Letter to the Editor

Headache Pain Res 2026;27(2):169-170
pISSN: 3022-9057 • eISSN: 3022-4764
https://doi.org/10.62087/hpr.2026.0015

Headache and Pain Research

Comments on "Brain Glymphatic and Lymphatic Systems in Migraine: Mechanistic Insights and Neuromodulation Perspectives with an Emphasis on Ultrasound-Based Approaches"

Soo-Jin Cho

Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea

Migraine is a chronic paroxysmal neurological disorder characterized by sensitization of neural networks and hypersensitivity to various stimuli.[1] Brain clearance pathways, particularly the glymphatic system and meningeal lymphatic vessels, regulate neuroinflammation and cerebrospinal fluid (CSF) dynamics and may therefore influence migraine occurrence and management.[2] The article titled "Brain Glymphatic and Lymphatic Systems in Migraine: Mechanistic Insights and Neuromodulation Perspectives with an Emphasis on Ultrasound-Based Approaches," published in the previous issue,[2] provides a comprehensive overview of this topic in addition to the review by Dr. Cha.[3]

As shown in Figure 1 of the article,[2] the association between migraine and the glymphatic system is presented as unidirectional, proceeding from migraine to glymphatic dysfunction. Experimental evidence suggests that calcitonin gene-related peptide may influence meningeal lymphatic tone and CSF efflux.[4] Conversely, the glymphatic system itself may also contribute to migraine pathophysiology. In addition to its role in waste clearance, CSF flow—a fundamental physiological process—may participate in migraine signaling pathways. Experimental studies have shown that solutes released during cortical spreading depolarization can be transported through the CSF to the trigeminal ganglion.[5] These findings support the possibility that CSF-mediated transport dynamics may modulate the temporal patterns of trigeminal nerve activation and the onset of migraine attacks.

It remains unclear whether alterations in glymphatic–lymphatic pathways in migraine represent a primary pathophysiological driver or a secondary phenomenon mediated by comorbid sleep disturbance. Robust experimental evidence indicates that glymphatic activity is markedly enhanced during non–rapid eye movement sleep and suppressed during wakefulness. Consequently, impaired clearance observed in patients with migraine may plausibly reflect fragmented sleep, insomnia, or circadian dysregulation rather than migraine-specific mechanisms. Epidemiological and mechanistic evidence further suggests that clearance dysfunction shows stronger and more reproducible associations with primary sleep disorders and neurodegenerative diseases than with primary headache disorders per se.[6]

In addition, the chronobiological dimension warrants further discussion. Brain clearance activity peaks during

Received: April 9, 2026; **Accepted:** April 29, 2026
Correspondence: Soo-Jin Cho, M.D., Ph.D.
Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, 7 Keunjaebong-gil, Hwaseong 18450, Republic of Korea
Tel +82-31-8086-2310, Fax +82-31-8086-2317, E-mail: dowonc@naver.com

nocturnal sleep states, whereas most primary headache disorders—including migraine and tension-type headache—occur predominantly during daytime hours. Cluster headache represents a notable exception because it demonstrates strong circadian and nocturnal periodicity and is frequently associated with sleep apnea.[7] If impaired nocturnal clearance were a central driver of headache pathophysiology, stronger temporal coupling between periods of glymphatic suppression and headache onset might be expected. The relative dissociation between nocturnal clearance enhancement and the predominantly diurnal occurrence of migraine raises the possibility that clearance alterations function as modulatory factors rather than primary triggers.

Overall, current analyses of diffusion tensor imaging and ultrasound data remain indirect and insufficient to establish glymphatic dysfunction or clearance modulation as validated mechanisms in migraine. Although preclinical studies suggest that focused ultrasound can alter CSF tracer movement, no clinical evidence currently demonstrates meaningful effects on migraine frequency, chronicity, or interictal burden.

In summary, although the brain clearance framework is conceptually attractive, current evidence does not definitively establish a direct causal relationship between glymphatic–lymphatic dysfunction and migraine. Distinguishing migraine-specific mechanisms from sleep-mediated or circadian effects will require innovative studies incorporating objective sleep metrics, CSF, glymphatic, and lymphatic imaging biomarkers, assessments of conventional migraine therapies, and neuromodulatory approaches aimed at restoring physiological states that facilitate clearance.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: SJC; Writing–original draft: SJC; Writing–review & editing: SJC.

CONFLICT OF INTEREST

Soo-Jin Cho is the Editor-in-Chief of *Headache and Pain Research* and was not involved in the review process of this article. The author has no other conflicts of interest to declare.

FUNDING STATEMENT

None.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Dodick DW. Migraine. Lancet 2018;391:1315-1330.
2. Kim J. Brain glymphatic and lymphatic systems in migraine: mechanistic insights and neuromodulation perspectives with an emphasis on ultrasound-based approaches. Headache Pain Res 2026;27:13-20.
3. Cha MJ, Kang KW, Shin JW, Kim H, Kim J. Understanding the connection between the glymphatic system and migraine: a systematic review. Headache Pain Res 2024;25:86-95.
4. Nelson-Maney NP, Bálint L, Beeson AL, et al. Meningeal lymphatic CGRP signaling governs pain via cerebrospinal fluid efflux and neuroinflammation in migraine models. J Clin Invest 2024;134:e175616.
5. Kaag Rasmussen M, Møllgård K, Bork PAR, et al. Trigeminal ganglion neurons are directly activated by influx of CSF solutes in a migraine model. Science 2024;385:80-86.
6. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurol 2018;17:1016-1024.
7. Hong Y, Kang MK, Chu MK, Cho SJ, Im HJ. Cluster headache characteristics and the severity of obstructive sleep apnea: insights from polysomnography analysis. Headache Pain Res 2024;25:63-71.