. We, subsequently, calculated the DTI-ALPS index (Figure 2) (Lee et al.,

2021; Taoka et al., 2017). We drew a rectangular region of interest (ROI) and obtained the fiber orientation and diffusivities of the three directions along the x-, y-, and z-axes as voxel levels at the ROI. Finally, the DTI-ALPS index was obtained using the following formula (Taoka et al., 2017):

$$ALPS\ index = \frac{\text{mean}(D_{xxproj}, D_{xxassoci})}{\text{mean}(D_{yyproj}, D_{zzassoci})}$$

where D_{xxproj} is diffusivity along the x-axis in the projection fiber, $D_{xxassoci}$ is diffusivity along the x-axis in the association fiber, D_{yyproj} is diffusivity along the y-axis in the projection fiber, and $D_{zzassoci}$ is diffusivity along the z-axis in the association fiber.

2.4 | Statistical analysis

A primary analysis of these data was conducted using an a priori test. No statistical power calculations were performed before the study. The sample size was based on the available data. Comparisons of the demographic characteristics of the patients with cluster headache and healthy controls were conducted using an independent sample *t*-test or the chi-squared test. Comparisons of the diffusivities and DTI-ALPS indexes of the groups were performed using an independent sample *t*-test. Correlation analysis was performed using Pearson's correlation coefficient. Categorical variables are presented as frequencies and percentages, whereas continuous variables are presented as mean \pm standard deviation or median. Statistical significance was set at a two-tailed $p < 0.05$. MedCalc® Statistical Software version 20.014 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>) was used for the statistical analysis.

TABLE 1 Demographic and clinical characteristics in patients with cluster headache and healthy controls

	Patients with cluster headache (N = 14)	Healthy controls (N = 23)	p-Value
Age, years	42.2 ± 16.9	40.6 ± 8.5	0.696
Male, n (%)	13 (92.8)	21 (91.3)	1.000
Disease duration, years	2.1 ± 1.6		
Headache intensity, visual analog scale	8.7 ± 0.8		
Right side attack, n (%)	7 (50.0)		

3 | RESULTS

3.1 | Demographic and clinical characteristics of the patients with cluster headache

We enrolled 14 patients with cluster headache and 23 healthy controls. Table 1 shows the demographic and clinical characteristics of patients with cluster headache. Their ages and sex were not different from those of the healthy controls (42.2 vs. 40.6 years, $p = 0.696$; 13/14 vs. 21/23, $p = 1.000$). Most of the patients with cluster headache were men.

3.2 | Differences between the diffusivities and diffusion tensor image analyses along with the perivascular indexes of the patients with cluster headache and healthy controls

The diffusivities along the x-, y-, and z-axis of the projection, association, and subcortical fibers of the patients with cluster headache and healthy controls were not statistically different (Table 2).

The DTI-ALPS indexes for the groups were significantly different. The DTI-ALPS index for patients with cluster headache was lower than that for healthy controls (1.586 vs. 1.786, $p = 0.044$).

3.3 | Correlation analysis of diffusion tensor image analysis with the perivascular index and demographic/clinical characteristics

There was a significant negative correlation between the DTI-ALPS index and age in patients with cluster headache ($r = -0.549$, $p = 0.042$) (Figure 3). However, the DTI-ALPS index was not correlated with other clinical characteristics, including disease duration and headache intensity ($r = -0.405$, $p = 0.150$; $r = -0.048$, $p = 0.869$, respectively).

4 | DISCUSSION

The following were the main findings of this study. (1) The DTI-ALPS indexes of the patients with cluster headache and healthy controls were different. The DTI-ALPS index was lower for patients with cluster

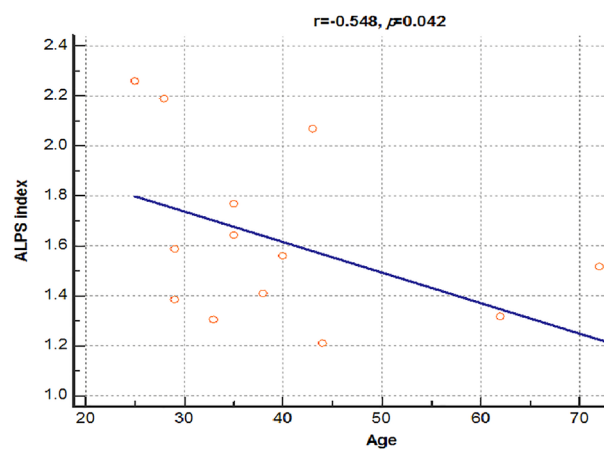


FIGURE 3 Correlation analysis of diffusion tensor image analysis with the perivascular space (DTI-ALPS) index and age in patients with cluster headache. There was a significant negative correlation between the DTI-ALPS index and age in patients with cluster headache

headache than for healthy controls. (2) There was a significant negative correlation between the DTI-ALPS index and age for the patients with cluster headache. (3) The DTI-ALPS index was not correlated with other clinical characteristics such as disease duration or headache intensity for patients with cluster headache.

This was the first study to evaluate glymphatic system function in patients with cluster headache. The lower DTI-ALPS index of patients with cluster headache than that of healthy controls in this study implies that patients with cluster headache have glymphatic system dysfunction. Glymphatic system dysfunction is important in the pathophysiology of neurovascular, neurodegenerative, neuro-inflammatory diseases, and traumatic brain injury, as well as age-related changes in brain functions (Sun et al., 2018). There are also reports of the potential role of the glymphatic system in headache disorders, especially migraine (Messlinger, 2018; Schain et al., 2017; Toriello et al., 2021; Vgontzas & Pavlovic, 2018). Cortical spreading depression, the neural event underlying migraine aura, results in a temporary impairment of glymphatic flow in a mouse model via paravascular space closure for several minutes after inducing cortical spreading depression, followed by a gradual recovery over half an hour (Schain et al., 2017; Toriello et al., 2021). In addition, calcitonin gene-related peptide plays a critical role in the pathophysiology of headaches, particularly migraine. The calcitonin gene-related peptide may be excreted in three

TABLE 2 Differences between the diffusivities and diffusion tensor image analysis with the perivascular space (DTI-ALPS) index in patients with cluster headache and healthy controls

	Patients with cluster headache (N = 14)	Healthy controls (N = 23)	p-Value
Projection fiber			
Dxx	0.602 ± 0.081	0.613 ± 0.099	0.715
Dyy	0.429 ± 0.133	0.381 ± 0.097	0.220
Dzz	1.034 ± 0.149	1.066 ± 0.142	0.518
Association fiber			
Dxx	0.598 ± 0.080	0.627 ± 0.111	0.410
Dyy	1.080 ± 0.121	1.166 ± 0.146	0.074
Dzz	0.347 ± 0.102	0.320 ± 0.065	0.336
Subcortical fiber			
Dxx	1.082 ± 0.163	1.144 ± 0.137	0.227
Dyy	0.620 ± 0.186	0.681 ± 0.196	0.362
Dzz	0.538 ± 0.197	0.649 ± 0.210	0.122
DTI-ALPS index	1.586 ± 0.371	1.786 ± 0.212	*0.044

($\times 10^{-3}$ mm²/s).

Abbreviations: Dxx, diffusivity along the x-axis; Dyy, diffusivity along the y-axis; Dzz, diffusivity along the z-axis; DTI-ALPS index, diffusion tensor image analysis with the perivascular space index.

* $p < 0.05$.

compartments: venous blood plasma, cerebrospinal fluid, and possibly the lymphatic system. Thus, glymphatic system dysfunction may be associated with increased levels of calcitonin gene-related peptide, which may produce a headache (Messlinger, 2018; Toriello et al., 2021)

Sleep is often associated with cluster headache. According to a polysomnographic study, patients with cluster headache have a lower proportion of sleep stage R (previously referred to as REM sleep), and a long latency for sleep stage R (Barloese, Jennum et al., 2015). Another study also demonstrated longer sleep latency and lower sleep efficiency in patients with cluster headache compared to healthy controls (Lund et al., 2019). Furthermore, numerous sleep disorders have been linked to cluster headaches (Weintraub, 2003). Cluster headaches have been treated with melatonin and other treatments that affect circadian rhythm. Cluster headache patients may develop obstructive sleep apnea (Weintraub, 2003). A study involving mice demonstrated that natural sleep is linked to a 60% increase in the interstitial space of the brain. Because of the high hydraulic resistance in the brain interstitial space during alertness, sleep can increase the convective flow of CSF plus ISF; therefore, there is an increase in the efficiency of the glymphatic system during sleep (Xie et al., 2013). Several patients with cluster headache have attacks that wake them up, but they usually have sleep difficulties before the attacks, and sleep disorders are common concomitant diseases for patients with cluster headache (Martins, 2015). In addition, cluster headache frequently begins during sleep (Barloese, Lund et al., 2015; Barloese, Jennum et al., 2015). Thus, sleep disturbance in patients with cluster headache is thought to diminish the efficacy of glymphatic system function by lowering the flow of CSF and ISF.

Aging is closely related to sleep; therefore, sleep quality deteriorates with age. With aging, insomnia becomes more common, the total duration of sleep becomes shortened, and sleep becomes more disrupted. More importantly, older people rarely reach the deep sleep stage N (previously referred to as non-REM sleep). In adults aged >60 years, the sleep stage N is predominantly shallow, consisting of the shallower sleep stage 1 or 2 (Landolt & Borbély, 2001). As a result, the older brain spends less time in sleep stage 3, potentially resulting in a catastrophic decrease in brain waste clearance, as the efficacy of glymphatic fluid transport is directly proportional to the prevalence of slow-wave activity (Hablitz et al., 2019). These sleep abnormalities in patients with cluster headache are comparable to those observed with age, and this is thought to represent a mechanism of glymphatic system dysfunction. The CSF formation rate and turnover in the rat brain decrease with age, which is consistent with evidence showing that glymphatic clearance decreases with age (Kress et al., 2014). In this study, there was a negative correlation between the DTI-ALPS index and age in patients with cluster headache, which is consistent with the results of previous animal experiments.

The limitations of this study are as follows. First, this was a retrospective study. The study confirmed that alterations in glymphatic system function were identified in patients with cluster headache; however, it is not clear whether this change is the result or cause of cluster headache. Second, there was a limited number of participants; therefore, it is difficult to generalize the results. However, cluster headache is not common, and we only enrolled newly diagnosed patients with cluster headache to exclude medication effects. Further studies with large sample size are needed to confirm our findings. Third, various factors can influence the DTI-ALPS index, including the

imaging plane, head position, and motion-proving gradients (Taoka et al., 2021). However, a previous study found that the results of the DTI-ALPS method were significantly related to glymphatic system function as measured by MRI after intrathecal administration of GBCA (Zhang et al., 2021), and another recent study successfully demonstrated good test-retest reproducibility and robustness (Taoka et al., 2021). Despite these limitations, this study is notable because, to the best of our knowledge, no studies have investigated the link between the glymphatic system and cluster headache.

5 | CONCLUSION

Patients with cluster headache had a lower DTI-ALPS index than the healthy controls. This might indicate glymphatic system dysfunction in patients with cluster headache. Further research is required to determine whether glymphatic system dysfunction is related to the pathophysiology of cluster headache.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jinseung Kim and Kang Min Park. *Acquisition of data, analysis and interpretation of data:* Dong Ah Lee, Ho-Joon Lee, Bong Soo Park, Junghae Ko, S Park, Yoo Jin Lee, Il Hwan Kim, Jin Han Park, and Kang Min Park. *Drafting the manuscript or revising:* Jinseung Kim and KM Park. *Final approval:* Kang Min Park.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1002/brb3.2631>

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