Headache and Pain Research Vol. 27, No. 1, February 2026 Pages 1-72

The Korean Headache Society

Headache and Pain Research

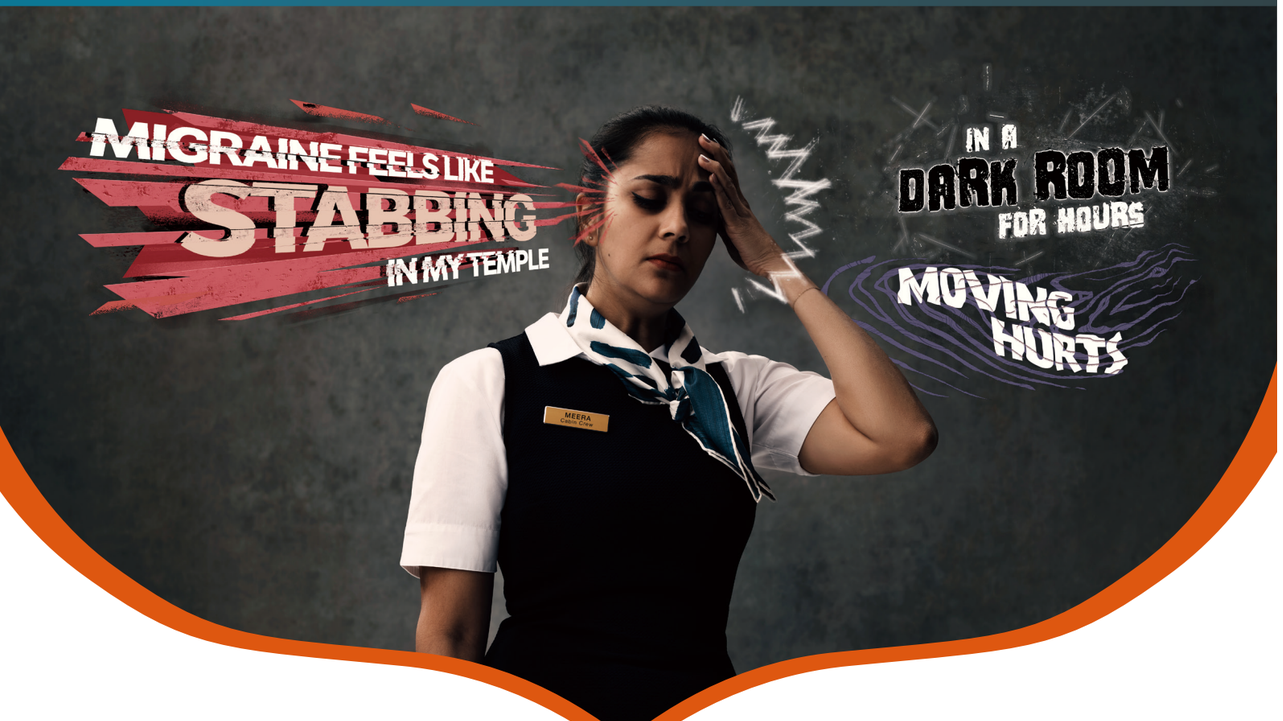
Open Access I pISSN 3022-9057 I eISSN 3022-4764

Vol. 27 No. 1, February 2026

https://e-hpr.org

The first* CGRP (Calcitonin Gene-Related Peptide) **receptor antagonist in South Korea for the prevention of migraines in adults**[1]

AQUIPTA® (atogepant) tablets



PREVENT
THE DISRUPTION OF MIGRAINE[1]

Only oral once-daily
Calcitonin gene-related peptide (CGRP) receptor antagonist for both
episodic and chronic migraine patients[1]

Not a real patient, Tablet not actual size.

*On the reference date of November 2023 **CGRP**, calcitonin gene-related peptide

References. 1. AQUIPTA® Product information (2025.09.01)

Please refer to the QR code or product manual for the latest and comprehensive product information.
※ Reporting Adverse Drug Reactions and Applying for Compensation: Korea Institute of Drug Safety & Risk Management (1644-6223 OR 14-3330, www.drugsafe.or.kr)
[Importer] AbbVie Ltd, 6th Floor, SamTan Bldg, 421 YoungDong-Daero, KangNam-Ku, Seoul, 06182, Korea

abbvie **AbbVie Ltd** 6th Floor, SamTan Bldg, 421 YoungDong-Daero, KangNam-Ku, Seoul, 06182, Korea **Tel.** +82.2.3429.9300 www.abbvie.co.kr

AQUIPTA (Atogepant 60 mg)

KR-AQP-230007 / Jan 25

Emgality® (galcanezumab) injection

Lilly | ORGANON

적절한 편두통 관리의 시작

앰겔러티® 투여를 통해 편두통을 적절히 관리할 수 있습니다.[1]

References 1. Sacco S *et al*., European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. *J Headache Pain*. 2022 Jun 11:23(1):67

앰겔러티® 120밀리그램/밀리리터프리필드펜주/갈카네주맙, 유전자재조합)[효능·효과] 성인에서의 편두통의 예방 **[용법·용량]** 부하용량으로 240 mg(120 mg씩 2회 연속 피하 주사)을 1회 투여하고, 이후 월 1회 120 mg을 피하 주사한다. 이 약의 투여를 잊은 경우 가능한 한 빨리 투여한다. 이후, 최초 투여 일자를 기준으로 이 약의 월 1회 투여 일정을 정할 수 있다. **[사용상의 주의사항] [금기]** 이 약 또는 이 약의 첨가제에 대해 중대한 과민성이 있는 환자 **[신중투여]** 1) 과민 반응. 임상시험 및 시판 후 환경에서 이 약에 대해 호흡 곤란, 두드러기 및 발진을 포함한 과민 반응이 발생하였으며, 아나필락시스 및 혈관 부종의 경우도 시판 후 환경에서 보고되었다. 중대하거나 중증인 과민 반응이 발생할 경우, 이 약 투여를 중지하고 적절한 치료를 시작한다. 과민 반응은 투여 며칠 후에 발생할 수 있으며 지속될 수 있다. **[이상반응]** 1) 이 약에 대한 3개의 위약 대조 임상시험에서, 3개월 또는 6개월의 이중 눈가림 투여 기간 동안 이 약 월 1회 용량(120 mg)을 1회 이상 투여 받은 705명의 편두통 환자(평균 연령: 41세, 여성: 85%, 백인: 77%) 중 이상반응으로 인해 투여를 중단한 환자는 1.8%였으며, 가장 흔한 약물이상반응은 주사 부위 반응(18% vs. 위약 13%)이었다. 2) 이 약에 대한 3개의 위약 대조 임상시험에서, 이 약을 최대 6개월간 월 1회 투여 받은 환자(in vitro 중화 활성을 평가받은 33명 중 32명)에서 항 갈카네주맙 항체의 발생률은 4.8%(33명/688명)였다. 이 약을 12개월간 투여한 공개 시험에서는 환자의 최대 12.5%(16명/128명)에서 항 갈카네주맙 항체가 나타났으며, 이 중 대부분이 중화 항체에 대해 양성으로 평가되었다. 이러한 환자에서 항 갈카네주맙 항체 발생은 이 약의 약동학, 안전성 또는 유효성에 영향을 주는 것으로 확인되지 않았으나, 이를 가능한 자료가 너무 제한적이어서 확실한 결론을 내릴 수는 없다. 3) 특정 주요 심혈관계 위험이 있는 환자는 임상시험에서 제외되었으며, 이들에 대한 이용 가능한 안전성 자료는 없다. 4) 이 약의 시판 후 사용 중에 확인된 약물이상반응은 다음과 같다. 면역계 장애 - 아나필락시스, 혈관 부종(2. 다음 환자에는 신중히 투여할 것을 참조), 피부 및 피하 조직 장애 - 발진. **[임부에 대한 투여]** 임부에서 이 약 사용과 관련된 발생(development) 측면의 위험성에 관한 충분한 자료가 없다. 임상적으로 예상되는 것보다 높은 혈장 노출의 이 약을 장기형성 기간 동안 랫드 및 토끼에게 투여한 경우와 임신 및 수유 기간 내내 랫드에게 투여한 경우에, 발생(development)에 대한 유해 영향은 초래되지 않았다. **[수유부에 대한 투여]** 인간 모유 내 이 약의 존재, 모유 수유 영아에 대한 영향, 또는 모유 생성에 미치는 영향에 관한 자료는 없다. 모유 수유의 발달 및 건강상 유익성과 함께, 모체의 이 약 투여에 대한 임상적 필요성 및 모유를 수유하는 영아에서 이 약 또는 수유부의 기저 상태로 인한 잠재적인 이상반응을 함께 고려하여야 한다. **[소아에 대한 투여]** 소아 환자에서의 안전성 및 유효성은 확립되지 않았다. **[고령자에 대한 투여]** 이 약에 대한 임상시험은 만 65세 이상 환자가 젊은 환자와 다른 반응을 보이는지 여부를 확인하기에 충분한 수의 만 65세 이상 환자를 포함하지 않았다. 개정일: 2021년 4월 14일
※ 처방하시기 전에 각 항목에 대한 자세한 내용은 제품설명서 전문을 참조하시기 바랍니다.

Lilly **한국릴리 유한회사** 서울특별시 중구 후암로 98 LG 서울역 빌딩 4층 우)04637
대표전화번호 : 02-3459-2676 I http://www.lilly.com/kr

ORGANON

우)03142 서울특별시 종로구 종로1길 50, 4층 (전화) 1577-8582 https://www.organon.com/korea

PP-GZ-KR-0274 [exp. Sep 2026]
KR-EMG-110004 09/2026

e-hpr.org

pISSN 3022-9057
eISSN 3022-4764

Headache and Pain Research

Vol. 27 No. 1, February 2026

Aims and scope

Headache and Pain Research (Headache Pain Res; pISSN: 3022-9057, eISSN: 3022-4764) publishes original articles, review articles, and short letters on all aspects of Headache and Pain Research. The main topics include migraine, cluster headache, tension-type headache, intracranial hypotension, intracranial hypertension, reversible cerebral vasoconstriction syndrome, other primary or secondary headache disorders, pediatric headache, and issues related to headache and pain such as dizziness, psychological, and cognitive problems, and Temporomandibular disorder and orofaical pain. *Headache and Pain Research*, the official journal of Korean Headache Society, aims to rapidly spread updated advances in the headache and pain field to readers and patients, while fostering a scientifically fair and progressive relationship with researchers and reviewers. It aims to be an international journal and welcomes outstanding editorial board members and submissions from all over the world.

Headache and Pain Research is published 3 times a year (February, June, and October) since 2025. Until 2024, HPR was published biannually (the last day of June and December) from 2000 to 2024.

This journal was first published in 2000 under the title '*Korean Journal of Headache*' (ISSN 1598-009X) and its title has been changed to '*Headache and Pain Research*' since 2024.

Open access

Publisher
The Korean Headache Society

Editor-in-Chief
Soo-Jin Cho, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, 7 Keunjaebong-gil, Hwaseong18450, Republic of Korea

Editorial office
Department of Neurology, Nowon Eulji Medical Center, Eulji University School of Medicine, 68 Hangeulbiseok-ro, Nowon-gu, Seoul 01830, Republic of Korea
Tel: +82-2-974-8606 E-mail: office@e-hpr.org

Printing office
M2PI
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
Tel: +82-2-6966-4930 Fax: +82-2-6966-4945 E-mail: support@m2-pi.com

Published on February 28, 2026

Editorial board

Headache and Pain Research

Editorial board

Headache and Pain Research

Contents

Headache and Pain Research

Vol. 27, No. 1, February 2026

Editorials

Review Articles

Original Articles

Letter to the Editor

Editorial

Headache Pain Res 2026;27(1):1-3
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2026.0002

Headache and Pain Research

Primary or Secondary Headache Disorders in Moyamoya Disease and Cerebral Infarction: Clinical Challenges and the Potential Role of Non-Vasoconstrictive Migraine Therapies

Soo-Jin Cho

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

Headaches are common and often disabling in patients with moyamoya disease and in stroke survivors, yet they are frequently overlooked in routine clinical practice.[1,2] Moyamoya disease is a rare, progressive cerebrovascular condition characterized by chronic stenosis or occlusion of the intracranial internal carotid arteries and is associated with diverse clinical manifestations, including ischemic strokes, transient ischemic attacks, intracranial hemorrhage, as well as headache. Although headache is not usually a dominant symptom of stroke in the absence of associated neurological deficits, notable exceptions include arterial dissection, venous stroke, reversible cerebral vasoconstriction, and strokes associated with meningitis. The reported prevalence of headaches ranges widely, from 17% to 85% in patients with moyamoya disease and from 7% to 65% in stroke populations.[1,2] This variability likely reflects differences in study design, patient populations, and headache definitions. Importantly, headache may precede, occur concomitantly with, or follow a vascular event, and its clinical relevance is often underestimated in everyday practice.

Clinically, headaches in these patients may arise through at least three distinct scenarios. First, patients may have pre-existing primary headache disorders, such as migraine or tension-type headache, which can be exacerbated by underlying vascular disease or altered cerebral hemodynamics. Second, headaches may occur as a direct consequence of moyamoya disease or stroke itself, representing secondary headaches attributable to cerebrovascular pathology. In this context, headache characteristics may vary according to stroke subtype, lesion location, and vascular territory, and may provide clues to underlying mechanisms such as cortical involvement, posterior circulation ischemia, or meningeal irritation. Third, new and unrelated headache disorders may develop after a vascular event.

In this context, a structured and comprehensive approach is required for the diagnostic evaluation of secondary headaches. This approach includes careful characterization of the current headache phenotype, assessment of prior headache history, evaluation of the temporal relationship between headache onset and vascular events, and performance of appropriate neuroimaging studies. A recent article on headaches associated with moyamoya disease has provided a detailed framework addressing clinical significance, underlying pathophysiology, and therapeutic considerations.[1] Importantly, headaches in patients with

Received: January 6, 2026; **Revised:** January 12, 2026; **Accepted:** January 26, 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

moyamoya disease may reflect unstable cerebral hemodynamics, and surgical revascularization can alleviate headaches by improving cerebral perfusion in selected cases. Similarly, headache patterns in certain stroke subtypes, such as arterial dissection, venous stroke, or reversible cerebral vasoconstriction syndrome, may serve as important diagnostic or prognostic markers.

Medical management is generally guided by headache phenotype. First-line therapies typically include simple analgesics or non-steroidal anti-inflammatory drugs, although these are often only partially effective. Non-vasoconstrictive, migraine-specific agents have gained increasing attention in this setting. Lasmiditan, a selective 5-HT1F agonist, is approved for primary migraine and lacks vasoconstrictive effects, making it a theoretically safer and valuable option for migraine or migraine-like headaches in patients with moyamoya disease or a history of stroke.[1,3] Unfortunately, the production of lasmiditan was suspended in November 2025 for business reasons. The withdrawal of this important migraine treatment is expected to negatively impact patient quality of life and safety by creating a significant "treatment gap" in clinical practice.[4]

Atogepant, a calcitonin gene-related peptide receptor antagonist, does not induce vasoconstriction; however, it produced significant capsaicin-induced dermal vasodilation when tested in rhesus monkeys.[5,6] Therefore, atogepant is not recommended for patients with moyamoya disease or reversible cerebral vasoconstriction syndrome, as drugs with vasodilatory properties have been reported to be beneficial in these conditions.[7] Recently, an expert consensus in Thailand suggested that gepants could be considered for the acute treatment of migraine attacks in adults for whom triptans or other acute migraine medications are contraindicated, such as those with established cerebrovascular diseases.[8] Accordingly, atogepant could potentially be used to treat clinically stable patients following a stroke, although robust evidence from dedicated clinical studies or additional real-world data remains limited.

Botulinum toxin A may be an option for patients with chronic migraine and comorbid cerebrovascular disease, provided meticulous attention is paid to hemostasis when antiplatelet agents or anticoagulants are prescribed.[1] Although verapamil has been reported as an effective preventive treatment for trigeminal autonomic cephalgia-like headaches following dorsolateral medullary infarction, appropriate caution regarding its mechanisms of action is warranted.[9]

In contrast, triptans are contraindicated due to their vasoconstrictive properties in patients with a history of stroke, uncontrolled hypertension, or established vascular disease. Real-world data further support this restriction, demonstrating a very rare but significantly higher risk of non-fatal stroke in patients with confirmed cardiovascular or cerebrovascular disease following triptan use (relative risk, 8.00; 0.23% vs. 0.03%).[10]

In patients with moyamoya disease or a history of stroke, headaches represent a common yet complex clinical manifestation rather than a benign comorbidity, necessitating careful classification based on phenotype, temporal context, and appropriate neuroimaging findings. As treatment paradigms evolve, non-vasoconstrictive therapies may expand therapeutic options for migraine or migraine-like secondary headaches in patients with a critical vascular burden, whereas vasoconstrictive agents should remain contraindicated in this population.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: SJC; Methodology: 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

Not applicable.

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1. Eun MY, Jung JM, Choi JC. A practical approach to headache in Moyamoya disease. Headache Pain Res 2025;26:173-183.
2. Kim JS. Headache and stroke: a review. Headache Pain Res 2026;27:7-12.
3. Jeong HJ, Lee MJ. Real-world experience of lasmiditan for the acute treatment of migraine. J Clin Neurol 2025;21:332-339.
4. VanderPluym JH. The implications of losing treatment options: Why lasmiditan's discontinuation matters. Headache 2026 Jan 5 [Epub]. https://doi.org/10.1111/head.70041.
5. Cho S, Chang K. Gepants for migraine: an update on long-term outcomes and safety profiles. Headache Pain Res 2025;26:184-192.
6. Moore E, Bell IM, Fraley ME, et al. Pharmacologic characterization of atogepant: a potent and selective calcitonin gene-related peptide receptor antagonist. Cephalalgia 2024;44:3331024231226186.
7. Kim JY, Kim HJ, Choi EH, et al. Vessel wall changes on serial high-resolution MRI and the use of cilostazol in patients with adult-onset Moyamoya disease. J Clin Neurol 2022;18:610-618.
8. Anukoolwittaya P, Rattanawong W, Vongvaivanich K, et al. Expert consensus on gepants for acute and preventive treatment of migraine in Thailand. J Headache Pain 2025;26:131.
9. Kim JM, Lee HL, Kang YR, Kim JT, Lee SH. Trigeminal autonomic cephalalgias following unilateral dorsolateral medullary infarction: a case series and literature review. Headache Pain Res 2025;26:218-225.
10. Wang Z, VanderPluym JH, Halker Singh RB, et al. Safety of triptans in patients who have or are at high risk for cardiovascular disease: a target trial emulation. Mayo Clin Proc 2024;99:1722-1731.

Editorial

Headache Pain Res 2026;27(1):4-6
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2026.0006

Headache and Pain Research

Pediatric Headache in Korea: Beyond a Common Complaint to a Chronic Neurological Condition

Yun Jin Lee[1,2]

[1]Department of Pediatrics, Pusan National University Children's Hospital, Pusan National University School of Medicine, Yangsan, Republic of Korea
[2]Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Republic of Korea

INTRODUCTION

Pediatric headache is frequently dismissed as a minor ailment rather than recognized as a chronic condition capable of causing substantial disability. However, the lived experiences of affected children—often characterized by chronic absenteeism, cognitive impairment, and strained family dynamics—present a markedly different reality. Three recent reviews in *Headache and Pain Research* help explain why this clinical gap persists: the challenges of diagnostic framing,[1] the neurological risks associated with undertreated attacks,[2] and the persistent "interictal" burden that affects patients even between episodes.[3] When these issues are examined in the context of Korean epidemiological data and healthcare realities, a consistent pattern emerges: pediatric headache in Korea is both widespread and disabling, yet structurally positioned for under-treatment.

THE REALITY: PREVALENCE IN THE KOREAN CONTEXT

Globally, pediatric headache represents a major public health concern, with prevalence increasing steadily as children progress into adolescence.[4] More recent syntheses commonly estimate migraine prevalence at approximately 11% among children and adolescents, and rates rise further during adolescence.[5] Korean data mirror these international trends with striking consistency. A nationwide survey of Korean schoolchildren reported a 1-year headache prevalence of 29.1%, with higher rates observed in girls and in urban or suburban settings.[6] At this level of frequency, multiple students in a typical classroom are likely to be living with recurrent headache. In addition, Kwon[1] reports that chronic primary headache affects 1%–2% of adolescents, while nearly one quarter experience broader functional somatic symptoms. Collectively, these findings place pediatricians at a complex intersection of neurology and stress-related biological processes.

THE BURDEN OR HIDDEN TOLL: LIFE BETWEEN ATTACKS

Even in the absence of active pain, migraine-related burden frequently persists. Kim and Schwedt[3] emphasize the concept of "interictal burden," defined as a constellation of fatigue, cognitive dysfunction ("brain fog"), sensory hypersensitivity, anticipatory anxiety, and social withdrawal that continues between acute attacks. This hidden burden is particularly consequential in Korea, where academic

Received: January 30, 2026; **Accepted:** January 31, 2026
Correspondence: Yun Jin Lee, M.D., Ph.D.
Department of Pediatrics, Pusan National University Children's Hospital, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Republic of Korea
Tel: +82-55-360-2180, Fax: +82-55-360-2181, E-mail: jinnyeye@naver.com

performance is closely tied to consistent daily attendance and sustained cognitive demand. Interictal symptoms—including impaired concentration, planning difficulties, and anxiety about future attacks—often result in school presenteeism (attending school while cognitively impaired) and reduced participation in after-school activities, accompanied by social withdrawal. Moreover, stigma surrounding invisible pain frequently compels children to conceal symptoms, delaying timely medical evaluation and intervention.[3]

THE TREATMENT GAP: DANGERS OF "MEDICATION UNDERUSE"

A common misconception is that medication overuse is the primary driver of headache worsening. Moon and Chung,[2] however, argue that medication underuse—manifesting as delayed or inadequate treatment—is equally hazardous because it plays a critical role in perpetuating neuroinflammation and central sensitization, thereby increasing attack frequency and treatment resistance. Families who are primarily cautioned about the risks of frequent analgesic use may delay intervention until attacks become severe, which reduces the effectiveness of acute therapy and increases the risk of chronification.[2]

In Korea, specific structural hurdles exacerbate this problem:

- Low utilization of migraine-specific acute therapy (triptans): A large population-based Korean analysis found that migraine-specific triptans are prescribed to only approximately 10% of migraine patients, despite established efficacy.[7] Although these data are not pediatric-specific, they reflect a broader national pattern of underutilization that likely influences pediatric practice.
- Limited approved pediatric triptan options: While multiple triptans are available internationally, only almotriptan is approved for use in Korean adolescents, narrowing clinician choice and encouraging reliance on non-specific analgesics.[8]
- Reliance on non-specific analgesics and early discontinuation: Newly diagnosed migraine patients are often treated primarily with nonsteroidal anti-inflammatory drugs or acetaminophen rather than migraine-specific agents, an approach that may fail to interrupt pathways leading to chronification.[2,9]

WHY DIAGNOSTIC FRAMING MATTERS: "SOMATIC" DOES NOT MEAN BENIGN

Kwon's review[1] addresses a critical diagnostic "gray zone": pediatric headache may meet the International Classification of Headache Disorders, third edition criteria for a primary headache disorder, may reflect somatic symptom and related disorders, or may involve overlapping features of both. In clinical practice, labeling headache as "stress-related" or "functional" can inadvertently result in therapeutic withdrawal, characterized by repeated diagnostic testing, reassurance without structured follow-up, and limited active management. Kwon[1] advocates a holistic approach that integrates psychoeducation with non-pharmacological interventions, such as cognitive behavioral therapy (CBT) and biofeedback, to support functional improvement across both primary headache and somatic presentations. Despite this recommendation, access to CBT, biofeedback, school-based accommodations, and interdisciplinary headache care remains inconsistent across Korea.

A STRATEGIC PATH FORWARD FOR KOREA

To improve outcomes, clinical priorities must shift from simply counting headache days to actively preventing disability:

- Prioritize early intervention (avoid underuse): Families require clear, explicit guidance regarding when to initiate treatment to reduce the risks associated with medication underuse.[2]
- Broaden assessment: Treatment success should be evaluated using functional outcomes, including school participation and interictal burden, rather than pain frequency alone.[3]
- Unified framework: Moving beyond the "organic versus psychogenic" dichotomy allows clinicians to focus on shared neurological mechanisms, such as central sensitization.[1]
- Korea-specific policy expansion: There is an urgent need to expand approved pediatric pharmacologic options and strengthen school-based support systems.[8]

CONCLUSION

Pediatric headache is common, disabling, and insufficiently treated largely because its clinical significance is underestimated. Recognizing headache as a chronic biopsychosocial disorder with both ictal and interictal consequences necessitates a fundamental shift in clinical priorities. Early, proactive, and integrated management—combining timely pharmacologic treatment, psychological support, and family-centered education—is essential to prevent long-term disability. Failure to act risks exposing children to prolonged and avoidable suffering, impaired development, and entrenched pain pathways. Pediatric headache represents a serious neurological challenge, and addressing this condition appropriately requires the healthcare system to deliver the same level of sustained therapeutic commitment typically reserved for other major chronic pediatric disorders.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

Yun Jin Lee is the Associate Editor 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

Not applicable.

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1. Kwon HE. Headache as a somatic symptom in pediatrics: diagnosis and integrated management. Headache Pain Res 2025;26:193-199.
2. Moon HS, Chung PW. The hidden risks of medication underuse in migraine progression. Headache Pain Res 2025;26:209-217.
3. Kim SK, Schwedt TJ. Interictal burden of migraine: a narrative review. Headache Pain Res 2025;26:200-208.
4. Abu-Arafeh I, Razak S, Sivaraman B, Graham C. Prevalence of headache and migraine in children and adolescents: a systematic review of population-based studies. Dev Med Child Neurol 2010;52:1088-1097.
5. Ishiyama S, Matsumura A, Hayakawa M, Kohno Y, Ishikawa E. Headache prevalence and impact among school-aged children in a Japanese town: the AMI-GRAINES study. Sci Rep 2026;16:1144.
6. Rho YI, Chung HJ, Lee KH, et al. Prevalence and clinical characteristics of primary headaches among school children in South Korea: a nationwide survey. Headache 2012;52:592-599.
7. Ha WS, Jeong J, Song S, Yum J, Chu MK. Trends in triptan usage in Korea: a population-based cohort study. J Korean Med Sci 2024;39:e222.
8. Kim S. Pediatric headache: a narrative review. J Yeungnam Med Sci 2022;39:278-284.
9. Rhew K. Medication prescribing status in pediatric patients with migraine. Korean J Clin Pharm 2022;32:178-184.

Review Article

Headache Pain Res 2026;27(1):7-12
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2025.0028

Headache and Pain Research

Headache and Stroke: A Review

Jong S. Kim

Department of Neurology, Gangneung Asan Hospital, University of Ulsan College of Medicine, Gangeung, Republic of Korea

Abstract

Headache is a common disorder that is usually unaccompanied by focal neurological dysfunction. Less commonly, headache may be associated with central nervous system diseases such as stroke. Headache can occur at the time of stroke onset, but it may also precede or follow the onset of stroke. Nevertheless, headaches associated with stroke have not been sufficiently studied, in part because stroke physicians are primarily focused on diagnosis, risk factors, pathophysiological mechanisms, imaging findings, and treatment (e.g., thrombolysis and endovascular therapy) rather than on headache. In this narrative review, I describe the frequency and characteristics of headache across various stroke subtypes, including ischemic stroke, transient ischemic attack, intracerebral hemorrhage, subarachnoid hemorrhage, and other miscellaneous conditions such as venous infarction, arterial dissection, and reversible cerebral vasoconstriction syndrome.

Keywords: Headache, Migraine, Stroke

INTRODUCTION

Headache is a common disorder. The two most common causes of headache are migraine and tension-type headache, and the vast majority of patients with these conditions do not show permanent neurological dysfunction or significant brain abnormality in computed tomography or magnetic resonance imaging (MRI). Less commonly, headache can be caused by head/neck trauma, central nervous system infection, cranial nerve or muscle diseases associated with a variety of causes. Undoubtedly, stroke is one of the etiologies of headache. However, headache is not a usual or dominant symptom of stroke, especially when there are no associated neurological dysfunctions. Exceptions are arterial dissection, venous stroke, reversible cerebral vasoconstriction syndrome (RCVS), or strokes associated with meningitis.

Headaches may precede, occur concomitantly or after the onset of stroke. The reported frequency of headache in stroke patients ranges from 7% to 65%. The extremely wide variation may be due to different enrollment criteria, and different degree of headache evaluation or inability of the headache assessment in patients with certain neurological dysfunction (e.g., altered consciousness, aphasia, dysarthria, etc.).[1] Most importantly, assessment of headache is often neglected in patients with acute stroke when changing neurological dysfunction associated with stroke per se is the primary interest for clinicians.

Received: December 21, 2025; **Revised:** January 23, 2026; **Accepted:** January 24, 2026
Correspondence: Jong S. Kim, M.D., Ph.D.
Department of Neurology, Gangneung Asan Hospital, University of Ulsan College of Medicine, 38 Bangdong-gil, Sacheon-myeon, Gangneung 25440, Republic of Korea
Tel: +82-33-641-4196, E-mail: jongskim@amc.seoul.kr

HEADACHES ASSOCIATED WITH VARIOUS SUBTYPES OF STROKE

1. Ischemic stroke

Among the patients with stroke who reported the presence of headache by the prospective interview from day 1 to day 8, 86% experienced headache on the day of stroke symptoms, and the remainder had headache at 2–5 days.[2] In another study, 31% had headache prior to, 11% simultaneous with, and 45% after the onset of stroke symptoms.[3] A recent meta-analysis reported that most patients experience headache symptoms on the day of stroke presentation.[1] The headache may disappear within days but can persist for months, or even years.[1]

In most cases (50%–80%), post-stroke headaches manifest as 'tension-type headache' with various descriptions such as pressure, aching or soreness. Symptoms of migraine, e.g., throbbing pain, photophobia, nausea/vomiting are uncommon.[3] The intensity of headache varies from patients to patients. Some studies showed that younger patients more often suffer from post-stroke headache,[4,5] whereas this argument was not supported by another study.[6] In general, female patients complain of headache more often than male patients.

Regarding the location of stroke, some studies reported that the incidence and the intensity of post-stroke headache may be associated with lesions affecting the insular cortex or somatosensory cortical brain. One study[7] used MRI lesion mapping to compare patients with and without headache in ischemic stroke. Authors identified the insular cortex as the region of maximal lesion overlap in those with stroke-related headache. As the insular cortex is a well-established region in pain processing, the results suggest that, at least in a subgroup of patients, acute stroke-related headache might be centrally driven.

In general, cortical strokes are more closely associated with headache than deep, subcortical lacunar infarcts.[1] Studies have also shown that strokes occurring in the posterior circulation, especially in the vertebra-basilar territory develop headache approximately two times more often than those affecting the anterior circulation.[1] There are several putative explanations for this observation that include a difference in trigeminal and autonomic innervation between anterior versus posterior cerebral vessels. Indeed, differences in the innervation pattern of the meninges overlying the posterior cerebral cortices and cerebellum raise the possibility that strokes involving these areas may have a greater chance to stimulate pain-sensing trigeminal fibers. The posterior circulation may also have differential cerebral auto-regulation and become more susceptible to fluctuations in vasomotor tone and permeability. Finally, it is possible that this observation may be related to a higher proportion of migraineurs in the subpopulation of patients with posterior circulation strokes as compared to those with anterior circulation strokes.[1]

1) Thrombotic arterial disease

Patients with ischemic stroke due to large artery atherothrombosis (LAD) often develop headache, that may be explained by dilation of the collaterals or distension of meningeal arteries or trigeminal nerves. Headache may be one of the main predictors for the stroke progression in these patients.[8]

2) Embolic disease

Embolic occlusion at the proximal part of the middle cerebral artery (MCA) or the top of the basilar artery may develop headache associated with corresponding neurological dysfunction. The headache may be caused by distension of the recipient arteries and dilatation of the collaterals.

3) Small vessel disease

Cerebral small vessel disease (SVD) is not associated with atherosclerosis. Rather, lipohyalinosis, fibrinoid degenerations are closely associated. The resultant changes in brain include white matter hyperintensities, microbleeds, lacunar infarction, or perivascular enlargement. Although SVD is associated with neurologic dysfunction such as lacunar syndromes as well as cognitive impairment, they less likely result in headache as compared to strokes associated with LAD or cardiac embolism.

However, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an exception. Migraine is a common symptom in patients with CADASIL, and has usually been shown to be the first neurological symptom.[9] In one review paper, 35% of the migraine patients with CADASIL reported symptoms of aura.[10] It seems that genetic abnormalities may be

related with both migraine and CADASIL, although there are arguments against the link between the subcortical nature of lacunar stroke and the occurrence of cortical migraine aura. Nevertheless, cortical spreading depression was found to be enhanced in CADASIL mouse model, and vascular NOTCH3 mutations may increase the susceptibility for spreading depression in CADASIL patients. Some suggest that there are reduced numbers of endothelial progenitor cells and endothelial vascular reactivity in both migraine and CADASIL patients suggesting that certain endothelial dysfunction may link between the two conditions.[8,11] The prevalence of migraine was reported to be higher in European (approximately 43%) than in Asian CADASIL patients (approximately 5%), suggesting the presence of different ethnic susceptibility.[9]

4) Transient ischemic attack

It has been shown that headache occurs in approximately 30% of transient ischemic attack (TIA) patients.[12] Considering the absence of a significant brain damage, it is difficult to understand the pathogenic mechanism of headache in these patients. However, ischemic brain damage, although transient and not readily detected by conventional imaging techniques, may be related to the development of headache. It also has been reported that headaches more often occur in patients with TIA occurring in the vertebrobasilar territory than in those involving the anterior circulation,[12] possibly due to the richer trigeminal innervation in the vertebrobasilar circulation.

2. Hemorrhagic stroke

1) Intracerebral hemorrhage

In general, headache is more common and severe in patients with intracerebral hemorrhage (ICH) than in those with ischemic stroke, probably because of the more severe mass effect that affects the pain-sensitive meninges and trigeminal fibers. Headaches were reported to occur in approximately 60% of ICH patients in the initial stage.[13] It is usually ipsilateral to the hemorrhage, but can be generalized when patients develop increased intracranial pressure and/or hydrocephalus. One study showed that location of the lesion (cerebellar, lobar), female sex, transtentorial herniation are factors associated with headache in ICH patients.[13]

2) Subarachnoid hemorrhage

Headache is the most important symptom of subarachnoid hemorrhage (SAH), that has traditionally been described as 'the worst headache in my life'. However, this expression does not necessarily indicate the presence of SAH because such symptoms may be described in patients with other conditions such as migraine, RCVS or thunderclap headache. Headache is usually maximal at onset of SAH, although some patients may have had one or more preceding headaches (sentinel headache).

3. Arterial dissection

Headache is a notable symptom associated with cerebral arterial dissection. When the affected artery is the extracranial internal carotid artery, the pain is usually located in the neck, often radiating to the ipsilateral face. When a dissection affects the extracranial vertebral artery (VA), the pain usually occurs at the ipsilateral mastoid bone and radiates to the occiput. Pain usually improves over a period of 3–6 months.

For intracranial arterial dissection, pain occurs in 90% of the cases. The pain is usually located to the ipsilateral temporal area in patients with MCA dissection, whereas posterior cerebral artery dissection is associated with ipsilateral eye or occipital pain. Basilar artery dissection is associated with pain in the area of occipital, vertex or diffuse area. With development of advanced imaging techniques such as high resolution vessel wall MRI, dissections occurring in other smaller vessels such as anterior cerebral artery, posterior inferior cerebral artery are occasionally observed, but the location and intensities of pain in these conditions are not properly investigated.

Partly because VA is one of the most frequent sites for dissection,[14] and partly because associated neurological symptoms/signs may be minimal or nonspecific (e.g., dizziness, ataxia, focal facial sensory dysfunction) without significant motor dysfunction, the presence of VA dissection needs to be suspected in patients with sudden neck/occipital pain especially when the symptoms are associated with dizziness or ataxia.

4. Venous stroke

Occlusion of one or several cerebral veins may lead to venous infarction, hemorrhage, or both. This is an uncommon condition, but partly because the symptoms are different from classical arterial stroke and partly because the patients are usually younger than those with usual stroke, the possibility of venous stroke needs to be considered especially when a history taking reveals certain vulnerable conditions: using birth control pills, the postpartum status, head trauma, certain drug ingestion, immunologic disorders such as systemic lupus erythematosis, Bechet's disease, ulcerative colitis, etc., hematologic diseases and infectious disease.

According to the location of venous occlusion, the clinical features vary greatly that include proptosis, conjunctival injection, facial edema, visual disturbances, ophthalmoplegia, hemiparesis etc. Regardless of the location of the venous occlusion, headache is a common symptom occurring in about 70%–80% of the patients. Although there are exceptions, the onset of headache is not as abrupt as SAH. Rather, it increases progressively for days or weeks. Patients are usually treated with anticoagulation. When there is a rapid progression despite the anticoagulation, endovascular therapy can be initiated, which often dramatically improve the patients' clinical symptoms including headache.

5. Reversible cerebral vasoconstriction syndrome

In the 1970s, several women patients were reported who during pregnancy or early puerperium, developed sudden severe headache, nausea, vomiting, seizures and focal neurological dysfunction, that recovered spontaneously within a few weeks. Cerebral angiogram showed arterial stenosis or irregularities that were reversible on repeated angiograms. This was initially called 'postpartum angiopathy'. Similar cases were also reported in patients with migraine or aneurysm. Boston physicians led by Miller Fisher noted the similarity of these cases, and collectively called this as 'Reversible cerebral arterial segmental vasoconstriction syndrome (RCVS)'.

RCVS predominantly affects women, and many are associated with pregnancy and puerperium. It may be associated with the use of vasoactive ergot derivatives. Symptoms may begin during delivery or during 1–2 weeks thereafter. Some patients may develop RCVS at the time of menopause. The headaches are usually generalized but can be localized to the occiput or vertex, and may be exacerbated by physical exertion, straining or coughing. Seizures may occur probably due to brain ischemia or hemorrhages associated with vasoconstriction. Neurological deficits may vary according to the location and extensiveness of brain ischemia or hemorrhages, i.e., motor/sensory dysfunction, dysarthria, aphasia, visual field defect, confusion, and usually improve within several weeks or months. Aneurysmal rupture, vasculitis, arterial dissections should be appropriately differentiated. Although the symptoms and angiographic abnormalities improve spontaneously, vasodilators (calcium channel blockers) with or without steroids are often used. RCVS can also be shown in patients with migraine.

6. Headaches associated with arterial revascularization

Carotid endarterectomy or angioplasty with or without stenting may be associated with headaches that usually begin within hours or weeks after the procedure. The intensity of headache varies from patient to patient. The headache may be accompanied by focal neurological deficits or seizures that are usually associated with newly developed brain lesions. The headache appears to be caused by sudden reperfusion (increased cerebral flow) and resultant severe brain edema or hemorrhage. Brain MRI demonstrates cerebral edema, hemorrhages or infarction. Patients usually show markedly increased blood pressure, and aggressive blood pressure reduction is needed to prevent and treat this so-called reperfusion syndrome.[15]

MIGRAINE AND PATENT FORAMEN OVALE

Although not fully explained, the patent foramen ovale (PFO) is suggested to play a role in the pathophysiology of migraine. Proposed mechanisms include the passage of micro-emboli, metabolites, and vasoactive substances through the PFO, and transient hypoxemia that results in micro-infarcts in the brain.[16] Nevertheless, the association between migraine and PFO has been questioned by previous studies.[17] Some randomized controlled trials (RCTs)

showed that PFO closure was associated with a significant reduction in the number of migraine attacks. However, complete resolution of migraine was only demonstrated by observational studies and not by RCTs. These results seem to provide insufficient support for PFO closure exclusively to treat migraine, although reduction of migraine symptoms may be observed in some patients. This notion is supported by recent comprehensive reviews,[18] which emphasized the need for additional evidence from RCTs. Instead, the guideline-recommended use of monoclonal antibodies targeting the calcitonin gene-related peptide pathway seems to offer another effective pharmacological alternative.[19] Within the context of mixed evidence from PFO closure and alternative pharmacological treatments, PFO closure is not considered as a first-line/routine treatment for migraine.[20]

MOYAMOYA DISEASE

Moyamoya disease (MMD) is a progressive steno-occlusive cerebrovascular disorder of the intracranial internal carotid arteries or proximal middle cerebral arteries characterized by fragile, compensatory collateral vessel formation. Although ischemic and hemorrhagic strokes are the best known clinical manifestations, headaches are relatively common and often disabling.[21] Epidemiological studies have reported that headache occurs in 17%–85% of MMD patients, with particularly high rates among pediatric patients.[22] Headache phenotypes include migraine-like headaches with or without aura, tension-type, cluster, and hemiplegic variants. A relatively large study showed that 44 of 204 children (21.6%) with MMD suffered from headache, and nausea/vomiting were seen in 12. In four, headache developed during hyperventilation, and in three, TIA and headache occurred simultaneously.[23]

These presentations mimic primary headaches, and there can be delays in the diagnosis of underlying MMD. The pathophysiology of MMD-related headaches seems to be multifactorial, involving vascular stenosis, abnormal collateral circulation, altered hemodynamics, and neurogenic inflammation.[21,22] Chronic hypoperfusion may lower the threshold for cortical spreading depression, contributing to migraine-like symptoms. Surgical revascularization may alleviate headaches,[21] but persistent or new headaches may develop postoperatively. Therefore, headaches are more often managed with analgesics or non-steroidal anti-inflammatory drugs. Vasoconstrictive agents (e.g., triptans) are not generally recommended, but non-vasoconstrictive agents are being developed.[22] Further studies are needed to elucidate the epidemiology, pathophysiological mechanisms, and appropriate management of headaches associated with MMD.

CONCLUSION

Headaches may precede, occur concomitantly, or after the onset of stroke. However, in the majority of the patients, headache is not a major symptom of stroke. Therefore, headache has not gained sufficient attention among stroke neurologists. In the clinical practice, careful observation of headaches may help us understand the etiologies of strokes especially SAH, arterial dissection, venous stroke, RCVS, or meningitis. It may also give us a clue for the progress of stroke. For instance, increasing intensity of headache suggests the presence of mass effect, increased ICP, and potential herniation, and may prompt us to detect and treat stroke cases appropriately. Headaches occurring in patients with CADASIL or PFO may allow us to understand the relationship between the two seemingly unrelated condition, migraine and cerebral ischemia. Further studies are needed that will eventually allow us to understand such theoretically and practically important issues in patients with cerebrovascular diseases.

AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING STATEMENT

Not applicable.

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1. Harriott AM, Karakaya F, Ayata C. Headache after ischemic stroke: a systematic review and meta-analysis. Neurology 2020;94:e75-e86.
2. Verdelho A, Ferro JM, Melo T, Canhão P, Falcão F. Headache in acute stroke. A prospective study in the first 8 days. Cephalalgia 2008;28:346-354.
3. van Os HJ, Mulder IA, van der Schaaf IC, et al. Role of atherosclerosis, clot extent, and penumbra volume in headache during ischemic stroke. Neurology 2016;87:1124-1130.
4. Kes VB, Jurašić MJ, Zavoreo I, Lisak M, Jelec V, Matovina LZ. Age and gender differences in acute stroke hospital patients. Acta Clin Croat 2016;55:69-78.
5. Lutski M, Zucker I, Shohat T, Tanne D. Characteristics and outcomes of young patients with first-ever ischemic stroke compared to older patients: the National Acute Stroke ISraeli registry. Front Neurol 2017;8:421.
6. Lisabeth LD, Brown DL, Hughes R, Majersik JJ, Morgenstern LB. Acute stroke symptoms: comparing women and men. Stroke 2009;40:2031-2036.
7. Seifert CL, Schönbach EM, Magon S, et al. Headache in acute ischaemic stroke: a lesion mapping study. Brain 2016;139:217-226.
8. Campolo J, De Maria R, Frontali M, et al. Impaired vasoreactivity in mildly disabled CADASIL patients. J Neurol Neurosurg Psychiatry 2012;83:268-274.
9. Liem MK, Oberstein SA, van der Grond J, Ferrari MD, Haan J. CADASIL and migraine: a narrative review. Cephalalgia 2010;30:1284-1289.
10. Sacco S, Degan D, Carolei A. Diagnostic criteria for CADASIL in the International Classification of Headache Disorders (ICHD-II): are they appropriate? J Headache Pain 2010;11:181-186.
11. Pescini F, Cesari F, Giusti B, et al. Bone marrow-derived progenitor cells in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Stroke 2010;41:218-223.
12. Loeb C, Gandolfo C, Dall'Agata D. Headache in transient ischemic attacks (TIA). Cephalalgia 1985;5 Suppl 2:17-19.
13. Melo TP, Pinto AN, Ferro JM. Headache in intracerebral hematomas. Neurology 1996;47:494-500.
14. Kwon JY, Kim NY, Suh DC, Kang DW, Kwon SU, Kim JS. Intracranial and extracranial arterial dissection presenting with ischemic stroke: lesion location and stroke mechanism. J Neurol Sci 2015;358:371-376.
15. Estol CJ. Carotid revascularization syndrome. Int J Stroke 2006;1:81-90.
16. Silalahi TDA, Hariyanto TI. Efficacy and safety of patent foramen ovale closure for mitigating migraine: a systematic review and meta-analysis of randomized trials and observational studies. Ther Adv Neurol Disord 2024;17:17562864241271033.
17. Honasoge AP, Suradi HS, Tobis JM, Kavinsky CJ. Patent foramen ovale closure for nonstroke indications. J Soc Cardiovasc Angiogr Interv 2023;2:101135.
18. Apostolos A, Alexiou P, Papanikolaou A, et al. Patent foramen ovale closure in special clinical situations: more questions than answers? Life (Basel) 2024;14:706.
19. Sacco S, Amin FM, Ashina M, et al. European Headache Federation guideline on the use of monoclonal antibodies targeting the calcitonin gene related peptide pathway for migraine prevention - 2022 update. J Headache Pain 2022;23:67.
20. Kim JS, Diener HC, Low TT, Albers B, Sharma VK, Kim BJ. Asian-Pacific expert opinion on patent foramen ovale closure: review of new evidence and focused update. J Stroke 2025;27:329-337.
21. Kim JS. Moyamoya disease: epidemiology, clinical features, and diagnosis. J Stroke 2016;18:2-11.
22. Eun MY, Jung JM, Choi JC. A practical approach to headache in Moyamoya disease. Headache Pain Res 2025;26:173-183.
23. Seol HJ, Wang KC, Kim SK, Hwang YS, Kim KJ, Cho BK. Headache in pediatric moyamoya disease: review of 204 consecutive cases. J Neurosurg 2005;103:439-442.

Review Article

Headache Pain Res 2026;27(1):13-20
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2026.0003

Headache and Pain Research

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

Jaeho Kim

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

Abstract

Migraine is a prevalent and disabling neurological disorder in which established pathophysiological mechanisms, including trigeminovascular activation and calcitonin gene-related peptide (CGRP) signaling, do not fully account for interindividual susceptibility, chronification, or treatment refractoriness. Advances in neurobiology have drawn attention to brain clearance pathways, specifically the glymphatic system and meningeal lymphatic vessels, as potential modulators of neuroinflammation and cerebrospinal fluid (CSF) dynamics. These systems regulate the exchange and drainage of CSF, interstitial solutes, and immune mediators and are strongly influenced by sleep and state-dependent physiology, both of which are closely linked to migraine pathophysiology. In this narrative review, we describe the anatomical and functional organization of brain lymphatic and glymphatic systems and critically evaluate emerging evidence connecting these pathways to migraine. Indirect human imaging studies and experimental models indicate that alterations in perivascular transport, meningeal lymphatic drainage, sleep disruption, and CGRP-related signaling may converge to modulate brain clearance efficiency in migraine. Although the available evidence remains heterogeneous and largely indirect, these findings offer a coherent framework for integrating clearance-related physiology into existing migraine models. We further discuss neuromodulation as a potential strategy for influencing brain clearance mechanisms. In particular, transcranial low-intensity ultrasound has been shown to enhance CSF movement in vivo, providing direct mechanistic support for clearance modulation. Other neuromodulation modalities may exert indirect effects through autonomic regulation, neural oscillations, or vascular dynamics. While clinical evidence remains preliminary, a clearance-oriented perspective may help guide future biomarker development and translational research in migraine.

Keywords: Glymphatic system, Lymphatic system, Migraine disorders, Ultrasonic therapy

INTRODUCTION

Migraine is a common and disabling neurological disorder characterized by recurrent head pain and sensory hypersensitivity. Although therapeutic advances—particularly agents targeting calcitonin gene-related peptide (CGRP)—have markedly improved outcomes for many patients, a substantial proportion continues to experience frequent

Received: January 12, 2026; **Revised:** January 27, 2026; **Accepted:** January 30, 2026
Correspondence: Jaeho Kim, M.D., Ph.D.
Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, 7 Keunjaebong-gil, Dongtan-gu, Hwaseong 18450, Republic of Korea
Tel: +82-31-8086-2310, Fax: +82-50-4068-1402, E-mail: ion8484@gmail.com

attacks or progression to chronic migraine. This observation underscores the need for complementary mechanistic frameworks that can provide additional insights into disease susceptibility and therapeutic targets. Beyond ictal headache episodes, migraine is increasingly recognized as a disorder associated with a substantial interictal burden, including persistent sensory and sleep-related disturbances. These features suggest that migraine-related pathophysiology may extend beyond discrete attacks and involve ongoing alterations in brain physiology between episodes, providing a relevant context for considering brain clearance mechanisms.[1]

Recent advances in neurobiology have identified specialized brain clearance pathways that contribute to the removal of interstitial solutes and inflammatory mediators. The glymphatic system facilitates cerebrospinal fluid (CSF)-interstitial fluid (ISF) exchange along perivascular spaces and appears to play a central role in metabolic waste clearance and immune signaling in the brain. Dysfunction of the glymphatic pathway has been implicated in a variety of neurological conditions and is proposed to contribute to headache pathophysiology as well.[2,3] In migraine, indirect imaging markers such as altered diffusion metrics along perivascular spaces have been interpreted as suggesting impaired glymphatic transport, consistent with emerging evidence of glymphatic disturbance in this disorder.[4]

Complementing glymphatic exchange, meningeal lymphatic vessels provide an anatomically distinct outflow route for CSF-derived solutes and immune cells toward deep cervical lymph nodes, linking central nervous system fluid dynamics with peripheral immune surveillance.[5]

Importantly, glymphatic function is strongly influenced by sleep and state-dependent physiology. Glymphatic transport is enhanced during sleep-like conditions, which may be relevant to migraine given the well-established interactions between sleep disruption and headache disorders.[6] Emerging imaging studies in humans have begun to explore clearance-related signatures in migraine, including meningeal lymphatic drainage abnormalities and alterations in perivascular fluid dynamics, although these findings are heterogeneous and require further validation.[7,8]

Mechanistically, CGRP signaling—a key driver of migraine pain—not only contributes to neurovascular inflammation but may also influence meningeal lymphatic function, thereby providing a possible link between classical migraine biology and brain clearance pathways.[3] From a therapeutic standpoint, the brain clearance framework suggests novel interventional opportunities. Neuromodulation may influence CSF movement and glymphatic exchange in ways that extend beyond neural excitability modulation.

In vivo imaging evidence has shown that transcranial focused ultrasound can enhance CSF movement and facilitate waste clearance in experimental models, providing a potential mechanistic basis for its exploration in migraine.[9] In addition, emerging translational studies, including our recent in-press work[10] support the broader concept that low-intensity ultrasound may modulate glymphatic-related processes in humans.

In this review, we provide a concise overview of brain glymphatic and lymphatic systems, summarize evidence linking these pathways to migraine, and discuss the therapeutic implications of neuromodulation—with a focus on ultrasound-based approaches. By integrating mechanistic insight with clinical perspective, we aim to present a pragmatic framework for future biomarker development and translational research in migraine. Figure 1 summarizes the proposed interactions between migraine pathophysiology, brain clearance systems, and neuromodulation discussed in this review.

OVERVIEW OF BRAIN CLEARANCE SYSTEMS

Brain homeostasis depends on specialized clearance pathways that regulate the movement and removal of CSF, interstitial solutes, and immune signals. Two anatomically and functionally distinct but interconnected systems are central to this process: the glymphatic system and the meningeal lymphatic system.

1. Glymphatic system

The glymphatic system operates at the parenchymal level and facilitates convective exchange between CSF and ISF along perivascular spaces. CSF enters the brain predominantly via periarterial pathways, mixes with ISF within the parenchyma, and exits along perivenous routes, thereby contributing to the clearance of metabolic byproducts and neuroactive solutes.[11] Glymphatic transport is strongly state dependent, with enhanced CSF-ISF exchange during

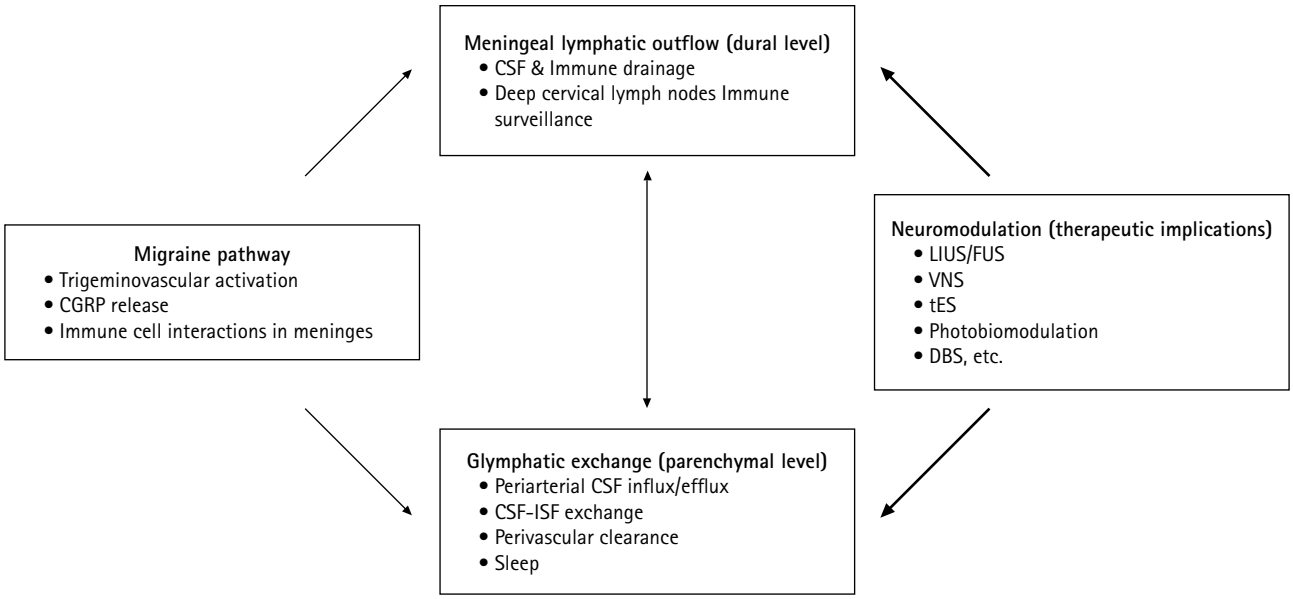


Figure 1. Proposed interactions between migraine pathophysiology, brain clearance systems, and neuromodulation. Migraine involves trigeminovascular activation with CGRP release and neuroimmune interactions in the meninges. Brain clearance operates at two interconnected levels: glymphatic exchange within the parenchyma, characterized by periarterial CSF influx, CSF-ISF exchange, and perivascular clearance that are modulated by sleep; and meningeal lymphatic outflow at the dural level, which drains CSF-derived solutes and immune components toward deep cervical lymph nodes. Experimental evidence suggests that migraine-related mechanisms, including CGRP signaling and sleep disruption, may impair these clearance pathways. Neuromodulation strategies—such as low-intensity or FUS and other noninvasive modalities—may influence CSF dynamics and glymphatic–lymphatic function, representing a potential therapeutic approach for modulating migraine susceptibility. Solid arrows indicate experimentally supported relationships, whereas bold arrows denote hypothesized interactions.
CGRP, calcitonin gene-related peptide; CSF, cerebrospinal fluid; ISF, interstitial fluid; LIUS, low-intensity ultrasound stimulation; FUS, focused ultrasound; VNS, vagus nerve stimulation; tES, transcranial electrical stimulation; DBS, deep brain stimulation.

sleep and suppression during wakefulness, reflecting physiological regulation of brain waste clearance.[12] From a clinical standpoint, this framework is relevant to migraine, a disorder in which sleep disturbance is both a common trigger and a frequent consequence of attacks, potentially predisposing patients to impaired brain clearance.

2. Meningeal lymphatic system

In contrast to the parenchymal glymphatic pathway, the meningeal lymphatic system functions at the dural level and represents a conventional lymphatic outflow route. Meningeal lymphatic vessels drain CSF-derived solutes, macromolecules, and immune cells toward the deep cervical lymph nodes, linking intracranial fluid dynamics with peripheral immune surveillance.[13,14] Because migraine pain arises from meningeal and trigeminovascular structures, alterations in meningeal lymphatic drainage may be particularly relevant to migraine pathophysiology.

3. Functional interaction and clinical relevance

Although distinct, the glymphatic and meningeal lymphatic systems are functionally interconnected. Solutes cleared from the brain parenchyma via glymphatic pathways ultimately rely on meningeal lymphatic vessels for extracranial drainage, and dysfunction at either level may compromise overall brain clearance efficiency.[13-15] In migraine, mechanisms such as sleep disturbance and neurogenic inflammation may disrupt this coordinated clearance network, providing a conceptual basis for emerging biomarker and therapeutic research.

EVIDENCE OF LYMPHATIC AND GLYMPHATIC DYSFUNCTION IN MIGRAINE

Current evidence linking migraine to dysfunction of brain clearance systems remains emerging and heterogeneous. Rather than definitive proof, the available data collectively suggest that alterations in CSF dynamics, perivascular transport, and meningeal immune drainage may accompany migraine susceptibility and chronification.

1. Indirect human imaging evidence of altered brain clearance

In humans, direct visualization of glymphatic flow remains technically challenging. As a result, most clinical evidence in migraine relies on indirect imaging markers that reflect perivascular fluid dynamics. Diffusion tensor imaging–based analysis along perivascular spaces (DTI-ALPS) has been proposed as a surrogate marker of glymphatic function and has been applied to patients with migraine. DTI-ALPS is based on the anatomical observation that perivascular spaces surrounding penetrating arteries and veins serve as major conduits for glymphatic fluid transport. Because diffusion along these spaces is directionally constrained, DTI can be used to estimate preferential water diffusivity parallel to perivascular pathways. The ALPS index therefore provides an indirect surrogate of perivascular fluid movement rather than a direct measure of glymphatic flow. Several studies report altered ALPS indices or perivascular imaging features in migraine compared with controls, although the direction and magnitude of these changes vary across cohorts.[3]

In migraine, DTI-ALPS studies have reported heterogeneous findings. Some studies suggest altered ALPS indices in chronic migraine compared with episodic migraine or controls, whereas data comparing migraine with and without aura remain limited and inconsistent. Importantly, several studies have reported null or variable results, and correlations between ALPS indices and clinical variables such as headache frequency or disease duration have not been consistently demonstrated.[3,4,8] Additional radiological findings associated with migraine, such as enlarged perivascular spaces and white matter hyperintensities-have also been discussed in the context of impaired ISF clearance.[16] However, these features are nonspecific and may reflect cumulative vascular, inflammatory, or aging-related processes rather than direct evidence of glymphatic dysfunction.

2. Experimental evidence linking migraine-related mechanisms to meningeal lymphatics

Beyond imaging, experimental studies provide more direct mechanistic insight. Recent preclinical work has demonstrated that meningeal lymphatic vessels are functionally responsive to migraine-related signaling pathways. In particular, CGRP signaling—central to migraine pathophysiology—has been shown to modulate meningeal lymphatic function, influencing CSF efflux, immune interactions, and pain-related behaviors in animal models. These findings suggest that meningeal lymphatics may represent an interface through which trigeminovascular activation and immune signaling converge.[17]

3. Sleep disturbance as a modifier of clearance in migraine

Sleep disturbance is one of the most consistent clinical features associated with migraine, acting as both a trigger and a consequence of attacks. Experimental studies outside the migraine field demonstrate that sleep strongly enhances glymphatic transport, whereas sleep deprivation suppresses CSF-ISF exchange. In migraine, recurrent sleep disruption may therefore represent a physiological mechanism by which brain clearance efficiency is reduced, potentially facilitating the accumulation of pro-inflammatory or pro-nociceptive mediators.[12,18]

4. Limitations of current evidence

Despite growing interest, several limitations should be acknowledged. Human studies largely rely on indirect imaging markers with variable reproducibility, while experimental models may not fully capture the complexity of migraine phenotypes. Moreover, whether observed clearance alterations are a cause, consequence, or epiphenomenon of migraine remains unresolved. These gaps underscore the need for standardized biomarkers and longitudinal studies integrating imaging, physiological measures, and clinical outcomes.

NEUROMODULATION AS A STRATEGY TO MODULATE BRAIN CLEARANCE

Neuromodulation refers to the application of electrical, magnetic, or acoustic stimulation to alter neural activity or physiological processes, and has been increasingly explored in migraine for both preventive and acute treatment. Traditionally, neuromodulation strategies have focused on modulating cortical excitability or nociceptive processing. In the context of brain clearance, however, neuromodulation may additionally influence CSF dynamics, vascular pulsatility, and state-dependent physiology. The brain clearance framework adds an additional, clinically testable dimension: whether neuromodulation can influence CSF dynamics and, by extension, glymphatic–lymphatic function. This perspective is particularly relevant because clearance pathways are state dependent and are tightly coupled to sleep physiology, arousal, and neurovascular tone.

1. Why neuromodulation is conceptually attractive in a clearance framework

From a translational standpoint, clearance dysfunction—if present in migraine—may not be optimally addressed by conventional analgesic or anti-inflammatory approaches alone. Neuromodulation offers a potentially complementary route by targeting upstream physiology that shapes CSF movement (e.g., vascular pulsatility, perivascular transport, and state-dependent fluid exchange). In this model, the therapeutic hypothesis is not limited to "pain inhibition," but extends to "restoring a physiological state that facilitates clearance."

2. Transcranial ultrasound: direct in vivo evidence of enhanced cerebrospinal fluid movement and clearance modulation

Among neuromodulation modalities, transcranial low-intensity ultrasound has particular relevance because it has been shown using real-time optical imaging to enhance CSF movement and cortical CSF influx in vivo, providing mechanistic support for the concept that stimulation may influence clearance-related fluid dynamics.[9] Clinically, this evidence is valuable because it establishes a measurable intermediate endpoint (CSF movement/CSF influx) that can be linked to imaging biomarkers and, ultimately, headache outcomes in future trials.

Consistent with this physiological effect on CSF dynamics, a related body of work in neurodegeneration provides proof-of-concept that ultrasound-based interventions can influence glymphatic–lymphatic drainage at a systems level. Focused ultrasound combined with microbubbles has been reported to enhance the drainage of soluble amyloid-β from the brain to CSF spaces and onward toward deep cervical lymph nodes, supporting the broader plausibility of ultrasound-mediated clearance modulation.[19] This line of evidence does not imply direct clinical efficacy for migraine, but it strengthens the mechanistic rationale that clearance pathways are modifiable rather than purely passive.

3. Other neuromodulation modalities

Beyond transcranial ultrasound, other neuromodulation techniques have been investigated for their potential influence on CSF dynamics and brain clearance pathways. Clinically patterned vagus nerve stimulation (VNS) has been shown to enhance CSF tracer penetrance in animal models, suggesting that VNS may alter CSF/ISF exchange and clearance mechanisms.[20] Low-frequency auricular VNS increased arterial vasomotion and cortical CSF influx in vivo, further supporting the concept that modulation of autonomic pathways can influence perivascular fluid movement.[21] Transcranial electrical stimulation (tES) modalities, such as transcranial direct current or alternating current stimulation, primarily target cortical excitability but also influence neural oscillations and neurovascular coupling. While direct evidence linking tES to glymphatic clearance is currently limited, recent studies demonstrate that slow vascular and neural rhythms—which can be influenced by neuromodulatory interventions such as tES-are associated with enhanced CSF movement and glymphatic function during states such as non-rapid eye movement sleep.[22,23] Photobiomodulation has been proposed to augment brain lymphatic and glymphatic drainage in preclinical models, potentially via vasodilatory effects on vascular and lymphatic pathways.[24] Although these modalities do not yet have direct clinical evidence of clearance modulation in migraine, their physiological

effects on autonomic tone, vascular dynamics, or neural rhythms provide a plausible mechanistic basis for future investigation in headache and pain disorders.

In addition to clearance-oriented neuromodulation strategies, several neuromodulation approaches have been investigated in migraine and pain disorders, primarily with the aim of modulating nociceptive processing or cortical excitability. For example, noninvasive stimulation techniques, including motor cortex stimulation and other brain stimulation paradigms, have demonstrated modulatory effects on pain perception and migraine-related symptoms in both experimental and clinical settings.[25-27] These approaches are generally conceptualized as preventive or abortive interventions depending on stimulation timing and target engagement. In contrast, focused ultrasound-based neuromodulation may occupy a distinct conceptual position. Rather than directly targeting pain networks, ultrasound has been shown to influence CSF movement and perivascular transport, suggesting a potential role in modulating the physiological state that shapes migraine susceptibility. From this perspective, ultrasound-based approaches may be more appropriately framed as modulators of underlying brain physiology, which could complement established preventive or abortive strategies rather than replace them.

4. Translational implications for migraine

In migraine, a clearance-oriented neuromodulation strategy is best framed as hypothesis-driven and staged. Near-term goals include identifying patients with the most convincing clearance-related signatures (e.g., indirect glymphatic markers or meningeal lymphatic-related imaging patterns), and testing whether neuromodulation produces measurable changes in CSF dynamics and clearance surrogates alongside clinical endpoints such as attack frequency and disability. Longer-term, mechanistic integration with established migraine biology-particularly meningeal neuroinflammation and CGRP-linked pathways-may help determine whether "clearance modulation" represents a distinct therapeutic mechanism or a convergent downstream effect.

CLINICAL PERSPECTIVES AND FUTURE DIRECTIONS

Emerging evidence suggests that brain lymphatic and glymphatic systems may contribute to migraine biology, but their clinical relevance remains to be clearly defined. Rather than proposing clearance modulation as a standalone therapeutic paradigm, future research should focus on how clearance-related mechanisms can refine biomarker development, patient stratification, and translational study design.

1. Biomarkers and patient stratification

At present, assessment of brain clearance function in humans relies largely on indirect imaging markers, including perivascular diffusion-based metrics and radiological features associated with altered ISF dynamics. While these measures are imperfect, they provide a practical foundation for exploratory studies in migraine, particularly in patients with chronic migraine, prominent sleep disturbance, or treatment-refractory disease. Standardization and validation across centers will be essential before such markers can inform routine clinical decision-making.[3,12]

2. Translational implications for neuromodulation

Neuromodulation approaches may offer a means to influence physiological processes that shape CSF dynamics and clearance efficiency. Among these, focused ultrasound is of particular interest because it has been shown to enhance CSF movement in vivo, providing a measurable intermediate endpoint that can be integrated into translational study designs. Importantly, early-phase studies should combine clinical outcomes with physiological or imaging-based measures to clarify whether neuromodulation effects are mediated through clearance-related mechanisms, pain network modulation, or both.[9,19]

3. Integration with established migraine mechanisms

Clearance-based concepts should be viewed as complementary to established migraine biology rather than as competing models. Interactions among CGRP signaling, meningeal immune activation, sleep disruption, and

clearance efficiency may converge to influence migraine susceptibility and long-term disease course. Determining whether altered clearance represents a driver, amplifier, or downstream consequence of migraine attacks will require carefully designed longitudinal and interventional studies.[13,17]

CONCLUSION

Emerging evidence suggests that brain lymphatic and glymphatic systems represent a relevant but still evolving dimension of migraine biology. While current data do not establish clearance dysfunction as a primary driver of migraine, they provide a coherent framework for integrating sleep physiology, meningeal immune interactions, and CSF dynamics into existing pathophysiological models. Continued translational research combining mechanistic insight with clinically grounded study design will determine whether modulation of brain clearance pathways can meaningfully contribute to future migraine management.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

Author has served as an advisory consultant for DeepsonBio. This role was not related to the content of the present review and the author has no other conflicts of interest to declare.

FUNDING STATEMENT

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2022-NR072047), and supported by the National Research Council of Science & Technology (NST) grant by the Korea government (MSIT) (No. GTL25071-000).

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1. Kim SK, Schwedt TJ. Interictal burden of migraine: a narrative review. Headache Pain Res 2025;26:200-208.
2. Yankova G, Bogomyakova O, Tulupov A. The glymphatic system and meningeal lymphatics of the brain: new understanding of brain clearance. Rev Neurosci 2021;32:693-705.
3. Vittorini MG, Sahin A, Trojan A, et al. The glymphatic system in migraine and other headaches. J Headache Pain 2024;25:34.
4. 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.
5. Ahn JH, Cho H, Kim JH, et al. Meningeal lymphatic vessels at the skull base drain cerebrospinal fluid. Nature 2019;572:62-66.
6. Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. Nat Commun 2020;11:4411.
7. Ren X, Wang H, He Y, et al. Impaired meningeal lymphatic drainage correlates with headache intensity in episodic migraine. J Headache Pain 2025;26:265.
8. Zhang X, Wang W, Bai X, et al. Increased glymphatic system activity in migraine chronification by diffusion tensor image analysis along the perivascular space. J Headache Pain 2023;24:147.
9. Choi S, Kum J, Hyun SY, et al. Transcranial focused ultrasound stimulation enhances cerebrospinal fluid movement: real-time in vivo two-photon and widefield imaging evidence. Brain Stimul 2024;17:1119-1130.
10. Jo SW, Park B, Yoo RE, et al. Effects of low-intensity ultrasound on amyloid-β clearance in early-stage Alzheimer's disease: a potential role of glymphatic activity. Acta Neurol Scand. 2026;2026:1538313.
11. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. Sci Transl Med 2012;4:147ra111.
12. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. Science 2013;342:373-377.
13. Louveau A, Smirnov I, Keyes TJ, et al. Structural and functional features of central nervous system lymphatic vessels. Nature 2015;523:337-341.
14. Aspelund A, Antila S, Proulx ST, et al. A dural lymphatic vascular

system that drains brain interstitial fluid and macromolecules. J Exp Med 2015;212:991-999.
15. Rasmussen MK, Mestre H, Nedergaard M. The glymphatic pathway in neurological disorders. Lancet Neurol 2018;17:1016-1024.
16. Cho JW, Lee GH, Kim J. Chronic migraine is associated with region-specific high-grade enlarged perivascular spaces: retrospective matched case-control study. J Clin Neurol 2026;22:113-121.
17. 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.
18. He Z, Sun J. Clearance mechanisms of the glymphatic/lymphatic system in the brain: new therapeutic perspectives for cognitive impairment. Cogn Neurodyn 2025;19:111.
19. Lee Y, Choi Y, Park EJ, et al. Improvement of glymphatic-lymphatic drainage of beta-amyloid by focused ultrasound in Alzheimer's disease model. Sci Rep 2020;10:16144.
20. Cheng KP, Brodnick SK, Blanz SL, et al. Clinically-derived vagus nerve stimulation enhances cerebrospinal fluid penetrance. Brain Stimul 2020;13:1024-1030.
21. Choi S, Baek IS, Lee K, Kim SK. Low-frequency auricular vagus nerve stimulation facilitates cerebrospinal fluid influx by promoting vasomotion. Korean J Physiol Pharmacol 2025;29:109-116.
22. Hauglund NL, Andersen M, Tokarska K, et al. Norepinephrine-mediated slow vasomotion drives glymphatic clearance during sleep. Cell 2025;188:606-622.e17.
23. Wang Y, Monai H. Transcranial direct current stimulation alters cerebrospinal fluid-interstitial fluid exchange in mouse brain. Brain Stimul 2024;17:620-632.
24. Salehpour F, Khademi M, Bragin DE, DiDuro JO. Photobiomodulation therapy and the glymphatic system: promising applications for augmenting the brain lymphatic drainage system. Int J Mol Sci 2022;23:2975.
25. Yao L, Chen R, Ji H, Wang X, Zhang X, Yuan Y. Preventive and therapeutic effects of low-intensity ultrasound stimulation on migraine in rats. IEEE Trans Neural Syst Rehabil Eng 2022;30:2332-2340.
26. Badran BW, Caulfield KA, Stomberg-Firestein S, et al. Sonication of the anterior thalamus with MRI-Guided transcranial focused ultrasound (tFUS) alters pain thresholds in healthy adults: a double-blind, sham-controlled study. Brain Stimul 2020;13:1805-1812.
27. Riis TS, Feldman DA, Losser AJ, Okifuji A, Kubanek J. Noninvasive targeted modulation of pain circuits with focused ultrasonic waves. Pain 2024;165:2829-2839.

Review Article

Headache Pain Res 2026;27(1):21-29
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2025.0027

Headache and Pain Research

Alcohol-Induced Headache: A Narrative Review Based on Migraine Pathophysiology

Woo-Seok Ha

Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Abstract

Alcohol-induced headache (AIH) is one of the most common headache experiences and is associated with a substantial socioeconomic burden; however, its pathophysiological mechanisms and clinical classification remain inadequately defined. Accumulating evidence indicates that AIH shares key biological pathways with migraine, particularly involving activation of the trigeminovascular system and calcitonin gene-related peptide (CGRP) signaling. Although currently available hangover remedies are supported by limited high-quality evidence, anti-CGRP treatments have emerged as a biologically plausible option for the situational prevention and acute treatment of AIH. A phenotype-based approach is therefore essential for achieving accurate diagnosis and effective management of alcohol-related headaches. Future well-designed clinical trials focusing on CGRP antagonists are warranted to address this common yet neglected disorder.

Keywords: Alcohol drinking, Calcitonin gene-related peptide, Ethanol, Headache disorders, Migraine disorders

INTRODUCTION

Alcohol-induced headache (AIH) is one of the most common headache experiences in the general population, with a lifetime prevalence of approximately 72%.[1] In a recent cross-sectional study of 347 Dutch adults, 8.1% of workers reported at least one episode of absenteeism per year due to alcohol hangover, and the estimated national annual cost exceeded €2.6 billion.[2] Despite this substantial individual and societal burden, scientific interest in alcohol hangover and AIH has remained surprisingly limited.[3] This neglect likely stems from a blend of cultural attitudes about drinking for leisure and the seemingly straightforward assumption that hangovers can be prevented by simply reducing alcohol consumption.

AIH has accompanied human history for as long as alcohol itself. Archaeological evidence from Israel has identified beer residues dating back approximately 13,000 years.[4] In ancient Persian medical texts describing headache disorders over 9,000 years ago, AIH was reported as one of the most frequently mentioned headache phenotypes, ranking third overall.[5] Yet, despite this long history, systematic attempts to classify AIH are relatively recent. The International Classification of Headache Disorders (ICHD) introduced the distinction between immediate and delayed AIH in ICHD-2, a framework that has been retained in

Received: December 18, 2025; **Revised:** January 27, 2026; **Accepted:** January 28, 2026
Correspondence: Woo-Seok Ha, M.D.
Department of Neurology, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
Tel: +82-2-2228-1600, Fax: +82-2-393-0705, E-mail: haha88@yuhs.ac

ICHD-3.[6,7] However, this classification has been occasionally questioned.[8,9] As acknowledged within the ICHD itself, alcohol is one of the most common triggers of migraine.[10,11] This creates an inherent diagnostic ambiguity. For example, if a patient with episodic migraine develops a bilateral pulsatile headache the day after drinking red wine, should this be classified as alcohol-triggered migraine or as delayed AIH? Furthermore, considering that alcohol consumption increases the production of nitric oxide (NO),[12] it may also be classified as "*Delayed NO donor-induced headache*". Although one of the core ICHD principles is that a diagnosis should be "not better accounted for by another disorder," this criterion becomes difficult to apply when headache phenotypes overlap substantially.

In clinical practice, such headaches are often managed as an extension of migraine, for example with triptan treatment. This pragmatic approach is not without rationale. Accumulating evidence suggests that many forms of AIH share key pathophysiological mechanisms with migraine, including trigeminovascular activation, calcitonin gene-related peptide (CGRP) signaling, and neuroinflammatory processes.[13] It should be emphasized, however, that alcohol avoidance or reduction remains the primary clinical recommendation for alcohol-related headache, and that pharmacological approaches discussed in this review are secondary and exploratory in nature.

In this narrative review we aim to interpret AIH through the framework of migraine pathophysiology. Due to the narrative nature of the review, formal systematic review reporting systems (e.g., PRISMA) could not be applied. Relevant literature was identified through targeted database searches and manual reference screening, based on the expertise of the authors. We discuss the mechanistic overlap between AIH and migraine, propose a phenotype-based approach to classification, and review current evidence on treatment and prevention, highlighting critical gaps for future research.

CLINICAL PHENOTYPES AND CLASSIFICATIONS

1. Immediate alcohol-induced headache (International Classification of Headache Disorders, 3rd edition code 8.1.4.1)

Immediate AIH, also referred to as "cocktail headache," is defined by the ICHD-3 diagnostic criteria shown in Table 1.[7] This headache can occur rapidly, within 3 hours, even after small amounts of alcohol (e.g., one or two glasses of wine). The pain is typically bilateral and pulsating and is aggravated by physical activity. Affected individuals often prefer to lie down, a behavior that may reflect difficulty maintaining cerebral perfusion pressure secondary to alcohol-induced cerebral vasodilation.[14]

2. Delayed alcohol-induced headache (International Classification of Headache Disorders, 3rd edition code 8.1.4.2)

Delayed AIH, commonly referred to as "*alcohol hangover headache*," develops 5–12 hours after heavy alcohol consumption and is defined by the ICHD-3 criteria summarized in Table 2.[7] Duration and severity of headache may correlate with the amount of alcohol intake.[15] Patients with delayed AIH also frequently report orthostatic headaches. In contrast to immediate AIH, delayed AIH occurs as part of a broader hangover syndrome and is accompanied by a cluster of autonomic, gastrointestinal, sleep-related, and cognitive symptoms.[16] A characteristic feature of delayed AIH typically emerges when blood alcohol concentration (BAC) is declining or has returned to near zero (Figure 1).[17] Experimental studies suggest that a peak BAC of at least 0.1% is generally required for a clinically relevant hangover to occur.[18] According to Widmark's equation,[19] this corresponds approximately to the BAC reached 90 minutes after a 60-kg adult consumes one bottle of soju.

Table 1. ICHD-3 criteria for immediate alcohol-induced headache (8.1.4.1)

A. Any headache fulfilling criterion C
B. Alcohol has been ingested
C. Evidence of causation demonstrated by all of the following:
1. headache has developed within 3 hours of alcohol ingestion
2. headache has resolved within 72 hours after alcohol ingestion has ceased
3. headache has at least one of the following three characteristics:
a) bilateral
b) pulsating quality
c) aggravated by physical activity
D. Not better accounted for by another ICHD-3 diagnosis.

ICHD, International Classification of Headache Disorders.

Table 2. ICHD-3 criteria for delayed alcohol-induced headache (8.1.4.2)

A. Any headache fulfilling criterion C
B. Alcohol has been ingested
C. Evidence of causation demonstrated by all of the following:
1. headache has developed within 5–12 hours after ingestion of alcohol
2. headache has resolved within 72 hours of onset
3. headache has at least one of the following three characteristics:
a) bilateral
b) pulsating quality
c) aggravated by physical activity
D. Not better accounted for by another ICHD-3 diagnosis.

ICHD, International Classification of Headache Disorders.

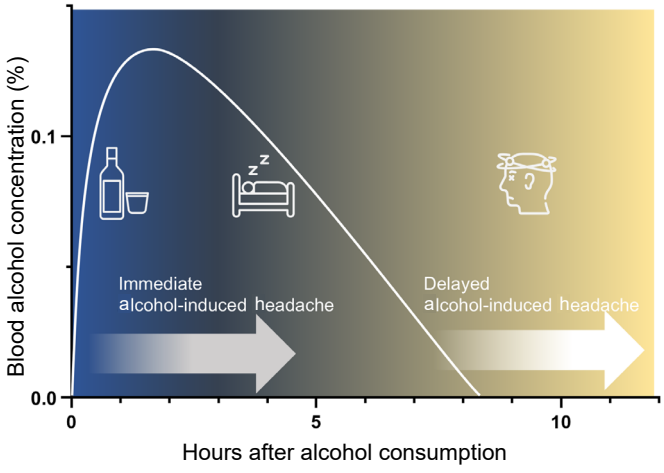


Figure 1. Schematic illustration of the temporal characteristics of alcohol-induced headache based on blood alcohol concentration.

The time-based distinction between immediate and delayed AIH in ICHD-3 is primarily operational and reflects consistent clinical observations rather than established mechanistic thresholds. To date, no definitive physiological evidence has validated a specific biological boundary underlying the 3-hour versus 5–12-hour cut-offs, and this classification should be interpreted as a pragmatic framework for clinical and research purposes.

3. Distinguishing alcohol-triggered migraine from alcohol-induced headache

According to a cohort study in Korea, alcohol consumption was associated with an odds ratio (OR) of 2.5 for attack occurrence in episodic migraine.[20] However, as discussed above, the current ICHD-3 framework does not clearly distinguish alcohol-triggered migraine from AIH in individuals with migraine. When patients present with recurrent headaches following alcohol consumption, we suggest that diagnosis should simultaneously consider temporal profile, headache phenotype, and individual susceptibility (Table 3). The most critical factor is whether the patient's habitual migraine phenotype is faithfully reproduced after alcohol intake. This includes classical migraine features such as unilateral pain, nausea or vomiting, photophobia, and phonophobia. If these features are present, the headache should be classified as alcohol-triggered migraine. Conversely, when headache is accompanied by symptoms commonly associated with hangover, such as thirst, impaired concentration, apathy, diarrhea, anorexia, and

Table 3. Clinical characteristics of alcohol-related headaches

Domain	Alcohol-triggered migraine	Delayed alcohol-induced headache
Onset	Variable; often within hours	Within 5–12 hours of consumption
Duration	4–72 hours	Mostly <10 hours
Location	Unilateral	Bilateral, frontal dominant
Quality	Pulsating	Pressing>pulsating
Aggravation by activity	++	++
Nausea/vomiting	++	++
Photophobia/phonophobia	++	+
Fatigue, dizziness, tremor	±	++
Cranial autonomic symptoms (lacrimation, conjunctival injection, etc.)	-	+
Systemic autonomic symptoms (sweating, palpitation, etc.)	-	+

Although both entities are classified as distinct entities within the International Classification of Headache Disorders, 3rd edition framework, this table is intended as a pragmatic tool for clinical differentiation rather than a nosological proposal.

autonomic symptoms, it should be classified as delayed AIH. However, despite this approach, many patients may exhibit overlapping or inconsistent clinical phenotypes. In such cases, we recommend assigning alcohol-triggered migraine as the primary diagnosis for clinical practicality, while interpreting non-headache symptoms and residual complaints as part of the hangover spectrum.

EPIDEMIOLOGICAL ASSOCIATIONS WITH PRIMARY HEADACHES AND SUSCEPTIBILITY

Evidence that alcohol precipitates headache can be found in numerous epidemiological studies. Paradoxically, many population-based studies consistently show that individuals with primary headache disorders consume less alcohol than those without headache. In a Norwegian study including 51,000 participants, headache prevalence increased 10%–20% in non-drinkers compared to moderate drinkers, across all age groups.[21] Similarly, a Danish cross-sectional study of 46,000 individuals reported that weekly alcohol consumption was associated with a lower odds of migraine compared with abstinence (OR=0.55).[22] This inverse association was replicated in analyses of the U.S. National Health and Nutrition Examination Survey (OR=0.54).[23] These findings do not suggest that alcohol protects against headache. Rather, they indicate that headache sufferers are more likely to avoid alcohol.

When stratified by headache subtype, the association between migraine and alcohol becomes more pronounced. A recent meta-analysis demonstrated that alcohol consumption was not significantly associated with the risk of tension-type headache, whereas drinkers had a 1.5-fold lower likelihood of migraine compared with nondrinkers.[24] Among patients with migraine, approximately 34%–35% report alcohol as a triggering factor.[25,26] Interestingly, however, only a minority of migraine patients who abstain from or avoid alcohol, ranging from 3% to 25%, explicitly report headache as the primary reason for avoidance.[26,27] This observation suggests that alcohol avoidance in migraineurs may occur both consciously and unconsciously, possibly reflecting learned or conditioned behavioral adaptation. Although alcohol avoidance can also be influenced by external and social factors such as religion, gender, and social norms, the consistent inverse association observed across diverse populations supports a prominent role of behavioral adaptation related to headache susceptibility.

Genetic susceptibility seems to play a critical role in AIH and hangover. A study analyzing 2,248 participants of twins found that over 40% of alcohol-related hangovers are determined by genetic factors.[28] Inactive variants of aldehyde dehydrogenase 2 (ALDH2) are strongly associated with alcohol flushing, severe hangover symptoms, and headache.[29,30] In a large Japanese cross-sectional study, ALDH2 deficiency demonstrated high sensitivity and specificity for alcohol flushing and hangover. Women and individuals exhibiting flushing reactions were significantly more likely to experience hangover headache. Notably, among individuals with migraine, those carrying inactive ALDH2 variants reported lower alcohol consumption and more pronounced adverse effects after drinking, supporting the presence of a gene–environment interaction in alcohol-related headache susceptibility.

Evidence regarding the role of specific alcoholic beverage types in triggering AIH remains limited. Fermented beverages generally contain higher levels of congeners produced during the fermentation process, which contribute to flavor and aroma but have also been implicated as potential contributors to hangover severity.[9] Accordingly, some studies have suggested that red wine may provoke headache more frequently than white wine,[31] whereas others have reported opposite or inconsistent findings.[25]

Importantly, no studies have systematically compared the severity of AIH across different beverage types under standardized BAC conditions. Moreover, most animal models of AIH rely on the administration of pure ethanol rather than alcohol beverages.[14,32,33] Given the substantial heterogeneity in beverage preferences, drinking patterns and cultural contexts across populations and nations, the present review focuses primarily on the effects of alcohol itself rather than beverage-specific factors.

PATHOPHYSIOLOGICAL MECHANISMS LINKING ALCOHOL AND MIGRAINE

1. Central mechanisms: trigeminovascular activation and calcitonin gene-related peptide signaling

AIH was historically attributed primarily to peripheral vasodilation.[34] However, accumulating evidence now indicates that activation of the trigeminovascular system and

enhanced CGRP signaling represent central mechanisms directly linked to migraine pathophysiology.[13,35,36] Migraine pain originates from activation of trigeminal afferents innervating the meninges and perivascular structures.[37,38] Following alcohol consumption, ethanol is metabolized to acetaldehyde, which directly stimulates this system and activates trigeminal afferents.

Experimental animal models have demonstrated that gastrointestinal administration of alcohol activates members of the transient receptor potential (TRP) ion channel family, including transient receptor potential cation channel subfamily V member 1 (TRPV1) and Transient receptor potential cation channel, subfamily A, member 1 (TRPA1), leading to increased CGRP release.[14,32] CGRP released from trigeminal nerve terminals acts on neurons and satellite glial cells within the trigeminal ganglion, promoting peripheral sensitization, while simultaneously activating second-order nociceptive neurons in the brainstem to induce central sensitization.[37] These mechanisms provide a biological explanation for why AIH frequently manifests not only as pain but also with migraine-like extracranial features such as cutaneous allodynia and photophobia.[32,39] Notably, these alcohol-induced effects are attenuated by CGRP antagonists, such as olcegepant, or by silencing receptor activity–modifying protein 1, a key component of the CGRP receptor complex, in animal model.[32] Together, these findings suggest that anti-CGRP therapies may be effective in suppressing the clinical expression of AIH.

2. Peripheral mechanisms: nitric oxide signaling, vascular reactivity, and inflammation

Both animal and human studies consistently demonstrate that alcohol induces complex and bidirectional changes in NO signaling.[12,39,40] Acute or low-dose alcohol exposure activates endothelial NO synthase, resulting in increased NO production and vasodilation. NO promotes cerebral blood flow while activating cyclic guanosine monophosphate signaling pathways that facilitate CGRP release from trigeminal nerve terminals.[37] In contrast, chronic exposure to high-dose alcohol leads to depletion of NO bioavailability and antioxidant defenses through oxidative stress.[12,33] Although this mechanism contributes to hypertension in chronic alcoholism, it may also offer insight into the paradoxically lower headache frequency reported in long-term heavy drinkers. Importantly, the delayed nature of NO-induced headache provides a plausible explanation for why delayed AIH is not strictly dose dependent and why headache frequently emerges during the declining phase of BAC.[41]

In parallel, alcohol consumption elicits systemic and central inflammatory responses. Elevated levels of cytokines, including interleukin-10, interleukin-12, and interferon-γ, as well as increased prostaglandin production, have been consistently observed during alcohol hangover.[16,42] These inflammatory mediators are related to headache, nausea, and malaise and overlap substantially with pathways implicated in migraine-related neuroinflammation.[43]

3. Metabolic and behavioral modifiers

The metabolic consequences of alcohol consumption are broad and help explain why certain individuals are particularly prone to migraine. Alcohol increases the production of reactive oxygen species and reactive nitrogen species, inducing oxidative stress within the trigeminovascular system.[44,45] This mechanism is well recognized in alcohol-related cardiovascular disease and may also be relevant to migraine biology. In migraine, thiobarbituric acid–reactive substances have been proposed as potential biomarkers, and preliminary studies suggesting therapeutic effects of antioxidants support a shared oxidative stress pathway linking AIH and migraine.[44,46] Alcohol also inhibits diamine oxidase, the primary enzyme responsible for histamine degradation, thereby increasing endogenous histamine levels.[47] Elevated histamine exerts vasodilatory effects and represents another potential mechanism contributing to migraine susceptibility following alcohol intake.[43]

Furthermore, alcohol disrupts sleep architecture and increases sleep fragmentation, while also elevating next-day anxiety levels.[48,49] These behavioral and neuropsychological effects may lower the migraine threshold and place susceptible individuals in a state that favors headache generation.

CURRENT EVIDENCE AND THERAPEUTIC CONSIDERATIONS

1. Current evidence

To date, no clinical trial has specifically evaluated AIH as

a primary outcome. Instead, most interventional studies have focused on the prevention or treatment of alcohol hangover as a broader syndrome.[50] Based on randomized controlled trials, the following agents have demonstrated some efficacy in reducing hangover symptoms: clovinol,[51] tolfenamic acid,[52] pyritinol,[53] *Hovenia dulcis* extract,[54] L-cysteine combined with vitamins B and C,[55] red ginseng,[56] Korean pear juice,[57] and HK-GCM-H01.[58] Notably, four of these eight agents were evaluated in studies conducted in Korea. These compounds have been proposed to act through anti-inflammatory or prostaglandin-related pathways, or through antioxidant and metabolic mechanisms.[50] In contrast, medications commonly considered anti-migraine agents, such as naproxen or propranolol,[59,60] have not demonstrated benefit.

However, important limitations prevent us from extrapolating these findings directly to AIH. A 2022 systematic review of seven of the eight agents listed above found that all randomized trials were rated as having "very low quality" according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology.[50] This was largely due to small sample sizes and substantial selection bias.

A more fundamental limitation lies in the heterogeneity of hangover definitions and outcome measures. Most studies assessed hangover severity using composite scores derived from multiple symptoms, such as fatigue, thirst, sweating, and headache. These scales were often investigator-developed, insufficiently validated, and remain controversial in the literature.[61] No single agent improved all symptom domains. Headache severity was usually evaluated using binary outcomes or simple numeric rating scales. These methodological issues substantially limit the applicability of existing hangover trials to AIH.

2. Interface with migraine treatment and the potential role of calcitonin gene-related peptide-pathway–based therapies

In clinical practice, when alcohol-triggered migraine is suspected, standard acute migraine treatments, such as triptans, are frequently used and appear effective. Most established acute migraine therapies can be considered in this setting, and there is currently no evidence suggesting clinically relevant drug–alcohol interactions for triptans.

In patients who experience migraine attacks with high probability following alcohol consumption, a strategy of mini-prophylaxis may be considered. For example, administration of a long-acting triptan, such as frovatriptan, at bedtime after alcohol intake may be conceptually analogous to mini-prophylaxis used for menstrual migraine.[62] More recently, Lipton and colleagues[63] introduced the concept of "situational prevention," in which imegepant is used for prophylactic purpose during periods with increased risk of migraine attacks. AIH is a prototypical example of such a high-risk situation, in which pharmacological prevention may be considered in the setting of anticipated alcohol exposure, such as wine consumption during travel.

Although current evidence remains limited, CGRP-targeted therapies represent the most biologically plausible candidate for AIH prevention from a migraine-based perspective.[13] Rimegepant, a CGRP receptor antagonist with both acute and preventive indications, is particularly attractive, as it may theoretically provide benefit in alcohol-triggered migraine as well as in immediate and delayed AIH.[64] Nevertheless, important safety considerations remain. While imegepant has demonstrated minimal hepatotoxicity with short-term use,[65] its safety profile when administered in the context of recent alcohol consumption, including repeated or situational use, remains insufficiently studied.

3. Key considerations for future clinical trials of calcitonin gene-related peptide antagonists in alcohol-induced headache

Several methodological issues must be addressed in future trials evaluating CGRP antagonists for the prevention or treatment of AIH. First, reproducibility of AIH must be ensured. AIH exhibits marked interindividual variability, and even within the same individual, identical alcohol exposure may or may not result in headache. A randomized, crossover trial design would therefore be optimal to control for this variability. Second, phenotypes of AIH should be clearly distinguished rather than pooled. For example, trials should separately evaluate migraineurs with reproducible alcohol-triggered migraine and non-migraineurs with reproducible delayed AIH. Third, alcohol exposure must be standardized. Target exposure should

be defined by BAC rather than by beverage volume alone, for example aiming for a peak BAC of ≥0.1%. Verification can be achieved using breath analyzers or blood sampling. Fourth, confounding hangover-related factors, including sleep quality, mood, gastrointestinal symptoms, and hydration status, should also be measured and controlled. Finally, ethical considerations exist. Investigators must carefully assess whether study designs inadvertently encourage alcohol consumption and must adhere strictly to institutional review board standards regarding participant safety.

CONCLUSIONS

AIH is more than a simple consequence of alcohol consumption; it is a complex neurological phenomenon that closely intersects with migraine biology. By understanding AIH, clinicians can move beyond reactive hangover management toward a more proactive, mechanism-based therapeutic approach. The integration of situational prevention strategies and the potential application of CGRP antagonists offer promising avenues for patients suffering from recurrent AIH. Continued research with standardized methodologies will be crucial to bridge the gap between bench evidence and clinical practice.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING STATEMENT

Not applicable.

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1. Rasmussen BK, Olesen J. Symptomatic and nonsymptomatic headaches in a general population. Neurology 1992;42:1225-1231.
2. Severeijns NR, Sips ASM, Merlo A, Bruce G, Verster JC. Absenteeism, presenteeism, and the economic costs of alcohol hangover in the Netherlands. Healthcare (Basel) 2024;12:335.
3. Verster JC, Penning R. Treatment and prevention of alcohol hangover. Curr Drug Abuse Rev 2010;3:103-109.
4. Liu L, Wang J, Rosenberg D, Zhao H, Lengyel G, Nadel D. Fermented beverage and food storage in 13,000 y-old stone mortars at Raqefet Cave, Israel: investigating Natufian ritual feasting. J Archaeol Sci Rep 2018;21:783-793.
5. Zarshenas MM, Petramfar P, Firoozabadi A, Moein MR, Mohagheghzadeh A. Types of headache and those remedies in traditional persian medicine. Pharmacogn Rev 2013;7:17-26.
6. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:9-160.
7. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
8. Dueland AN. Headache and alcohol. Headache 2015;55:1045-1049.
9. Evans RW, Sun C, Lay C. Alcohol hangover headache. Headache 2007;47:277-279.
10. Hindiyeh NA, Zhang N, Farrar M, Banerjee P, Lombard L, Aurora SK. The role of diet and nutrition in migraine triggers and treatment: a systematic literature review. Headache 2020;60:1300-1316.
11. Kim BK, Bae HJ, Koo JS, Kwon OH, Park JM. Clinical characteristics of migraine and tension-type headache: the experience in Eulji Hospital. Korean J Headache 2005;6:103.
12. Syapin PJ. Alcohol and nitric oxide production by cells of the brain. Alcohol 1998;16:159-165.
13. Hakim SM. The potential role of calcitonin gene-related peptide antagonists for the management of hangover headaches. Curr Opin Anaesthesiol 2025;38:669-673.
14. Nicoletti P, Trevisani M, Manconi M, et al. Ethanol causes neurogenic vasodilation by TRPV1 activation and CGRP release

in the trigeminovascular system of the guinea pig. Cephalalgia 2008;28:9-17.
15. García-Azorín D, Aparicio-Cordero L, Talavera B, Johnson A, Schytz HW, Guerrero-Peral ÁL. Clinical characterization of delayed alcohol-induced headache: a study of 1,108 participants. Neurology 2020;95:e2161-e2169.
16. Penning R, van Nuland M, Fliervoet LA, Olivier B, Verster JC. The pathology of alcohol hangover. Curr Drug Abuse Rev 2010;3:68-75.
17. Ylikahri RH, Leino T, Huttunen MO, Pösö AR, Eriksson CJP, Nikkilä EA. Effects of fructose and glucose on ethanol-induced metabolic changes and on the intensity of alcohol intoxication and hangover. Eur J Clin Invest 1976;6:93-102.
18. Penning R, de Haan L, Verster JC. Caffeinated drinks, alcohol consumption, and hangover severity. Open Neuropsychopharmacol J 2011;4:36-39.
19. Gullberg RG. Estimating the uncertainty associated with Widmark's equation as commonly applied in forensic toxicology. Forensic Sci Int 2007;172:33-39.
20. Park JW, Chu MK, Kim JM, Park SG, Cho SJ. Analysis of trigger factors in episodic migraineurs using a smartphone headache diary applications. PLoS One 2016;11:e0149577.
21. Aamodt AH, Stovner LJ, Hagen K, Bråthen G, Zwart J. Headache prevalence related to smoking and alcohol use. The Head-HUNT Study. Eur J Neurol 2006;13:1233-1238.
22. Le H, Tfelt-Hansen P, Skytthe A, Kyvik KO, Olesen J. Association between migraine, lifestyle and socioeconomic factors: a population-based cross-sectional study. J Headache Pain 2011;12:157-172.
23. Tang Y, Zhang K, Zhang Y, et al. Association between dietary alcohol intake and migraine or severe headache miscellaneous pain: the NHANES 1999-2004. Brain Behav 2025;15:e70400.
24. Błaszczyk B, Straburzyński M, Więckiewicz M, et al. Relationship between alcohol and primary headaches: a systematic review and meta-analysis. J Headache Pain 2023;24:116.
25. Panconesi A. Alcohol and migraine: trigger factor, consumption, mechanisms. A review. J Headache Pain 2008;9:19-27.
26. Onderwater GLJ, van Oosterhout WPJ, Schoonman GG, Ferrari MD, Terwindt GM. Alcoholic beverages as trigger factor and the effect on alcohol consumption behavior in patients with migraine. Eur J Neurol 2019;26:588-595.
27. Panconesi A, Franchini M, Bartolozzi ML, Mugnai S, Guidi L. Alcoholic drinks as triggers in primary headaches. Pain Med 2013;14:1254-1259.
28. Slutske WS, Piasecki TM, Nathanson L, Statham DJ, Martin NG. Genetic influences on alcohol-related hangover. Addiction 2014;109:2027-2034.
29. Yokoyama M, Suzuki N, Yokoyama T, et al. Interactions between migraine and tension-type headache and alcohol drinking, alcohol flushing, and hangover in Japanese. J Headache Pain 2012;13:137-145.
30. Wall TL, Shea SH, Luczak SE, Cook TA, Carr LG. Genetic associations of alcohol dehydrogenase with alcohol use disorders and endophenotypes in white college students. J Abnorm Psychol 2005;114:456-465.
31. Krymchantowski AV, da Cunha Jevoux C. Wine and headache. Headache 2014;54:967-975.
32. Landini L, Souza Monteiro de Araujo D, Chieca M, et al. Acetaldehyde via CGRP receptor and TRPA1 in Schwann cells mediates ethanol-evoked periorbital mechanical allodynia in mice: relevance for migraine. J Biomed Sci 2023;30:28.
33. Husain K, Mejia J, Lalla J, Kazim S. Dose response of alcohol-induced changes in BP, nitric oxide and antioxidants in rat plasma. Pharmacol Res 2005;51:337-343.
34. Mathew RJ, Wilson WH. Regional cerebral blood flow changes associated with ethanol intoxication. Stroke 1986;17:1156-1159.
35. Panconesi A. Alcohol-induced headaches: evidence for a central mechanism? J Neurosci Rural Pract 2016;7:269-275.
36. Paolucci M, Altamura C, Vernieri F. The role of endothelial dysfunction in the pathophysiology and cerebrovascular effects of migraine: a narrative review. J Clin Neurol 2021;17:164-175.
37. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the trigeminal system in migraine. Headache 2019;59:659-681.
38. Moon HS, Chung PW, Kim BK. New targeted drugs for acute treatment of migraine. Korean J Headache 2023;24:56-65.
39. Lu S, Zhang Y, Yang Y, et al. Hangover headache and its behavioral changes in rats. Iran J Basic Med Sci 2023;26:326-334.
40. Cheng Y, Liu X, Ma X, Garcia R, Belfield K, Haorah J. Alcohol promotes waste clearance in the CNS via brain vascular reactivity. Free Radic Biol Med 2019;143:115-126.
41. Olesen J. Provocation of attacks to discover migraine signaling mechanisms and new drug targets: early history and future perspectives - a narrative review. J Headache Pain 2024;25:105.
42. Kim DJ, Kim W, Yoon SJ, et al. Effects of alcohol hangover on cytokine production in healthy subjects. Alcohol 2003;31:167-170.
43. Ha WS, Chu MK. Altered immunity in migraine: a comprehensive scoping review. J Headache Pain 2024;25:95.
44. Gao XM, Dong WH, Xia CL, et al. Centranthera grandiflore alleviates alcohol-induced oxidative stress and cell apoptosis. Chin J Nat Med 2022;20:572-579.

45. Wu D, Zhai Q, Shi X. Alcohol-induced oxidative stress and cell responses. J Gastroenterol Hepatol 2006;21 Suppl 3:S26-S29.
46. Jiménez-Jiménez FJ, Alonso-Navarro H, García-Martín E, Espada-Rubio S, Agúndez JAG. Oxidative stress and migraine. Mol Neurobiol 2024;61:8344-8360.
47. Panula P. Histamine, histamine H3 receptor, and alcohol use disorder. Br J Pharmacol 2020;177:634-641.
48. Rossetti I, Zambusi L, Maccioni P, et al. Predisposition to alcohol drinking and alcohol consumption alter expression of calcitonin gene-related peptide, neuropeptide Y, and microglia in bed nucleus of stria terminalis in a subnucleus-specific manner. Front Cell Neurosci 2019;13:158.
49. Gardiner C, Weakley J, Burke LM, et al. The effect of alcohol on subsequent sleep in healthy adults: a systematic review and meta-analysis. Sleep Med Rev 2025;80:102030.
50. Roberts E, Smith R, Hotopf M, Drummond C. The efficacy and tolerability of pharmacologically active interventions for alcohol-induced hangover symptomatology: a systematic review of the evidence from randomised placebo-controlled trials. Addiction 2022;117:2157-2167.
51. Mammen RR, Natinga Mulakal J, Mohanan R, Maliakel B, Illathu Madhavamenon K. Clove bud polyphenols alleviate alterations in inflammation and oxidative stress markers associated with binge drinking: a randomized double-blinded placebo-controlled crossover study. J Med Food 2018;21:1188-1196.
52. Kaivola S, Parantainen J, Osterman T, Timonen H. Hangover headache and prostaglandins: prophylactic treatment with tolfenamic acid. Cephalalgia 1983;3:31-36.
53. Khan MA, Jensen K, Krogh HJ. Alcohol-induced hangover. A double-blind comparison of pyritinol and placebo in preventing hangover symptoms. Q J Stud Alcohol 1973;34:1195-1201.
54. Kim H, Kim YJ, Jeong HY, et al. A standardized extract of the fruit of Hovenia dulcis alleviated alcohol-induced hangover in healthy subjects with heterozygous ALDH2: a randomized, controlled, crossover trial. J Ethnopharmacol 2017;209:167-174.
55. Eriksson CJP, Metsälä M, Möykkynen T, et al. L-cysteine containing vitamin supplement which prevents or alleviates alcohol-related hangover symptoms: nausea, headache, stress and anxiety. Alcohol Alcohol 2020;55:660-666.
56. Lee MH, Kwak JH, Jeon G, et al. Red ginseng relieves the effects of alcohol consumption and hangover symptoms in healthy men: a randomized crossover study. Food Funct 2014;5:528-534.
57. Lee HS, Isse T, Kawamoto T, Baik HW, Park JY, Yang M. Effect of Korean pear (Pyruspyrifolia cv. Shingo) juice on hangover severity following alcohol consumption. Food Chem Toxicol 2013;58:101-106.
58. Jang YL, Park MK. Advanced clinical symptoms of the antihangover compound HK-GCM-H01 in healthy Koreans. Transl Clin Pharmacol 2024;32:137-149.
59. Verster JC, Dahl TA, Scholey A, Iversen JM. The effects of SJP-001 on alcohol hangover severity: a pilot study. J Clin Med 2020;9:932.
60. Bogin RM, Nostrant TT, Young MJ. Propranolol for the treatment of the alcoholic hangover. Am J Drug Alcohol Abuse 1987;13:175-180.
61. Verster JC, van de Loo AJAE, Benson S, Scholey A, Stock AK. The assessment of overall hangover severity. J Clin Med 2020;9:786.
62. Zhang H, Qi JZ, Zhang ZH. Comparative efficacy of different treatments for menstrual migraine: a systematic review and network meta-analysis. J Headache Pain 2023;24:81.
63. Lipton RB, Ailani J, Mullin K, et al. Situational prevention: pharmacotherapy during periods of increased risk for migraine attacks. Headache 2024;64:859-864.
64. Kim BS, Chung PW, Chung JM, et al. Evidence-based recommendations on pharmacologic treatment for migraine prevention: a clinical practice guideline from the Korean Headache Society. Headache Pain Res 2025;26:5-20.
65. Bertz R, Bhardwaj R, Morris BA, Ashbrenner E, Coric V, Croop R. A placebo-controlled, randomized, single and multiple dose study to evaluate the safety, tolerability, and pharmacokinetics of rimegepant in healthy participants. Cephalalgia 2023;43:3331024231179131.

Original Article

Headache Pain Res 2026;27(1):30-42
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2026.0004

Headache and Pain Research

Natural Diagnostic Classes of Headache Disorders: Latent Class Analysis of a Population-Based Study

Wonwoo Lee[1], Seok-Jae Heo[2], Jungyon Yum[1], Min Kyung Chu[3]

[1]Department of Neurology, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Republic of Korea
[2]Biostatistics Collaboration Unit, Department of Biomedical Systems Informatics, Yonsei University College of Medicine, Seoul, Republic of Korea
[3]Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Abstract

Purpose: The International Classification of Headache Disorders, 3rd edition (ICHD-3), diagnoses headache based on combinations of clinical symptoms. Overlap is common, and symptom variability complicates diagnosis. We evaluated natural classes of headache disorders using a statistical approach and compared them with ICHD-3 diagnostic categories.

Methods: Data from a nationwide, population-based web survey on headache and sleep conducted in South Korea (n=3,030) were analyzed. Participants with headache (n=1,938) were included. Latent class analysis was performed using categorical ICHD-3 diagnostic criteria to identify distinct classes. The characteristics of each class and the distribution of ICHD-3 primary headache diagnoses were examined.

Results: Nine classes were identified, comprising 626, 54, 248, 148, 187, 143, 79, 61, and 392 individuals. Three classes were tension-type headache (TTH)–like: Class 1 was male-dominant mild bilateral TTH, Class 8 represented classic, severe TTH, and Class 9 was mild unilateral TTH. Class 4 showed a typical migraine phenotype and contained most migraine cases. Classes 5 and 6 were dominated by probable migraine (PM) and differed mainly in sensory sensitivity and disability, which were higher in Class 6. Classes 2, 3, and 7 were categorized as "other headache." Class 2 had the highest prevalence of medication-overuse headache (MOH), whereas Class 3 was characterized by mild headache with nausea. Class 7 showed a mixed-type profile with prominent photophobia. Severity and central sensitization markers were key classifiers.

Conclusion: Latent class analysis identified nine clinically distinct headache classes. PM was clearly distinct from both TTH and migraine. One subtype of "other headache" showed the highest MOH burden.

Keywords: Cluster analysis, Migraine disorders, Precision medicine, Statistical data interpretation, Tension-type headache

Received: January 14, 2026; **Revised:** January 31, 2026; **Accepted:** February 5, 2026
Correspondence: Min Kyung Chu, M.D., Ph.D.
Department of Neurology, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Republic of Korea
Tel: +82-2-2228-1600, Fax: +82-2-393-0705, E-mail: chumk@yonsei.ac.kr

INTRODUCTION

The diagnosis of headache disorders relies on clinical criteria based on International Classification of Headache Disorders, 3rd edition (ICHD-3).[1] Although there is well established pathophysiologic evidence of different headache diagnosis, there being no biomarker, the diagnosis is based on a combination of clinical profiles. However, substantial variability in the time between attacks is often observed in individual patients. Prior studies of natural subgroups of migraine and tension-type headache (TTH), as well as concurrent ICHD-3 diagnoses, have demonstrated heterogeneity and overlap between several headache disorders.[2-7] Also, current diagnosis of headache only allows definitive diagnosis, but frequently, there are occasions when a definite diagnosis and probable diagnosis are both present, such as those with definite diagnosis of TTH, but also who fit for the diagnosis of probable migraine (PM). In Korea where prevalence of PM is higher than migraine, the diagnostic and treatment challenges are greater, thus delaying patient diagnosis and appropriate treatment.[8] Statistical analysis of ICHD-3 criteria revealed coexisting diagnoses[5], suggesting alternative diagnostic classifications for headache disorders.

Statistical methods have been utilized to identify different subgroups of migraine amd TTH based on clinical characteristics or comorbidities.[2-4] Identifying such subgroups could enhance our understanding of disease heterogeneity and support more precise classification and management, thereby improving precision medicine. Latent class analysis (LCA) is a model-based, probabilistic approach that identifies unobserved (latent) subgroups from a set of categorical variables and has been previously applied to classify headache disorders.[2-4,9] Beyond the categorical structure of the data, LCA is particularly suitable for headache research because it allows for the identification of clinically interpretable phenotypic patterns while accounting for uncertainty in class membership. Given that the ICHD-3 diagnostic criteria consist largely of categorical symptom-based indicators, we applied LCA to a population-based sample of headache disorders to identify natural headache classes and to compare these data-driven classes with ICHD-3 diagnosis.

MATERIALS AND METHODS

1. Ethical approval

The present study was approved by the Institutional Review Board of the Severance Hospital, Yonsei University (approval no. 2022-2189-003). This study was conducted in accordance with the principles of the Declaration of Helsinki, and all participants provided written informed consent.

2. Data

We used the data of Circannual Change in Headache and Sleep (CHASE) study for the analysis. The CHASE study is a web-based survey on headache and sleep that was designed to represent the Korean population. The acquisition of the study was described previously in detail.[10] In short, the study was a web-based questionnaire supported by Hankook Research (Seoul, Republic of Korea). An email with link to the survey was sent to those selected by a two-stage stratified clustered random sampling method proportional to population distribution. The survey included baseline and follow-up evaluation every 3 months for a year. This study is a cross-sectional analysis of the baseline data conducted in October 2020. Individuals aged 20–59 years were included according to socioeconomic and demographic strata derived from the 2015 National Statistical Office Population and Housing Census.[11] Those with history of COVID-19 infection were excluded. The estimated sampling error was ±1.8%.

3. Diagnosis of headache disorders

The Headache disorders were diagnosed using a validated web-based questionnaire based on ICHD-3 with reasonable sensitivity (92.6, 85.0, and 78.4), specificity (94.8, 92.9, and 98.4), and accuracy (93.8, 91.0, and 92.6), for migraine, PM, and TTH, respectively.[12] The diagnosis was based on ICHD-3 criteria for Migraine without aura (code 1.1), PM without aura (code 1.5.1), and infrequent episodic TTH (code 2.1).[1] PM was diagnosed only when there was no definite headache diagnosis and there was no overlap in the diagnosis of headaches. Headache duration in this study was assessed as “Please specify the duration of your most severe headache in the past 3 months. If you

use acute (rescue) medication, report the duration as if you had not taken it." The frequency criteria was not used to differentiate episodic and chronic headache but was analyzed as a separate variable. The diagnostic criteria for migraine with aura (code 1.2) requires diagnosis of fulfilling criteria for migraine without aura. Visual aura was assessed by the Visual Aura Rating Scale, with score of ≥3 defined as having visual aura. Migraine in this study refers to migraine with and without aura, and chronic migraine. In the same way, TTH in this study refers to infrequent episodic TTH, frequent episodic TTH (code 2.2), and chronic TTH (code 2.3). PM stands for PM without and with aura (code 1.5.2). Those with headache not diagnosed as migraine, PM, and TTH were classified as other headache disorder. Medication-overuse headache (MOH) was diagnosed using ICHD-3 criteria.

4. Impact and disability of headache, cutaneous allodynia

The impact of headache disorder was assessed using the Headache Impact Test-6 (HIT-6).[13] The disability of headache was assessed using the Migraine Disability Assessment (MIDAS).[14] The higher scores indicated more impact and disability.

Allodynia Symptom Checklist-12 (ASC-12) questionnaire was used to assess cutaneous allodynia (CA).[15] ASC-12 score ≥3 indicates CA.

5. Assessment of comorbid symptoms: anxiety, depression, fibromyalgia, and sleep related indices

Anxiety was assessed with General Anxiety Disorder-7 (GAD-7).[16] GAD-7 scores ≥8 was defined as anxiety. Depression was assessed with Patient Health Questionnaire (PHQ-9), PHQ-9 scores ≥10 indicated depression.[17] Fibromyalgia syndrome (FMS) was assessed using widespread pain index and symptoms severity score, and was diagnosed using 2016 criteria of American College of Rheumatology.[18] Excessive daytime sleepiness (EDS) was assessed with Epworth Sleepiness Scale score ≥11 indicating EDS.[19] Quality of sleep was assessed using the Pittsburgh Sleep Quality Index, ≥8.5 indicating poor sleep quality.[20] Insomnia was assessed using Insomnia Severity Index (ISI), with ISI ≥15 defined as clinical insomnia.[21]

6. Statistical analysis and latent class analysis modeling

LCA is a probabilistic analytic method deriving 'latent' classes by stratifying observations with similar response from latent mixture of underlying distributions from categorical variables.[9] Observations that are similar, though not identical, are clustered into the same class, thereby identifying subgroups with distinct characteristics. We conducted LCA using the 'poLCA' package 1.6.0.1 version in R, frequently used for LCA.[22] As the categorical variables, the major variables used for diagnosis in ICHD-3 were selected; headache intensity, unilateral location, pulsating quality, aggravation by routine physical activity, nausea, vomiting, photophobia, and phonophobia were included. Headache frequency per month was categorized into four classes (<2, ≥2 to <8, ≥8 to <15, and ≥15 days). Headache duration was categorized as <30 minutes, ≥30 minutes to <4 hours, ≥4 hours to ≤72 hours, >72 hours to ≤7 days, and >7 days. Model quality was assessed using posterior class membership probabilities and class-conditional item-response probabilities. The local independence assumption was assessed by examining bivariate residuals for all pairs of observed indicators following model estimation (Supplementary Table 1, available online). To avoid convergence to local maxima during the expectation–maximization algorithm, each model was estimated 20 times using different sets of random starting values. Model fit was evaluated using the log-likelihood, Akaike information criterion (AIC), Bayesian information criterion (BIC), relative entropy, and the Lo–Mendell–Rubin likelihood ratio test (LMR-LRT).[23,24] The optimal number of latent classes was determined based on a combination of statistical indices and clinical interpretability. Lower AIC and BIC values indicated better model fit, whereas higher relative entropy and a significant LMR-LRT supported superior classification performance. Descriptive statistics were summarized as means with standard deviations or medians with interquartile ranges for continuous variables, depending on their distribution, and as counts with percentages for categorical variables. To compare clinical and demographic characteristics across latent classes, one-way analysis of variance or the Kruskal–Wallis test was applied for continuous variables, depending on normality assumptions. Normality was assessed using the Shapiro–Wilk test and

visual inspection of histograms and Q–Q plots. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Multiple comparisons were adjusted using the Bonferroni correction. All statistical analyses were performed using R software (version 4.4.1; R Foundation for Statistical Computing). Two-sided p-values <0.05 were considered statistically significant.

RESULTS

1. Participants with headache

Of 91,153 individuals invited by email, 10,699 consented to participate. Among them, 6,215 discontinued the survey, 1,075 declined enrollment after screening, and 379 were excluded because a quota had been reached, leaving 3,030 participants who completed the survey (Figure 1). The distributions of age, sex, and residential area were similar to those of the Korean population.[25]

Among the participants, 1,938 reported having a headache within the past year. The numbers meeting criteria for migraine, PM, TTH, and other headache diagnoses were 170, 337, 954, and 477, respectively. A total of 597 participants reported using rescue medication on more than 1 day in the past 30 days. There was no missing data because the survey required all fields to be completed.

2. Model selection and classification

Nine models, ranging from two to ten classes, were evaluated using LCA. Balancing statistical fit and classification quality with clinical interpretability, we selected the nine-class model because it best represented distinct class characteristics and had the lowest AIC and BIC, the LMR-LRT statistic, and the third-highest classification entropy (Table 1). The standard errors for the estimated class prior probabilities and the class-conditional response probabilities for the indicators were within acceptable ranges.

3. Sociodemographic characters of the nine classes

Table 2 summarizes the sociodemographic features across the nine classes. There were no differences in education level or in comorbid hypertension, diabetes, or dyslipid-

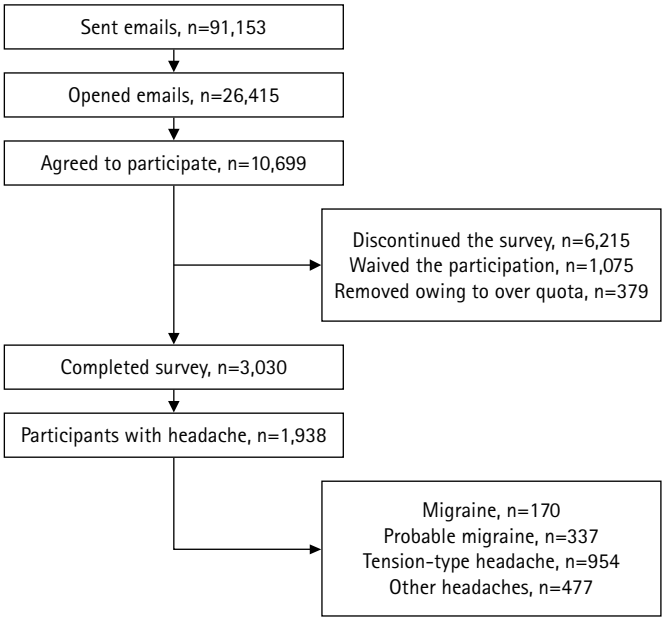


Figure 1. Recruitment of participants in the Circannual Change in Headache and Sleep (CHASE) study and diagnosis of headache.

Table 1. Model fit indices and class sizes for latent class analysis

Number of classes	df	log-likelihood	AIC	BIC	Relative entropy	LMR	p-value	Size of each class
2	1,905	−13,415.19	26,896.38	27,080.17	0.867	1,115.581	<0.001	286|1652
3	1,888	−13,066.55	26,233.09	26,511.56	0.856	667.880	<0.001	353|490|1095
4	1,871	−12,753.56	25,641.12	26,014.27	0.839	599.565	<0.001	324|483|516|615
5	1,854	−12,637.72	25,443.44	25,911.27	0.872	221.913	<0.001	61|365|402|491|619
6	1,837	−12,519.00	25,240.00	25,802.51	0.893	227.423	<0.001	60|186|194|415|464|619
7	1,820	−12,435.96	25,107.91	25,765.10	0.905	159.083	<0.001	60|63|169|184|394|443|625
8	1,803	−12,371.25	25,012.51	25,764.38	0.917	123.946	<0.001	51|60|165|171|185|286|393|627
9	1,786	−12,304.99	24,913.98	25,760.53	0.895	126.934	<0.001	54|61|79|143|148|187|248|392|626
10	1,769	−12,296.13	24,930.26	25,871.49	0.888	16.977	0.456	41|61|86|129|142|150|163|261|396|509

df, degrees of freedom; AIC, Akaike information criterion; BIC, Bayesian information criterion; LMR, Lo–Mendell–Rubin likelihood ratio test.

Table 2. Sociodemographic features of the nine classes

Characteristic	Total	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8	Class 9	p-value
Participant (n)	1,938 (100)	626 (100)	54 (100)	248 (100)	148 (100)	187 (100)	143 (100)	79 (100)	61 (100)	392 (100)	
Age (yr)	40.44±10.74	41.78±10.89	38.33±9.44	40.85±11.22	39.64±9.90	40.08±10.53	39.06±10.55	39.62±11.00	37.93±10.62	39.86±10.60	0.004
Sex											<0.001
Male	851 (43.9)	339 (54.2)	18 (33.3)	125 (50.4)	31 (20.9)	78 (41.7)	49 (34.3)	39 (49.4)	23 (37.7)	149 (38.0)	
Female	1,087 (56.1)	287 (45.8)	36 (66.7)	123 (49.6)	117 (79.1)	109 (58.3)	94 (65.7)	40 (50.6)	38 (62.3)	243 (62.0)	
Education											0.632
Middle school or lower	9 (0.5)	1 (0.2)	0 (0.0)	1 (0.4)	1 (0.7)	1 (0.5)	1 (0.7)	0 (0.0)	0 (0.0)	4 (1.0)	
High school	756 (39.0)	248 (39.6)	21 (38.9)	94 (37.9)	58 (39.2)	60 (32.1)	61 (42.7)	25 (31.6)	27 (44.3)	162 (41.3)	
College or higher	1,173 (60.5)	377 (60.2)	33 (61.1)	153 (61.7)	89 (60.1)	126 (67.4)	81 (56.6)	54 (68.4)	34 (55.7)	226 (57.7)	
BMI (kg/m^2)	23.96±3.81	24.25±3.52	23.14±3.77	23.63±3.82	23.15±3.63	23.82±4.06	24.09±4.81	24.29±4.19	23.20±3.36	24.20±3.74	<0.001
Hypertension	377 (19.5)	129 (20.6)	8 (14.8)	44 (17.7)	21 (14.2)	37 (19.8)	39 (27.3)	19 (24.1)	11 (18.0)	69 (17.6)	0.153
Diabetes	141 (7.3)	48 (7.7)	1 (1.9)	18 (7.3)	6 (4.1)	16 (8.6)	18 (12.6)	8 (10.1)	3 (4.9)	23 (5.9)	0.087
Dyslipidemia	308 (15.9)	100 (16.0)	7 (13.0)	37 (14.9)	23 (15.5)	31 (16.6)	26 (18.2)	12 (15.2)	7 (11.5)	65 (16.6)	0.973

Values are presented as number (%) or mean±standard deviation. Pairwise comparison with Bonferroni correction; Significant p-values with Age: none, Sex: 1 vs. 4, 1 vs. 6, 1 vs. 9, 3 vs. 4, 4 vs. 5, 4 vs. 7, 4 vs. 9, BMI: 1 vs. 4.
BMI, body mass index.

emia. Class 1 was oldest group (41.78±10.89 years) and Class 8 was the youngest (37.93±10.62 years). However, this difference was not significant when multiple comparisons were made. Females comprised 56.1% of the overall headache cohort. However, Class 1 showed male predominance (54.2%) and differed significantly from Classes 4, 6, and 9, which showed female predominance (79.1%, 65.7%, and 62.0%, respectively). Class 4 had the strongest female predominance (79.1%) and differed significantly from Classes 3, 5, 7, and 9. Class 3 had a balanced sex distribution (50.4% male, 49.6% female). Body mass index (BMI) was significantly higher in Class 1 than in Class 4.

4. Clinical features and associated characteristics of the nine classes

Headache characteristics and associated symptoms defined by the ICHD-3 criteria for migraine and TTH were used as variables in the LCA. Headache intensity, location, pulsating quality, aggravation by routine physical activity, nausea, vomiting, photophobia, phonophobia, headache frequency, and headache duration all differed significantly across classes (Table 3). Results of pairwise multiple comparisons are provided in the supplementary tables (Supplementary Table 2, available online).

Other clinical characteristics, including headache-related impact, disability, comorbid symptoms, and the distribution of original ICHD-3 diagnoses across classes, are summarized in Table 4. The corresponding multiple comparisons are provided in the supplementary tables (Supplementary Table 3, available online).

Class 1 was the largest class, comprising 626 individuals (32.3%). Class 1 was characterized by mild headache intensity without nausea or vomiting, short duration (<30 minutes), and infrequent attacks (<8 day/mo). It also had the lowest HIT-6 and MIDAS scores and the lowest burden of anxiety, CA, fatigue, and EDS. 93.9% of Class 1 were TTH.

Class 2 (n=54) was characterized by uniformly moderate-intensity headache (100%) with nausea in 94.4%. Attacks lasted 30 minutes to 4 hours and were infrequent. Headache was predominantly bilateral, non-pulsatile, and not aggravated by routine physical activity. HIT-6 and MIDAS scores were moderately elevated. The presence of anxiety and depression was moderate across classes. The

Table 3. Differences in ICHD-3 diagnostic features across the nine latent classes

Characteristic	Total	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8	Class 9	p-value
Participant (n)	1,938 (100)	626 (100)	54 (100)	248 (100)	148 (100)	187 (100)	143 (100)	79 (100)	61 (100)	392 (100)	
Headache intensity											<0.001
Mild	1,067 (55.1)	612 (97.8)	0 (0.0)	240 (96.8)	0 (0.0)	45 (24.1)	56 (39.2)	61 (77.2)	0 (0.0)	53 (13.5)	
Moderate	747 (38.5)	14 (2.2)	54 (100.0)	8 (3.2)	71 (48.0)	136 (72.7)	86 (60.1)	0 (0.0)	56 (91.8)	322 (82.1)	
Severe	124 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	77 (52.0)	6 (3.2)	1 (0.7)	18 (22.8)	5 (8.2)	17 (4.3)	
Unilateral location	994 (51.3)	329 (52.6)	0 (0.0)	116 (46.8)	74 (50.0)	117 (62.6)	87 (60.8)	10 (12.7)	0 (0.0)	261 (66.6)	<0.001
Pulsating quality	873 (45.0)	213 (34.0)	0 (0.0)	99 (39.9)	90 (60.8)	139 (74.3)	74 (51.7)	18 (22.8)	1 (1.6)	239 (61.0)	<0.001
Aggravation by routine physical activity	623 (32.1)	113 (18.1)	0 (0.0)	0 (0.0)	127 (85.8)	48 (25.7)	143 (100.0)	29 (36.7)	0 (0.0)	163 (41.6)	<0.001
Nausea	749 (38.6)	1 (0.2)	51 (94.4)	246 (99.2)	97 (65.5)	171 (91.4)	134 (93.7)	49 (62.0)	0 (0.0)	0 (0.0)	<0.001
Vomiting	358 (18.5)	0 (0.0)	19 (35.2)	54 (21.8)	66 (44.6)	110 (58.8)	64 (44.8)	45 (57.0)	0 (0.0)	0 (0.0)	<0.001
Photophobia	495 (25.5)	78 (12.5)	8 (14.8)	0 (0.0)	122 (82.4)	45 (24.1)	84 (58.7)	67 (84.8)	7 (11.5)	84 (21.4)	<0.001
Phonophobia	860 (44.4)	298 (47.6)	1 (1.9)	0 (0.0)	138 (93.2)	0 (0.0)	143 (100.0)	53 (67.1)	26 (42.6)	201 (51.3)	<0.001
Headache frequency (day/mo)											<0.001
<2	820 (42.3)	379 (60.5)	14 (25.9)	126 (50.8)	32 (21.6)	50 (26.7)	37 (25.9)	48 (60.8)	16 (26.2)	118 (30.1)	
2–7	947 (48.9)	219 (35.0)	30 (55.6)	115 (46.4)	87 (58.8)	115 (61.5)	77 (53.8)	29 (36.7)	35 (57.4)	240 (61.2)	
8–14	97 (5.0)	14 (2.2)	3 (5.6)	2 (0.8)	18 (12.2)	11 (5.9)	17 (11.9)	0 (0.0)	7 (11.5)	25 (6.4)	
≥15	74 (3.8)	14 (2.2)	7 (13.0)	5 (2.0)	11 (7.4)	11 (5.9)	12 (8.4)	2 (2.5)	3 (4.9)	9 (2.3)	
Headache duration											<0.001
<30 min	1,240 (64.0)	619 (98.9)	0 (0.0)	184 (74.2)	0 (0.0)	164 (87.7)	143 (100.0)	23 (29.1)	0 (0.0)	107 (27.3)	
30 min-4 hr	459 (23.7)	0 (0.0)	54 (100.0)	64 (25.8)	0 (0.0)	0 (0.0)	0 (0.0)	56 (70.9)	0 (0.0)	285 (72.7)	
4–72 hr	200 (10.3)	7 (1.1)	0 (0.0)	0 (0.0)	127 (85.8)	23 (12.3)	0 (0.0)	0 (0.0)	43 (70.5)	0 (0.0)	
72 hr–7 day	26 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	15 (10.1)	0 (0.0)	0 (0.0)	0 (0.0)	11 (18.0)	0 (0.0)	
>7 day	13 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	7 (11.5)	0 (0.0)	

Values are presented as number (%). Pairwise comparisons with Bonferroni correction are provided in the supplementary tables (Supplementary Table 2, available online).
ICHD-3, International Classification of Headache Disorders, 3rd edition.

Table 4. Comparison of clinical characteristics of the nine classes

	Total	Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 7	Class 8	Class 9	p-value
Participant (n)	1,938 (100)	626 (100)	54 (100)	248 (100)	148 (100)	187 (100)	143 (100)	79 (100)	61 (100)	392 (100)	
Monthly headache frequency	2.0 (1.0–3.0)	1.0 (1.0–2.0)	3.0 (1.0–7.0)	1.0 (1.0–3.0)	3.0 (2.0–6.0)	2.0 (1.0–3.0)	3.0 (1.0–6.0)	1.0 (1.0–2.0)	2.0 (1.0–5.0)	2.0 (1.0–4.0)	<0.001
By category (day)											<0.001
<2	820 (42.3)	379 (60.5)	14 (25.9)	126 (50.8)	32 (21.6)	50 (26.7)	37 (25.9)	48 (60.8)	16 (26.2)	118 (30.1)	
2–7	947 (48.9)	219 (35.0)	30 (55.6)	115 (46.4)	87 (58.8)	115 (61.5)	77 (53.8)	29 (36.7)	35 (57.4)	240 (61.2)	
8–14	97 (5.0)	14 (2.2)	3 (5.6)	2 (0.8)	18 (12.2)	11 (5.9)	17 (11.9)	0 (0.0)	7 (11.5)	25 (6.4)	
≥15	74 (3.8)	14 (2.2)	7 (13.0)	5 (2.0)	11 (7.4)	11 (5.9)	12 (8.4)	2 (2.5)	3 (4.9)	9 (2.3)	
Aura (VARS score≥3)	522 (26.9)	138 (22.0)	17 (31.5)	54 (21.8)	51 (34.5)	49 (26.2)	55 (38.5)	25 (31.6)	14 (23.0)	119 (30.4)	<0.001
HIT-6 score	53.0 (47.0–60.0)	48.0 (42.0–53.0)	56.0 (52.0–61.0)	49.0 (44.5–55.0)	63.0 (59.0–67.0)	56.0 (51.0–61.0)	59.0 (54.0–63.0)	54.0 (49.0–60.0)	56.0 (48.0–61.0)	56.0 (50.0–61.0)	<0.001
MIDAS score	4.0 (1.0–10.0)	1.0 (0.0–5.0)	7.0 (3.0–23.0)	2.0 (0.0–6.0)	13.0 (6.0–29.0)	6.0 (2.0–14.0)	10.0 (4.0–25.0)	4.0 (2.0–9.0)	3.0 (1.0–14.0)	5.5 (2.0–12.0)	<0.001
Anxiety (GAD-7 score≥8)	479 (24.7)	99 (15.8)	16 (29.6)	44 (17.7)	60 (40.5)	48 (25.7)	57 (39.9)	24 (30.4)	23 (37.7)	108 (27.6)	<0.001
Depression (PHQ-9 score≥10)	185 (9.5)	41 (6.5)	8 (14.8)	11 (4.4)	25 (16.9)	21 (11.2)	27 (18.9)	9 (11.4)	9 (14.8)	34 (8.7)	<0.001
Cutaneous allodynia (ASC-12 score≥3)	469 (24.2)	70 (11.2)	18 (33.3)	41 (16.5)	77 (52.0)	52 (27.8)	65 (45.5)	26 (32.9)	20 (32.8)	100 (25.5)	<0.001
Fatigue (FSS score≥4)	1,054 (54.4)	274 (43.8)	28 (51.9)	117 (47.2)	109 (73.6)	118 (63.1)	108 (75.5)	41 (51.9)	33 (54.1)	226 (57.7)	<0.001
Excessive daytime sleepiness (ESS score≥11)	450 (23.2)	117 (18.7)	13 (24.1)	58 (23.4)	38 (25.7)	47 (25.1)	48 (33.6)	19 (24.1)	18 (29.5)	92 (23.5)	0.020
Fibromyalgia syndrome	162 (8.4)	31 (5.0)	8 (14.8)	11 (4.4)	26 (17.6)	19 (10.2)	24 (16.8)	8 (10.1)	7 (11.5)	28 (7.1)	<0.001
Poor sleep quality (PSQI score≥8.5)	335 (17.3)	81 (12.9)	13 (24.1)	26 (10.5)	47 (31.8)	34 (18.2)	42 (29.4)	15 (19.0)	13 (21.3)	64 (16.3)	<0.001
Insomnia (ISI score≥15)	127 (6.6)	35 (5.6)	5 (9.3)	9 (3.6)	24 (16.2)	7 (3.7)	12 (8.4)	6 (7.6)	3 (4.9)	26 (6.6)	<0.001
ICHD-3 headache diagnosis											
Migraine	170 (8.8)	0 (0.0)	0 (0.0)	0 (0.0)	147 (99.3)	23 (12.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Probable migraine	337 (17.4)	16 (2.6)	0 (0.0)	34 (13.7)	0 (0.0)	135 (72.2)	127 (88.8)	8 (10.1)	0 (0.0)	17 (4.3)	<0.001
Tension-type headache	954 (49.2)	588 (93.9)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	61 (100.0)	304 (77.6)	<0.001
Other headache	477 (24.6)	22 (3.5)	54 (100.0)	214 (86.3)	0 (0.0)	29 (15.5)	16 (11.2)	71 (89.9)	0 (0.0)	71 (18.1)	<0.001
Medication overuse headache	29 (1.5)	2 (0.3)	3 (5.6)	2 (0.8)	8 (5.4)	5 (2.7)	7 (4.9)	0 (0.0)	1 (1.6)	1 (0.3)	<0.001

Values are presented as number (%) or median (interquartile range). Pairwise comparisons with Bonferroni correction are provided in the supplementary tables (Supplementary Table 3, available online).

VARS, Visual Aura Rating Scale; HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; ASC-12, Allodynia Symptom Checklist-12; FSS, Fatigue Severity Scale; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; ICHD-3, International Classification of Headache Disorders, 3rd edition.

phenotype did not meet ICHD-3 criteria for migraine or TTH and all cases were classified as other headache disorder.

Class 3 (n=248) was characterized by mild headache intensity, nausea in 99.2%, absent photophobia and phonophobia, short duration (<4 hours), and infrequent attacks (<8 day/mo). Although this pattern resembles PM with short-duration, 86.3% were classified as other headache disorders, due to brief duration and mild headache intensity.

Class 4 (n=148) was characterized by moderate to severe headache intensity, unilateral location and pulsating quality in >50%, nausea and vomiting, and >80% of aggravation by routine physical activity, photophobia, and phonophobia. All attacks lasted ≥4 hours. Showing typical migraine features, 99.3% were migraine with one exception of TTH. Class 4 had the highest HIT-6 and MIDAS scores, the highest CA, anxiety, and FMS proportion. Depression presence was second highest.

Class 5 (n=187) was characterized by predominantly moderate-intensity headache with high proportion of unilateral location, pulsating quality, vomiting, and more nausea (91.4%). Photophobia was present in 24.1%, and phonophobia was absent. Attacks were generally infrequent (<8 day/mo) and of short duration. Of ICHD-3 headache diagnosis, 72.2% met criteria for PM and 12.3% for migraine.

Class 6 (n=143) was characterized by mild to moderate headache intensity with 100% aggravation by routine physical activity and 100% phonophobia. Photophobia occurred in 44.8%, and >50% had unilateral headache and pulsating quality. Attacks were brief (<30 minutes). Class 6 showed second-highest HIT-6, MIDAS, anxiety, FMS, and CA following Class 4. Class 6 showed the highest depression and visual aura. PM comprised 88.8% of this class.

Class 7 (n=79) was characterized by headache intensity that was either mild or severe (no moderate intensity), predominantly bilateral, non-pulsating, and with high rates of nausea, vomiting, photophobia (84.8%), and phonophobia. All attacks were short (<4 hours) and infrequent (<8 day/mo). Photophobia prevalence was the highest across classes. Visual aura was third highest, following Classes 6 and 4. In the original ICHD-3 diagnosis, 89.9% were other headache disorders.

Class 8 (n=61) was characterized by predominantly moderate to severe intensity, 100% bilateral location, and 98.4% non-pulsating quality, with no nausea, vomiting, or aggravation by routine physical activity. Photophobia occurred in 11.5% and phonophobia in 42.6%. Attacks lasted ≥4 hours. Headache impact, disability, and comorbidity burdens were moderate. All cases were classified as ICHD-3 TTH.

Class 9 (n=392) was the second-largest class, characterized by predominantly moderate-intensity headache, >60% unilateral and pulsating, no nausea or vomiting, photophobia in 21.4%, and phonophobia in 51.3%. Attacks were usually <4 hours. On ICHD-3 diagnosis, 77.6% were classified as TTH and 18.1% as other headache disorders.

DISCUSSION

The main findings were: 1) using ICHD-3 diagnostic features as variables, LCA identified nine headache classes; 2) class characteristics broadly mirrored established diagnostic categories (migraine, PM, TTH) while differing in severity, duration, and indices of sensory hypersensitization; 3) PM formed classes distinct from both migraine and TTH and showed a higher depression burden and more visual aura, supporting its clinical validity and the need for focused study; 4) several "other headache" classes were noted and showed meaningful burden with high proportion of photophobia or MOH, warranting clinical attention.

Diagnosing headache disorders is challenging.[26] It relies on clinical criteria from the ICHD-3, with which many general practitioners are unfamiliar.[27] Though there are proven pathophysiological differences between migraine, TTH, and cluster headache (CH), the ICHD-3 diagnostic criteria are defined by a combination of multiple variables, resulting in a variety of possible diagnoses.[5] Furthermore, symptoms overlap between headache diagnoses, resulting in a grey zone, such as those with TTH and PM, whose final diagnosis is TTH.[1,5,28] In other cases, a single headache diagnosis may present as multiple phenotypes, or multiple headache diagnosis may be made for a single patient.[29,30] Consequently, a substantial proportion of patients are misdiagnosed and undertreated.[26,31,32] Accurate diagnosis matters because migraine, TTH, and CH differ in their prognosis and their optimal treatment.[33-35] Using a statistical approach, we examined overlap and potential misclassification in current criteria and identified natural diagnostic classes. Nine classes broadly mapped to ICHD-

3 categories (Classes 1, 8, 9: TTH; Class 4: migraine; Classes 5, 6: PM; Classes 2, 3, 7: other headache) but differed in clinically relevant details. Whereas ICHD-3 primarily relies on frequency and duration to distinguish episodic from chronic phenotypes, our results indicate that severity and markers of central sensitization, specifically sensory hypersensitivities (photophobia, phonophobia) better differentiate classes. Photophobia, phonophobia, and CA have been associated with greater migraine severity and chronification.[15,36] Our findings suggest these markers may be of more relevance than monthly frequency for classification of headache disorders.

Classes 1, 8, and 9 consisted mostly of TTH, but their characteristics differed. Together they comprised 1,079 participants (55.7%), slightly exceeding the number of TTH by ICHD-3 (n=954). Class 1 was male-predominant, had higher BMI, and was the most frequent. The profile reflects mild TTH (mild pain without nausea/vomiting), and the male predominance with a milder phenotype is consistent with prior epidemiologic studies.[37] Class 9 was the second largest notable for >60% female, unilateral, and pulsating pain. However, most cases did not meet migraine or PM criteria because nausea or vomiting were absent, both photophobia and phonophobia were not present, and attacks were short (<4 hours). Only 17 individuals (4.3%) met PM criteria. Considered together, Classes 1 and 9, the two largest, were predominantly mild and more unilateral consistent with our prior report on unilateral TTH.[2] Unilateral TTH warrants attention because it challenges the classical concept of TTH and may be misdiagnosed as migraine.[2] Although both Class 1 and Class 9 reflected mild TTH, Class 9 showed greater headache impact, disability, depression, anxiety, and CA, indicating a mild but disabling phenotype that merits clinical attention. Differences between the two classes may reflect sex differences, as women tend to experience greater pain and disability than men, and treatment strategies should incorporate sex-specific considerations.[38]

In contrast, Class 8 showed classic bilateral headache without nausea or vomiting and had greater headache impact with poorer sleep indices, indicating the highest burden among TTH-like classes. Longer duration and more frequent attacks suggest a more severe, frequent or chronic TTH. Although relatively small, this subgroup may require more clinical care. The predominance of severe bilateral pain may have shaped the classic TTH concept, while milder phenotypes received less clinical attention. The high prevalence of TTH and variability emphasize the need for careful phenotyping and management, which remains under-recognized in clinical practice and research.[2,34,37]

Classes 2, 3, and 7 were predominantly other headaches (Class 2: 100%; Class 3: 86.3%; Class 7: 89.9%). Class 2 presented as a moderate-intensity other-headache phenotype. It had the highest attack frequency, with the largest proportion reporting ≥15 headache days per month. Headache was uniformly moderate, bilateral, non-pulsating, not aggravated by routine physical activity, and <4 hours in duration. The profile resembled TTH, but TTH was excluded because nausea was frequent (94.4%). Class 2 also had the highest prevalence of MOH (5.6%). In pairwise comparisons, MOH prevalence in Class 2 did not differ significantly from Class 4 (migraine) or Class 6 (PM with higher sensory sensitivity). Although much MOH literature focuses on migraine, TTH, and trigeminal autonomic cephalalgias such as CH, the MOH burden observed in this class warrants clinical attention given its potential for disability.[39] Class 3 showed mild, short-duration headaches with frequent nausea (99.2%), without photophobia, phonophobia, or aggravation by routine physical activity. This class was predominantly other headache (86.3%), with only 13.7% meeting PM criteria. This class may represent a milder form of PM, positioned on the PM–migraine spectrum due to missing one or more diagnostic criteria. Because an "other headache" category in the current ICHD-3 can also present predominantly with nausea, more careful approach is recommended when using migraine screening tools that rely heavily on nausea.[40,41] Class 7 was an "other headache" class with pronounced photophobia. It comprised short-duration headaches with the highest photophobia (84.8%) and the third highest phonophobia (67.1%), indicating prominent sensory hypersensitivity. However, CA was only the fourth most frequent across classes, and headache impact and disability were modest. This pattern likely reflects non-migraine phenotypes with heightened sensory sensitivity but without marked CA. Prior studies suggest that coexisting sensory hypersensitivities and CA are associated with greater disease burden than CA alone.[42] The greater CA, depression, and headache impact in Class 6 relative to Class 7 may reflect these findings.

Class 4 displayed classic migraine features. ICHD-3 migraine comprised 99.3% (147/148) of individuals in this

class and accounted for 86.5% (147/170) of all migraines in the study. Class 4 also had the highest burden across clinical scales (headache impact and disability) and the highest rates of CA, anxiety, fatigue, poor sleep quality, and insomnia. The proportion with MOH was second highest after Class 2. These findings support efficient ICHD-3 classification of the migraine phenotype in light of known pathophysiology.[1,28] Migraine diagnoses outside Class 4 clustered mainly in Class 5 with PM, which showed a milder phenotype with fewer sensory hypersensitivities. Although migraine formed a distinct entity, several features commonly considered migraine-specific were not unique to Class 4. Unilateral pain was more frequent in Class 9 (predominantly TTH), pulsating quality in Class 5, and nausea was more prominent in Classes 3, 5, and 6. Prior population-based studies also report that up to 40% of individuals with migraine have bilateral pain.[43] These observations indicate that the specificity of individual migraine symptoms warrants careful reappraisal given phenotypic heterogeneity and overlap.[3,5]

Classes 5 and 6 were predominantly PM. Both showed high nausea rates, moderate pain intensity, and frequent unilateral location. Headache duration was <30 minutes in all of Class 6 and in most of Class 5, consistent with prior Korean data in which short duration was the most common reason for PM diagnosis.[8] Regional epidemiology should be considered, as lower migraine prevalence and higher PM rates have been reported in Korean, African American populations compared with white populations.[8,32] The concentration of PM in these two classes suggests that PM, often not coded when a more definitive diagnosis is assigned, warrants greater diagnostic attention as a distinct phenotype within the migraine spectrum. The classes differed in that Class 6 had 100% aggravation by routine physical activity and 100% phonophobia, whereas phonophobia was absent in Class 5. Class 5 represents a comparatively milder PM profile without phonophobia. Class 6 represents PM with prominent sensory hypersensitivity. Class 6 showed a higher burden. It had second-highest HIT-6, MIDAS, and CA after Class 4, and the highest proportion of visual aura, depression, fatigue, and EDS. It is important to note that the burden in class 6 exceeded that in class 4, migraine. The finding stresses the need for targeted assessment and management of PM, which remains undertreated.[32]

Photophobia, phonophobia, and CA, hallmarks of central sensitization, were among the most discriminative features separating classes with similar ICHD-3 diagnosis (e.g., 5 vs. 6 and 7 vs. 2 or 3). Sensory hypersensitivities and CA are clinical correlates of central sensitization and are associated with greater migraine burden and a higher risk of progression to chronic migraine.[36,44] Co-existence of multiple hypersensitivities (photophobia, phonophobia, osmophobia) and CA correlates with more severe migraine, through central sensitization and nociceptive pathway alteration.[36,42] While ICHD-3 distinguishes episodic and chronic forms by monthly headache days, our findings suggest that features of central sensitization may reflect disease severity.[1]

While ICHD-3 migraine diagnosis requires photophobia and phonophobia for a diagnostic criterion,[1] in our data, photophobia and phonophobia contributed differently to class separation, which may reflect distinct pathophysiology. Photophobia has been linked to a retino–thalamo–cortical pathway, whereas phonophobia has been associated with auditory neurons and brainstem auditory systems.[45,46] Recognizing possible pathophysiologic heterogeneity, additional research is required for development of more precise diagnostic criteria.

Our study has several limitations. First, headache diagnoses relied on patient self-report, which may introduce bias. Recall of headache characteristics and frequency may have been influenced, and duration may have been affected by medication use. However, we queried duration as if rescue medication had not been taken, and the diagnostic algorithm has been validated with acceptable sensitivity and specificity.[12] Second, because the survey queried only each participant's most severe headache, overlapping or concurrent diagnoses were not captured. However, diagnosing multiple headaches is difficult without a headache diary,[30] particularly in a population-based study. Third, the questionnaire was designed to diagnose migraine, PM, and TTH and was not intended to diagnose other primary headaches or post-traumatic headache, so some "other headache" cases could include TACs such as CH. However, the predominantly bilateral pattern, mild to moderate severity distribution, and the low population prevalence of TACs make substantial inclusion unlikely. Fourth, although nationwide, the sample comprised only Korean adults, so generalizability to other populations is uncertain

given racial differences in migraine and PM prevalence,[32] and replication in more diverse cohorts is warranted. In addition, although local independence is a fundamental assumption of LCA, post-estimation checks using bivariate residuals indicated only limited residual associations. These were primarily observed among clinically related symptom pairs and did not meaningfully alter the emergent class structure. Lastly, the statistically derived classes were interpreted clinically but do not by themselves establish distinct pathophysiology. Further studies are needed to confirm the proposed classification.

Conclusions

In this population-based study, we identified natural classes of headache by LCA of ICHD-3 diagnostic features. Nine clinically distinct classes emerged whose core characteristics paralleled migraine, PM, TTH, and other headaches, while differing in severity, duration, and markers of sensory hypersensitization. One migraine and three TTH phenotypes were noted. PM formed discrete classes separable from both migraine and TTH. One of the two PM classes with exclusive phonophobia had the highest depression burden, and one of the three "other headache" classes carried a high MOH burden, drawing clinical attention. These findings challenge current diagnostic frameworks and motivate studies to refine diagnostic classification with pathophysiologic evidence.

AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: WL, MKC; Data curation: WL, SJH, JY, MKC; Formal analysis: WL, SJH, MKC; Investigation: WL, JY, MKC; Methodology: WL, SJH; Writing–original draft: WL, SJH; Writing–review & editing: WL, SJH, JY, MKC.

CONFLICT OF INTEREST

Seok-Jae Heo and Jungyon Yum declare no conflicts of interest. Wonwoo Lee was involved as a site investigator in a multicenter trial sponsored by Eli Lilly and Co., WhanIn Pharm Co. Ltd., and Handok-Teva. He has received lecture honoraria from Abbott and SK chemical in the past 24 months. Min Kyung Chu was a site investigator for a multicenter trial sponsored by Allergan Korea, Biohaven Pharmaceuticals, and Lundbeck Korea. He has received lecture honoraria from Allergan Korea, Handok-Teva, Eli Lilly and Company, and Yuyu Pharmaceutical Company in the past 24 months. Additionally, he received grants from Yonsei University College of Medicine (6-2021-0229), the Korea Health Industry Development Institute (KHIDI) (HV22C0106), and National Research Foundation of Korea (2022R1A2C1091767).

FUNDING STATEMENT

This study was supported by a 2023 research grant for the headache research group, from the Headache Research Committee of the Korean Headache Society.

ACKNOWLEDGMENTS

Grammatical revisions were supported by ChatGPT (versions 4o–5.2).

SUPPLEMENTARY MATERIAL

Supplementary materials are available from https://doi.org/10.62087/hpr.2026.0004.

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38:1-211.
2. Lee W, Heo SJ, Chu MK. Natural subgroups of tension-type headache: a population-based study. Headache 2025;65:1160-1169.
3. Lee W, Min IK, Yang KI, Kim D, Yun CH, Chu MK. Classifying migraine subtypes and their characteristics by latent class analysis using data of a nation-wide population-based study. Sci Rep 2021;11:21595.
4. Lipton RB, Fanning KM, Buse DC, et al. Identifying natural subgroups of migraine based on comorbidity and concomitant condition profiles: results of the Chronic Migraine Epidemiolo-

gy and Outcomes (CaMEO) study. Headache 2018;58:933-947.
5. Zhang P. Which headache disorders can be diagnosed concurrently? An analysis of ICHD3 criteria using prime encoding system. Front Neurol 2023;14:1221209.
6. Chang Y, Choi S, Kim BS, Song TJ. Validity of migraine diagnoses in Korean National Health Insurance Claims data. Headache Pain Res 2025;26:154-161.
7. Lee W, Chu MK. The current role of artificial intelligence in the field of headache disorders, with a focus on migraine: a systemic review. Headache Pain Res 2025;26:48-65.
8. Kim BK, Chung YK, Kim JM, Lee KS, Chu MK. Prevalence, clinical characteristics and disability of migraine and probable migraine: a nationwide population-based survey in Korea. Cephalalgia 2013;33:1106-1116.
9. Sinha P, Calfee CS, Delucchi KL. Practitioner's guide to latent class analysis: methodological considerations and common pitfalls. Crit Care Med 2021;49:e63-e79.
10. Lee W, Cho SJ, Hwang H, et al. Crystal-clear days and unclear days in migraine: a population-based study. Headache 2022;62:818-827.
11. Korean Statistical Information Service. Statistical database: population, households and housing unit [Internet]. Statistics Korea; 2018 [cited 2026 Jan 13]. Available from: https://kosis.kr/eng/statisticsList/statisticsListIndex.do?menuId=M_01_01&vwcd=MT_ETITLE&parmTabId=M_01_01&statId=1962001&themaId=#SelectStatsBoxDiv
12. Kim KM, Kim AR, Lee W, Jang BH, Heo K, Chu MK. Development and validation of a web-based headache diagnosis questionnaire. Sci Rep 2022;12:7032.
13. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 2003;12:963-974.
14. Stewart WF, Lipton RB, Kolodner KB, Sawyer J, Lee C, Liberman JN. Validity of the Migraine Disability Assessment (MIDAS) score in comparison to a diary-based measure in a population sample of migraine sufferers. Pain 2000;88:41-52.
15. Han SM, Kim KM, Cho SJ, et al. Prevalence and characteristics of cutaneous allodynia in probable migraine. Sci Rep 2021;11:2467.
16. Seo JG, Park SP. Validation of the Generalized Anxiety Disorder-7 (GAD-7) and GAD-2 in patients with migraine. J Headache Pain 2015;16:97.
17. Kim M, Jung S, Park JE, et al. Validation of the Patient Health Questionnaire-9 and Patient Health Questionnaire-2 in the general Korean population. Psychiatry Investig 2023;20:853-860.
18. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319-329.
19. Cho YW, Lee JH, Son HK, Lee SH, Shin C, Johns MW. The reliability and validity of the Korean version of the Epworth sleepiness scale. Sleep Breath 2011;15:377-384.
20. Sohn SI, Kim DH, Lee MY, Cho YW. The reliability and validity of the Korean version of the Pittsburgh Sleep Quality Index. Sleep Breath 2012;16:803-812.
21. Cho YW, Song ML, Morin CM. Validation of a Korean version of the insomnia severity index. J Clin Neurol 2014;10:210-215.
22. Linzer DA, Lewis JB. poLCA: an R Package for polytomous variable latent class analysis. J Stat Softw 2011;42:1-29.
23. Dean N, Raftery AE. Latent class analysis variable selection. Ann Inst Stat Math 2010;62:11-35.
24. Wurpts IC, Geiser C. Is adding more indicators to a latent class analysis beneficial or detrimental? Results of a Monte-Carlo study. Front Psychol 2014;5:920.
25. Kim KM, Cho SJ, Shin HJ, et al. Prevalence, disability, and management patterns of migraine in Korea: nationwide survey data from 2009 and 2018. J Clin Neurol 2021;17:77-85.
26. Viana M, Khaliq F, Zecca C, et al. Poor patient awareness and frequent misdiagnosis of migraine: findings from a large transcontinental cohort. Eur J Neurol 2020;27:536-541.
27. Kristoffersen ES, Faiz KW, Hansen JM, et al. The management and clinical knowledge of headache disorders among general practitioners in Norway: a questionnaire survey. J Headache Pain 2021;22:136.
28. Onan D, Younis S, Wellsgatnik WD, et al. Debate: differences and similarities between tension-type headache and migraine. J Headache Pain 2023;24:92.
29. Baha M, Nachit-Ouinekh F, El Hasnaoui A. Intrapatient variability of migraine attacks: stability analysis of the MIGSEV scale. Headache 2008;48:79-85.
30. Vandenbussche N, Van Der Donckt J, De Brouwer M, et al. Tracking migraine symptoms: a longitudinal comparison of smartphone-based headache diaries and clinical interviews. Neurol Int 2025;17:33.
31. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343-349.
32. Silberstein S, Loder E, Diamond S, et al. Probable migraine in the United States: results of the American Migraine Prevalence and Prevention (AMPP) study. Cephalalgia 2007;27:220-229.
33. Kim BS, Chung PW, Chung JM, Park KY, Moon HS, Park HK, et

al. Evidence-based recommendations on pharmacologic treatment for migraine prevention: a clinical practice guideline from the Korean Headache Society. Headache Pain Res 2025;26:5-20.
34. Lee HJ, Cho SJ, Seo JG, Schytz HW. Update on tension-type headache. Headache Pain Res 2025;26:38-47.
35. Kim M, Yu JK, Kim YH. Update on cluster headaches: from genetic to novel therapeutic approaches. Headache Pain Res 2024;25:42-53.
36. Suzuki K, Suzuki S, Shiina T, et al. Investigating the relationships between the burden of multiple sensory hypersensitivity symptoms and headache-related disability in patents with migraine. J Headache Pain 2021;22:77.
37. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. JAMA 1998;279:381-383.
38. Fuensalida-Novo S, Jiménez-Antona C, Benito-González E, Cigarán-Méndez M, Parás-Bravo P, Fernández-De-Las-Peñas C. Current perspectives on sex differences in tension-type headache. Expert Rev Neurother 2020;20:659-666.
39. Ashina S, Terwindt GM, Steiner TJ, et al. Medication overuse headache. Nat Rev Dis Primers 2023;9:5.
40. Smetana GW. The diagnostic value of historical features in primary headache syndromes: a comprehensive review. Arch Intern Med 2000;160:2729-2737.
41. Cousins G, Hijazze S, Van de Laar FA, Fahey T. Diagnostic accuracy of the ID Migraine: a systematic review and meta-analysis. Headache 2011;51:1140-1148.
42. Seo JG, Park SP. Clinical significance of sensory hypersensitivities in migraine patients: does allodynia have a priority on it? Neurol Sci 2019;40:393-398.
43. Rasmussen BK, Olesen J. Migraine with aura and migraine without aura: an epidemiological study. Cephalalgia 1992;12:221-228.
44. Lipton RB, Bigal ME, Ashina S, et al. Cutaneous allodynia in the migraine population. Ann Neurol 2008;63:148-158.
45. Kalita J, Misra UK, Bansal R. Phonophobia and brainstem excitability in migraine. Eur J Neurosci 2021;53:1988-1997.
46. Burstein R, Noseda R, Fulton AB. Neurobiology of photophobia. J Neuroophthalmol 2019;39:94-102.

Original Article

Headache Pain Res 2026;27(1):43-51
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2025.0022

Headache and Pain Research

The Impact of Anti-Calcitonin Gene-Related Peptide Monoclonal Antibodies on Sleep Quality and Daytime Sleepiness in Migraine Patients: A Multicenter Study

Rita Cagigal[1,*], Ângelo Fonseca[2,*], Bárbara Martins[3], Catarina Fernandes[4], Sandra Palma[5], Carolina Guerreiro[6], Carla Morgado[7], Diana Valente[8], Miguel Miranda[9], Joana Silva[10], Miguel Saianda-Duarte[11], Sofia Casanova[1], Mariana Branco[1], Ana Luísa Rocha[1], Henrique Delgado[12], Elsa Parreira[5], Filipe Palavra[13]

For further information on the authors' affiliations, see **Additional information**.

Abstract

Purpose: This study aimed to determine whether patients with migraine experience improvements in self-reported sleep quality and daytime sleepiness after starting monoclonal antibody (mAb) therapy targeting the calcitonin gene-related peptide (CGRP) or its receptor, and to explore the association between treatment efficacy and improvements in sleep quality.

Methods: This prospective, multicenter, observational, longitudinal study was conducted across 12 headache centers. Adults with episodic or chronic migraine who began anti-CGRP mAb therapy were assessed at baseline, 3 months, and 6 months. Sleep quality and daytime sleepiness were evaluated using the Portuguese version of the Pittsburgh Sleep Quality Index (PSQI-PT) and the Portuguese version of the Epworth Sleepiness Scale (ESS-PT), respectively.

Results: Of 118 enrolled patients, 109 completed the study (86.4% female; mean age, 43.6 years). A significant improvement in sleep quality was observed, with median PSQI-PT scores decreasing from 9 at baseline to 6 at 6 months ($p<0.001$). Daytime sleepiness also improved, with median ESS-PT scores decreasing from 7 to 6 ($p=0.04$). Migraine frequency decreased significantly, from a median of 13 to 4 monthly migraine days ($p<0.001$). Greater migraine improvement was independently associated with greater PSQI-PT improvement ($p<0.001$), whereas changes in ESS-PT were not correlated with treatment efficacy.

Conclusion: Anti-CGRP mAb therapy was associated with significant improvements in sleep quality, likely mediated through migraine relief. Changes in ESS-PT were not correlated with treatment efficacy, suggesting a possible interaction between migraine mechanisms and CGRP-mediated sleep–wake regulation. Future research should focus on clarifying the mechanisms underlying these associations.

Keywords: Calcitonin gene-related peptide receptor antagonists, Disorders of excessive somnolence, Migraine disorders, Migraine prophylaxis, Sleep quality

Received: October 3, 2025; **Revised:** November 14, 2025; **Accepted:** November 14, 2025

Correspondence: Rita Cagigal, M.D.
Neurology Department, Unidade Local de Saúde de Gaia e Espinho, Rua Conceição Fernandes 4434-502 Vilar de Andorinho, Vila Nova de Gaia, Porto, Portugal
Tel: +351-22-786-5100, Fax: +351-22-783-0209, E-mail: 13909@ulsge.min-saude.pt

*These authors contributed equally to this study as co-first authors.

INTRODUCTION

Migraine is a prevalent neurological disorder, affecting up to 15% of the adult population, with a higher prevalence in women. Beyond its significant personal and socio-economic impact, migraine is a leading cause of disability.[1,2] The term 'migraine burden' refers to the overall impact of migraine on patients' functional capacity, quality of life, and headache frequency and severity, encompassing both clinical and psychosocial dimensions.[2]

Sleep and migraine are closely interconnected.[3,4] Many migraine sufferers report poor sleep quality and excessive daytime sleepiness, while disruptions in sleep patterns are well-known triggers for migraine attacks and may even contribute to its chronification.[5,6]

Calcitonin gene-related peptide (CGRP) is a key neuropeptide in migraine pathophysiology. The functional trigeminovascular system theory suggests that its activation during a migraine attack triggers the release of various neuropeptides, including CGRP. This cascade leads to neurogenic inflammation, vasodilation, and increased cerebral blood flow, ultimately resulting in pain.[3,4,7] As a result, anti-CGRP monoclonal antibody (mAb) therapy has emerged as a promising approach to migraine treatment.[8,9] Emerging evidence suggests that this same peptide may also be involved in circadian cycle and sleep regulation, particularly through maintaining wakefulness.[10]

Therefore, since CGRP may act as a common link between migraine pathophysiology and the sleep disturbances frequently associated with it, it is plausible that anti-CGRP mAb therapy could also improve sleep quality in migraine patients—either indirectly by reducing attack frequency or through a direct effect on CGRP. Other studies have tried to demonstrate this relation.[11,12]

The present study aims to determine whether patients with migraine experience an improvement in self-reported sleep quality and reduction of daytime sleepiness after initiating treatment with mAbs targeting CGRP or its receptor and assessing the relationship between treatment efficacy and sleep quality improvement.

MATERIALS AND METHODS

1. Ethics approval and consent to participate

This study was approved by the Ethics Committee for Health of Unidade Local de Saúde de Gaia e Espinho on March 28, 2023 (approval number 42/2023-1) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

2. Study design and population

This was a prospective, multicenter, observational, and longitudinal study conducted between March 1, 2023, and December 31, 2023. Twelve headache centers were included. A detailed standardized study protocol was distributed to all centers prior to patient recruitment, defining inclusion/exclusion criteria, data collection instruments, visit timelines, and follow-up procedures. Before study initiation, all investigators and research staff participated in an online training session coordinated by the lead center (Unidade Local de Saúde de Gaia e Espinho), focusing on protocol adherence, correct administration of the Portuguese version of the Pittsburgh Sleep Quality Index (PSQI-PT) and Portuguese version of the Epworth Sleepiness Scale (ESS-PT) questionnaires, and uniform interpretation of headache diaries. To ensure consistency, each site used identical electronic templates for data entry, and any protocol-related queries were resolved through monthly coordination meetings and direct communication with the central coordinating team.

The study included patients initiating mAb therapy against CGRP for the first time, which included fremanezumab (225 mg, monthly), galcanezumab (120 mg, monthly), and erenumab (70 or 140 mg, monthly). Participants were recruited from outpatient neurology clinics at participating hospitals, provided they met the eligibility criteria, and written informed consent was signed.

Inclusion criteria encompassed adults aged 18–70 years diagnosed with episodic or chronic migraine, according to The International Classification of Headache Disorders, 3rd edition criteria, with at least 4 monthly migraine days. Patients starting anti-CGRP mAbs, either as monotherapy or in combination with stable preventive treatment, were

eligible. Exclusion criteria included prior mAb treatment or contraindications to this therapy.

3. Data collection and analysis

Patients underwent assessments at baseline (T0) and follow-ups at 3 (T1) and 6 months (T2). Data collection included demographic and clinical characteristics, migraine frequency and severity, comorbid sleep disorders, and medication use. The PSQI-PT[13] and ESS-PT[14] were applied to evaluate subjective sleep quality and daytime sleepiness, respectively. Headache diaries were maintained to track migraine days, pain intensity, and medication use.

To reduce inter-rater variability, all questionnaires were administered by trained investigators using a unified instruction guide.

The primary endpoint was the change in PSQI-PT score at T2 compared to T0. Secondary endpoints included changes in PSQI-PT and ESS-PT scores at T1 and T2 and correlations between sleep quality, daytime sleepiness, and migraine frequency.

All collected data were anonymized, encrypted, and stored in a restricted-access database. Data were centrally reviewed by the lead center. External monitoring ensured compliance with study protocols and data integrity.

4. Endpoints

The primary endpoint was the change in the PSQI-PT score from T0 to T2 after initiating treatment with mAbs targeting CGRP or its receptor. A PSQI-PT score ≤5 was considered the threshold for good sleep quality.

Secondary endpoints included the variation in PSQI-PT score at T1 compared to T0, as well as the variation in the ESS-PT score at T1 and T2, with an ESS-PT score ≤10 considered within the normal range. Additionally, correlations were analyzed between PSQI-PT scores and the average number of monthly migraine days at T1 and T2 of treatment, as well as between ESS-PT scores and the number of migraine days over the same period.

To address potential inflation of type I error due to multiple outcome testing, p-values were adjusted using the Benjamini–Hochberg false discovery rate (FDR) correction. A two-tailed adjusted $p<0.05$ was considered statistically significant.

5. Variables description

The study assessed demographic and clinical variables. Demographic variables included age, recorded as a continuous variable, sex as a nominal categorical variable, and body mass index (BMI) as a continuous variable. Clinical variables included the presence of previously diagnosed sleep disorders, classified and categorized ordinally according to "The American Academy of Sleep Medicine International Classification of Sleep Disorders – Third Edition," and the use of sleep medication (defined any prescribed pharmacological agent used primarily for sleep initiation or maintenance, excluding over-the-counter supplements), recorded as a nominal categorical variable. The type of migraine, the specific mAb used, and the number of concurrent preventive medications were categorized ordinally. Changes in preventive treatment were assessed as a nominal categorical variable, while the number of monthly migraine days, the number of days with moderate or severe pain, and the number of days requiring acute pain medication were analyzed as continuous variables. The PSQI-PT and ESS-PT questionnaire scores were also recorded as continuous variables. Effective treatment (categorical variable) was defined as the reduction of monthly migraine days by at least 50% after T1–T2.

Normality of continuous variables was assessed using the Shapiro–Wilk test. For non-normally distributed variables, comparisons across time points (T0, T1, and T2) were performed using the Friedman test followed by pairwise Wilcoxon signed-rank tests with FDR adjustment. Given the non-parametric distribution of most continuous variables, results are reported as medians with interquartile ranges (IQRs) rather than means with 95% confidence intervals, which are less appropriate for skewed data. The IQR was calculated by subtracting the 25th percentile (Q1) from the 75th percentile (Q3), i.e., IQR=Q3–Q1. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Correlations between continuous variables were explored using Spearman's rank correlation coefficients. A multivariable linear regression model was used to assess predictors of PSQI-PT and ESS-PT changes, adjusting for age, sex, BMI, migraine subtype, and use of sleep medication.

In addition to demographic and migraine-related variables, the regression model included sleep medication use

as a covariate, given its potential influence on subjective sleep measures. The presence of a diagnosed sleep disorder at T0 was explored descriptively and in subgroup analyses (Table 1) but was not entered in the multivariate model due to limited sample size per diagnostic category and risk of model overfitting. As PSQI and ESS change scores were calculated within subjects (T2–T0), T0 variability in sleep quality and sleepiness was inherently controlled for.

6. Data management

Data collected during the study were recorded anonymously in a specifically designed database. This database was stored in a restricted-access folder, encrypted, and password-protected, ensuring patient confidentiality and security.

RESULTS

1. Cohort characteristics

A total of 118 patients were enrolled across 12 centers, with 109 completing the study. Nine participants (7.6%) discontinued the study: three due to treatment inefficacy at the T1 evaluation, and six while lost to follow-up (Figure 1). The cohort was predominantly female (86.4%), with a mean age of 43.6 years (range, 24–74 years) (Table 2).

At T0, 40.7% of patients had a diagnosed sleep disorder, with 91% of these cases being Insomnia Disorders. Other reported sleep disorders included: Sleep-Related Breathing Disorders (obstructive sleep apnea), Sleep-Related Movement Disorders (restless leg syndrome and periodic limb movement disorder), and Circadian Rhythm Sleep-Wake Disorders (shift work disorder). In what concerns migraine classification, 52% had episodic migraine whereas 48% had chronic migraine. Fremanezumab was the most frequently used mAbs (66%).

No significant T0 differences were found among centers regarding demographic or clinical characteristics (Kruskal–Wallis and chi-square tests, all p>0.1).

Table 1. Subgroup analysis of sleep quality (PSQI) based on clinical variables

	PSQI-T0	PSQI-T2	p-value
Age			0.543
Sex			0.855
BMI			0.515
Aura			0.906
Yes	9 (9)	6 (9)	
No	9 (9)	5 (8)	
Sleep medication use			0.341
Yes	8 (8)	5 (8)	
No	11.5 (7)	8 (9)	
Episodic vs. chronic			0.247
Episodic	8 (7)	5 (9)	
Chronic	10 (6)	7 (9)	
Sleep medication after T0			0.375
Yes (n=9)	8 (7)	6 (10)	
No (n=100)	12 (9)	12 (4)	
Effective treatment			0.007*
Yes (n=72)	9 (9)	5 (5)	<0.001*
No (n=37)	8 (8)	8 (9)	0.099

Values are presented as median (interquartile range). *Asterisk indicates a statistically significant (p<0.05).
PSQI, Pittsburgh Sleep Quality Index; T0, baseline; T2, 6 months; BMI, body mass index.

2. Changes in sleep quality and daytime sleepiness

A statistically significant improvement in sleep quality, as assessed by the PSQI-PT, was observed in patients initiating CGRP mAb therapy. The median PSQI-PT score decreased from 9 (IQR: 9) at T0 to 6 (IQR: 5) at T2 (Z=–5.5, p<0.001), suggesting an improvement in subjective sleep quality (Table 3, Figure 2).

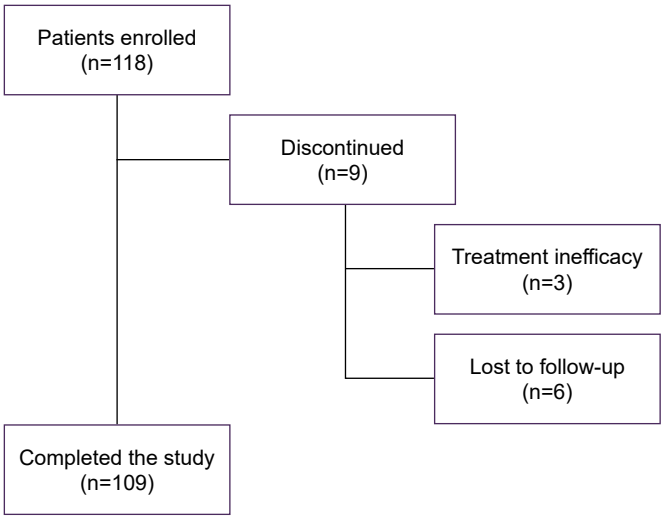


Figure 1. Patient disposition. Of 118 enrolled patients, 109 completed the study. Nine (7.6%) discontinued: six were lost to follow-up and three due to treatment inefficacy at 3 months.

Table 2. Baseline demographic and clinical characteristics of patients who completed the study, those who discontinued, and the overall study population

Baseline feature	Completed the study (n=109)	Discontinued (n=9)	All (n=118)
Sex, female	94 (86.2)	8 (88.9)	102 (86.4)
Age (yr)*	44.2 (24–74)	41.1 (29–65)	43.6 (24–74)
BMI (kg/m^2)	24.11 (15.81–42.32)	22.78 (18.31–25.13)	23.87 (15.81–42.32)
Sleep disorder, yes	42 (38.5)	2 (22.2)	44 (37.3)
Use of sleep medication, yes	36 (33.0)	4 (44.4)	40 (33.9)
Migraine†			
Episodic	52	44	52
Without aura	82	78	81
Chronic	48	56	48
Antibody†			
Fremanezumab (225 mg, monthly)	63	100	66
Galcanezumab (120 mg, monthly)	24	-	22
Erenumab (70 or 140 mg, monthly)	13	-	12
Number of prophylactic drugs at T0	1 (0.5)	1 (1.0)	1 (0.5)

Values are presented as number (%) or median (range) only unless otherwise specified.
BMI, body mass index; T0, baseline.
*Mean (range); †Percent only.

Similarly, a significant reduction in daytime sleepiness, as measured by the ESS-PT, was observed, with the median ESS score decreasing from 7 (IQR: 8) at T0 to 6 (IQR: 8) at T2 (Z=–2.041, p=0.04) (Table 3).

After FDR correction for multiple comparisons, both PSQI-PT (q<0.001) and ESS-PT (q=0.048) improvements remained statistically significant.

3. Treatment effectiveness and its association with sleep quality improvements

A significant reduction in migraine burden was observed following T2 of anti-CGRP mAb treatment. The median number of headache days per month decreased from 13 (IQR: 8) at T0 to 4 (IQR: 7) at T2 (p<0.001). Additionally, the number of days with severe headache decreased from 10 (IQR: 7) to 2 (IQR: 4) (p<0.001). The use of rescue pain medication (Where there is SOS it should be rescue pain medication) also declined from 10 (IQR: 8) to 2 (IQR: 5) (p<0.001) (Table 3, Figure 3). All p-values remained significant after FDR correction (q<0.001).

A strong association was observed between treatment efficacy and improvement in sleep quality (p<0.05). Patients who experienced a greater reduction in migraine frequency and severity also showed greater improvements in PSQI-PT scores. However, no significant correlation was found between ESS-PT scores and treatment efficacy (Table 4).

Table 3. Longitudinal changes in sleep quality (PSQI-PT), daytime sleepiness (ESS-PT), and migraine severity at T0, T1, and T2

	T0	T1	T2	p-value
PSQI-PT score	9 (9)	7 (6)	6 (5)	<0.001
ESS-PT score	7 (8)	6 (8)	6 (8)	0.04
Days with pain	13 (8)	5 (7)	4 (7)	<0.001
Reduction (day), %		58.3 (37)	70 (48)	
Days with severe pain	10 (7)	2 (7)	2 (4)	<0.001
Reduction, %		6.5 (5)	6 (6.5)	
SOS use (day)	10 (8)	2 (4)	2 (5)	<0.001
Reduction, %		71.4 (42)	75 (50)	

Values are presented as median (interquartile range). The p-values refer to the Friedman test across time points. The pairwise Wilcoxon signed-rank test with false discovery rate correction confirmed significance at T1 and T2 versus T0. The median reduction in PSQI-PT from T0 to T2 was 3 points (33% improvement), representing an absolute decrease in subjective sleep disturbance.
PSQI-PT, Portuguese version of the Pittsburgh Sleep Quality Index; ESS-PT, Portuguese version of the Epworth Sleepiness Scale; T0, baseline; T1, 3 months; T2, 6 months.

Spearman's rho for ΔPSQI-PT and reduction in monthly migraine days=0.42, p<0.001 (q=0.002). To control for potential confounders, a multivariate linear regression adjusted for age, sex, BMI, migraine subtype, and sleep med-

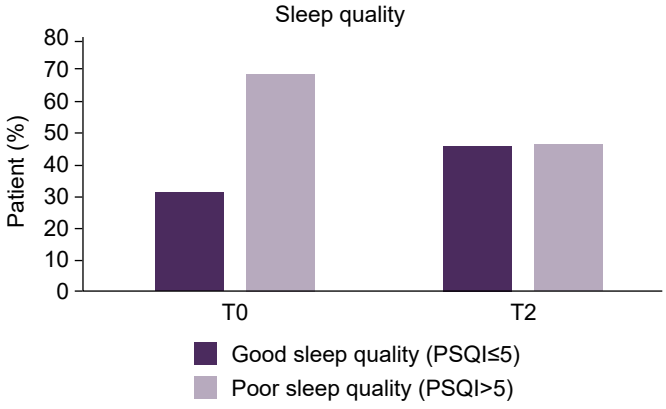


Figure 2. Proportion of patients with clinically defined good sleep quality (Portuguese version of the Pittsburgh Sleep Quality Index [PSQI-PT] score≤5) versus poor sleep quality (PSQI-PT score>5) at baseline (T0) and after 6 months (T2) of anti-calcitonin gene-related peptide monoclonal antibody therapy. Sleep quality was assessed using the validated PSQI-PT.

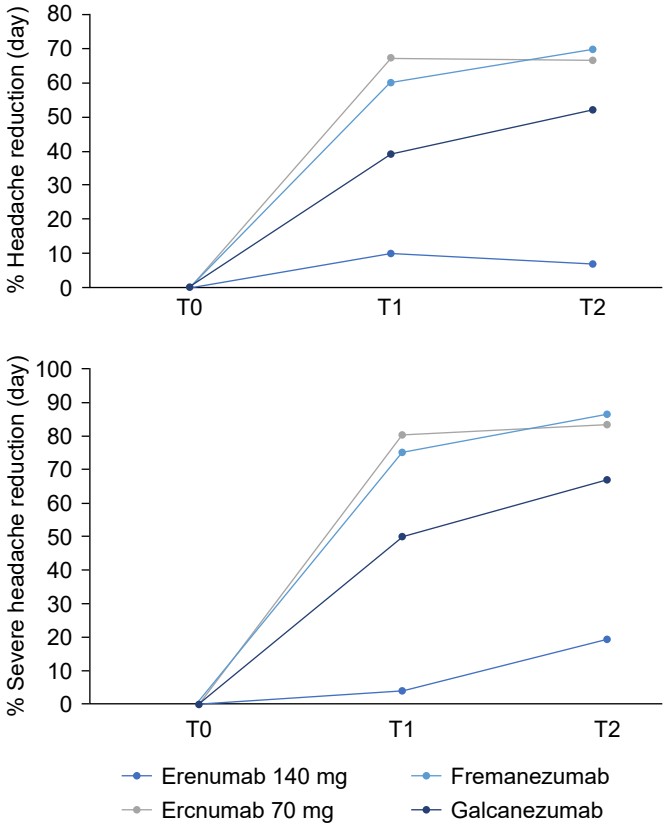


Figure 3. Reduction in total headache days (left) and moderate-to-severe migraine days (right) following anti-calcitonin gene-related peptide monoclonal antibody therapy over time (T0: baseline, T1: 3 months, T2: 6 months). Data are presented as percentage reduction from baseline.

Table 4. Subgroup analysis of daytime sleepiness (ESS) based on clinical variables

	ESS-T0	ESS-T2	p-value
Age			0.112
Sex			0.752
BMI			0.834
Aura			0.248
Yes	7 (8)	6 (8)	
No	7 (5)	5 (6)	
Sleep medication use			0.209
Yes	8 (9)	6 (9)	
No	6 (3)	5 (9)	
Episodic vs. chronic			0.071
Episodic	8 (7)	6 (9)	
Chronic	6 (4)	5.5 (6)	
Sleep medication after T0			0.010*
Yes (n=9)	7 (8)	6 (12)	0.205
No (n=100)	5 (8)	12 (7)	0.002*
Effective treatment			0.341
Yes (n=72)	8 (8)	6 (8)	
No (n=37)	5 (9)	6 (9)	

Values are presented as median (interquartile range). *Asterisk indicates a statistically significant (p<0.05).
ESS, Epworth Sleepiness Scale; T0, baseline; T2, 6 months; BMI, body mass index.

ication use confirmed that treatment response remained an independent predictor of ΔPSQI-PT improvement (β=–0.38, p<0.001).

4. Subgroup analysis

A subgroup analysis was conducted to evaluate potential confounding factors influencing sleep quality and daytime sleepiness. No significant correlations were found between changes in PSQI-PT or ESS-PT scores and age, sex, BMI, migraine subtype (episodic vs. chronic), or aura presence (Table 1).

There was, however, a significant association between ESS-PT score improvement and patients who did not initiate sleep medication (p<0.05) (Table 4).

Furthermore, patients classified as "effective treatment responders" showed a greater improvement in PSQI-PT scores (p<0.001).

After multiple-testing correction, only the association between treatment response and PSQI-PT improvement remained statistically significant (q<0.001). No collinearity

was detected among covariates (VIF<2 for all predictors).

Importantly, neither the presence of a pre-existing sleep disorder nor the use of sleep medication significantly modified the magnitude of PSQI-PT or ESS-PT change, suggesting that the observed improvements were consistent across these subgroups.

DISCUSSION

At T0, the majority of patients reported poor sleep quality (Figure 2), though only 40.7% were formally diagnosed with a sleep disorder, with insomnia being the most common. The high prevalence of sleep disturbances in this cohort aligns with existing literature linking migraine and sleep dysfunction,[5,6] but also suggests that such conditions could be significantly underdiagnosed.

A key finding of this study is the observation of a statistically significant association between anti-CGRP therapy and sleep quality. The median PSQI-PT score decreased from 9 at T0 to 6 after T2, suggesting that patients who experienced migraine improvement tended to report better sleep quality, rather than demonstrating a direct therapeutic effect on sleep. This finding was particularly evident in patients classified as "effective treatment responders." However, given the observational nature of the study, these results should be interpreted as associations rather than causal relationships. Although the potential role of CGRP in sleep–wake balance has been proposed, further studies are warranted to clarify whether any direct pharmacological influence might contribute to these associations.

Daytime sleepiness, as measured by the ESS-PT, also showed a statistically significant reduction, though the effect was less pronounced than that observed for sleep quality. To our knowledge, this is the first study to evaluate daytime sleepiness in migraine patients treated with anti-CGRP mAbs. Notably, there was no significant correlation between ESS-PT score improvements and migraine burden reduction. This suggests that the relationship between migraine improvement and daytime alertness is complex and potentially influenced by additional physiological or behavioral factors, rather than a direct medication effect. This finding is particularly intriguing given that CGRP has been hypothesized to play a role in wakefulness regulation in *Drosophila*.[10] In fact, CGRP may influence the circadian cycle by structuring sleep and regulating its rhythm in these animals. Nevertheless, extrapolation of such mechanistic hypotheses from animal models to humans should be made cautiously.

Our data suggests overall that prophylactic migraine treatment with anti-CGRP mAbs is associated with improvements in both subjective sleep quality and daytime sleepiness.

Treatment with anti-CGRP or its receptor mAbs was effective in managing migraine, leading to a reduction in the number of monthly migraine days, the frequency of moderate to severe pain episodes, and the need for acute pain medication. Notably, a sustained improvement in sleep quality, as assessed by the PSQI-PT, was observed at both 3 and 6 months, suggesting a beneficial impact of anti-CGRP therapy on sleep. However, the observed sleep improvements appear to parallel migraine relief, supporting the interpretation that better sleep outcomes are likely mediated indirectly through migraine improvement rather than a direct pharmacological effect of CGRP blockade. While previous studies with smaller sample sizes or shorter follow-up periods have reported similar associations, our results provide a more robust dataset supporting this indirect relationship.[11,12,15]

Subgroup analysis revealed that improvements in PSQI-PT scores were independent of age, sex, BMI, migraine subtype, or aura presence, indicating that the observed associations were not driven by these demographic or clinical factors. However, a significant association was found between ESS-PT score improvement and the absence of sleep medication initiation. This finding suggests that the use of sleep medication may mask potential improvements in daytime sleepiness, warranting further investigation into the interaction between migraine treatment and pharmacological sleep interventions.

The findings of this study have important clinical implications emphasizing the association between reduced migraine burden and better subjective sleep quality in patients treated with anti-CGRP mAbs, rather than implying a direct therapeutic sleep effect. Given the high prevalence of sleep disturbances in migraine patients, routine assessment of sleep parameters in clinical practice may enhance patient management and optimize treatment outcomes.

Despite the strengths of this study, several limitations must be acknowledged. First, the study relied on subjective sleep measures (PSQI-PT and ESS-PT), which, while validated, may not fully capture objective sleep architec-

ture changes. Future research should integrate polysomnography or actigraphy to assess the associations between anti-CGRP therapy and sleep patterns more accurately. Additionally, potential confounders, such as medication adherence and comorbid psychiatric conditions (e.g., anxiety and depression), were not extensively analysed, which could influence sleep outcomes. Another consideration is that approximately 40% of participants had a pre-existing sleep disorder and 37% reported using sleep medication. While the latter variable was included as a covariate in multivariate analyses, T0 sleep disorder diagnosis was not formally modeled due to heterogeneity of conditions and small subgroup sizes. Nonetheless, subgroup comparisons revealed no significant interaction between these factors and changes in PSQI or ESS, suggesting that they did not substantially bias the observed improvements. Moreover, as within-subject change scores inherently account for T0 PSQI and ESS levels, residual confounding by T0 severity is expected to be minimal.

Future studies should explore the mechanistic links between migraine relief and sleep improvements, including the role of neuropeptides such as CGRP in sleep regulation.

Additionally, longitudinal studies with objective sleep assessments, such as polysomnography, may provide deeper insights into the relationship between anti-CGRP therapy and sleep architecture and circadian rhythms.

1. Conclusions

This study reports a significant association between anti-CGRP mAb therapy and improved sleep quality in migraine patients, primarily in parallel with reductions in migraine burden. While our findings do not confirm a direct pharmacological effect of anti-CGRP therapy on sleep regulation, they reinforce the potential role of migraine treatment in addressing sleep disturbances.

Notably, daytime sleepiness also showed improvement over the study period, independently of treatment response and despite the limited blood-brain barrier penetration of anti-CGRP therapy, suggesting a physiological interaction between migraine pathophysiology and sleep–wake regulation.

Given the larger sample size and extended follow-up period compared to prior studies, our results offer robust support for these observed associations. These findings also underscore the intricate relationship between migraine and sleep disturbances and suggest that optimizing migraine treatment may have far-reaching benefits for sleep health, regardless of migraine type. Future research should focus on elucidating the precise mechanisms underlying these associations. Objective sleep measures such as polysomnography and actigraphy could provide deeper insights into how migraine improvement correlates with changes in sleep quality. A deeper understanding of CGRP's role in sleep-wake regulation could not only refine migraine treatment but also unlock new therapeutic strategies for sleep disorders. As CGRP-targeted therapies continue to evolve, their potential impact on both migraine burden and sleep health warrants further exploration.

ADDITIONAL INFORMATION

[1]Neurology Department, Unidade Local de Saúde de Gaia e Espinho, Porto, Portugal
[2]Neurology Department, Unidade Local de Saúde de Matosinhos, Porto, Portugal
[3]Neurology Department, Unidade Local de Saúde de São João, Porto, Portugal
[4]Neurology Department, Unidade Local de Saúde de Coimbra, Coimbra, Portugal
[5]Neurology Department, Hospital Garcia de Orta, Unidade Local de Saúde de Almada/Seixal, Lisboa, Portugal
[6]Neurology Department, Unidade Local de Saúde de Lisboa Central, Lisboa, Portugal
[7]Neurology Department, Unidade Local de Saúde de Braga, Braga, Portugal
[8]Neurology Department, Unidade Local de Saúde do Algarve, Faro, Portugal
[9]Functional Neurology Unit, Hospital de Cascais Dr. José de Almeida, Lisboa, Portugal
[10]Neurology Department, Hospital Fernando Fonseca, Unidade Local de Saúde de Amadora-Sintra, Lisboa, Portugal
[11]Neurology Department, Hospital Beatriz Ângelo, Unidade de Saúde Local Loures-Odivelas, Lisboa, Portugal
[12]Neurology Department, Hospital das Forças Armadas de Lisboa, Lisboa, Portugal
[13]Center for Child Development – Neuropediatrics Unit, Hospital Pediátrico, Unidade Local de Saúde de Coimbra, Coimbra, Portugal

AVAILABILITY OF DATA AND MATERIAL

The datasets generated and analyzed during the current study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: RC, AF, BM, CF, HD, EP, FP; Data curation: RC, AF, BM, CF, SP, CG, CM, DV, MM, JS, MSD, SC, MB, ALR, HD, EP, FP; Formal analysis: RC, AF, BM, CF, HD, EP, FP; Investigation: RC, AF, BM, CF, HD, EP, FP; Methodology: RC, AF, BM, CF, HD, EP, FP; Supervision: HD, EP, FP, Validation: HD, EP, FP; Writing–original draft: RC, AF, BM, CF, SP, CG, CM, DV, MM, JS, MSD, SC, MB, ALR, HD, EP, FP; Writing–review & editing: RC, AF, BM, CF, SP, CG, CM, DV, MM, JS, MSD, SC, MB, ALR, HD, EP, FP.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING STATEMENT

Not applicable.

ACKNOWLEDGMENTS

The authors would like to thank all participating patients and the clinical teams from the twelve collaborating headache centers for their invaluable contribution to data collection and follow-up.

REFERENCES

1. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders 3rd edition. International Headache Society; 2018.
2. Frimpong-Manson K, Ortiz YT, McMahon LR, Wilkerson JL. Advances in understanding migraine pathophysiology: a bench to bedside review of research insights and therapeutics. Front Mol Neurosci 2024;17:1355281.
3. Waliszewska-Prosół M, Nowakowska-Kotas M, Chojdak-Łukasiewicz J, Budrewicz S. Migraine and sleep: an unexplained association? Int J Mol Sci 2021;22:5539.
4. Vgontzas A, Pavlović JM. Sleep disorders and migraine: review of literature and potential pathophysiology mechanisms. Headache 2018;58:1030-1039.
5. Sullivan DP, Martin PR. Sleep and headaches: relationships between migraine and non-migraine headaches and sleep duration, sleep quality, chronotype, and obstructive sleep apnoea risk. Aust J Psychol 2017;69:210-217.
6. Stanyer EC, Creeney H, Nesbitt AD, Holland PR, Hoffmann J. Subjective sleep quality and sleep architecture in patients with migraine: a meta-analysis. Neurology 2021;97:e1620-e1631.
7. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. Expert Opin Ther Targets 2020;24:91-100.
8. Giffin NJ. Calcitonin gene-related peptide (CGRP) monoclonal antibodies for migraine. Pract Neurol 2023;23:200-207.
9. Drellia K, Kokoti L, Deligianni CI, Papadopoulos D, Mitsikostas DD. Anti-CGRP monoclonal antibodies for migraine prevention: a systematic review and likelihood to help or harm analysis. Cephalalgia 2021;41:851-864.
10. Kunst M, Hughes ME, Raccuglia D, et al. Calcitonin gene-related peptide neurons mediate sleep-specific circadian output in Drosophila. Curr Biol 2014;24:2652-2664.
11. Pellitteri G, Pez S, Nilo A, et al. Erenumab impact on sleep assessed with questionnaires and home-polysomnography in patients with migraine: the ERESON study. Front Neurol 2022;13:869677.
12. Viticchi G, Di Stefano V, Altamura C, et al. Effects of prophylactic drug therapies and anti-calcitonin peptide-related monoclonal antibodies on subjective sleep quality: an Italian multicenter study. Sleep Med 2024;117:87-94.
13. Del Rio João KA, Becker NB, de Neves Jesus S, Isabel Santos Martins R. Validation of the Portuguese version of the Pittsburgh Sleep Quality Index (PSQI-PT). Psychiatry Res 2017;247:225-229.
14. Johns MW. Escala de Sonolência de Epworth-versão portuguesa (ESS-PT) [Internet]. Sleep Disorders Unit, Epworth Hospital; 1991 [cited 2025 Oct 2]. Available from: https://www.heldernovaisbastos.pt/ficheiros/escala_de_sonolencia_epworth_.pdf
15. Iannone LF, Boccalini A, Lo Castro F, et al. Effect of atogepant on sleep quality and sleep-related adverse events in adult patients with migraine: a prospective observational 12-week study. CNS Drugs 2025;39:1341-1354.

Original Article

Headache Pain Res 2026;27(1):52-63
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2025.0029

Headache and Pain Research

Cerebrovascular Hemodynamic Responses to Breath-Holding in Migraine: A Longitudinal Functional Near-Infrared Spectroscopy Study Comparing a Calcitonin Gene-Related Peptide Monoclonal Antibody and Oral Preventive Treatment

Dong A. Yea[1], Jong Kwan Choi[2], Yoo Hwan Kim[1]

[1]Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea
[2]OBELAB Inc., Seoul, Republic of Korea

Abstract

Purpose: Altered cerebrovascular reactivity has been reported in migraine; however, longitudinal changes during preventive treatment remain unclear. This observational study aimed to describe and compare longitudinal cerebrovascular responses derived from functional near-infrared spectroscopy (fNIRS) during a breath-holding test between patients treated with a calcitonin gene-related peptide (CGRP) monoclonal antibody and those receiving oral preventive medications.

Methods: Twenty-four patients with migraine were enrolled (CGRP group, n=12; oral group, n=12). fNIRS over the prefrontal cortex was performed at baseline and after 3 months during a standardized breath-holding protocol. Oxygenated (HbO), deoxygenated, and total hemoglobin signals were used to derive breath-holding and recovery indices. Clinical outcomes included monthly headache days, acute medication days, disability, mood scales, and Patient Global Impression of Change.

Results: Monthly headache days decreased in both groups (CGRP: Δ=−2.00, p=0.26; oral: Δ=−1.50, p=0.48), with no between-group difference (p=0.85). Acute medication days were significantly reduced only in the CGRP group (Δ=−7.00, p=0.03). Migraine Disability Assessment (MIDAS) scores improved significantly in the CGRP group (Δ=−21.25, p=0.02), with no significant between-group differences. During breath-holding, HbO increased across channels in both groups and was followed by a gradual decline during the recovery phase. Longitudinal analyses demonstrated group-dependent differences in temporal change patterns, with a treatment×time interaction reaching significance at the uncorrected level in a representative channel (Channel 6: F(1,16)=8.448, p=0.010), but not after multiple-comparison correction (p=0.155).

Conclusion: fNIRS with a breath-holding challenge enables longitudinal assessment of cerebrovascular responses during migraine preventive treatment. The observed differences should be interpreted descriptively in terms of temporal change patterns. Larger studies are needed to clarify clinical significance.

Keywords: Breath holding, Calcitonin gene-related peptide, Migraine without aura, Monoclonal antibodies, Near-infrared spectroscopy

Received: December 30, 2025; **Revised:** February 2, 2026; **Accepted:** February 5, 2026

Correspondence: Yoo Hwan Kim, M.D., Ph.D.
Department of Neurology, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22 Gwanpyeong-ro 170beon-gil, Dongan-gu, Anyang 14068, Republic of Korea
Tel: +82-31-380-3740, Fax: +82-31-380-4118, E-mail: drneuroneo@gmail.com

INTRODUCTION

Migraine is a common neurological disorder characterized by recurrent headache attacks. Increasing evidence suggests that migraine is better understood as a disorder involving abnormal activation of the trigeminovascular system rather than a purely neuronal condition.[1-3] Cerebrovascular reactivity (CVR) and vasomotor reserve have been investigated in patients with migraine; however, previous studies have reported heterogeneous findings, reflecting variability in study populations, imaging modalities, and assessment paradigms rather than a consistent cerebrovascular abnormality.[4-6]

Calcitonin gene-related peptide (CGRP) plays a central role in migraine pathophysiology and is a potent vasodilatory neuropeptide released from trigeminal afferents during migraine attacks.[7] Through its effects on trigeminovascular system, including neurogenic inflammation and modulation of cerebral arterial tone, CGRP contributes to migraine pain generation and associated vascular responses.[8-10] On this basis, monoclonal antibodies targeting the CGRP pathway including fremanezumab have been developed and have demonstrated robust efficacy in reducing migraine frequency and headache-related disability.[11,12]

Despite these established clinical benefits, the physiological effects of CGRP monoclonal antibodies on cerebral vascular function remain incompletely understood. In particular, it is unclear whether clinical improvement following CGRP pathway inhibition is accompanied by measurable changes in CVR.[13]

Cerebral vasomotor reactivity refers to the capacity of cerebral arterioles to dilate or constrict in response to changes in arterial carbon dioxide tension, thereby contributing to the regulation of cerebral blood flow. This concept is distinct from cerebrovascular autoregulation, which refers to the maintenance of stable cerebral blood flow across changes in perfusion pressure.[14,15] Altered CVR in migraine therefore reflects differences in CO_2-mediated vasodilatory capacity rather than heightened nociceptive sensitivity or exaggerated vascular responsiveness.[16,17] Neuroimaging studies using positron emission tomography, single-photon emission computed tomography, and blood oxygenation level dependent functional magnetic resonance imaging have demonstrated alterations in cerebral perfusion and cortical excitability in migraine; however, their longitudinal applicability is limited by cost, accessibility constraints, and susceptibility to motion artifacts.[18,19]

Functional near-infrared spectroscopy (fNIRS) is a non-invasive optical neuroimaging modality that enables continuous monitoring of cortical hemodynamic responses through quantification of oxygenated and deoxygenated hemoglobin (HbR) concentrations. Owing to its portability, safety, and relative tolerance to movement, fNIRS is well suited for longitudinal evaluation of cerebrovascular hemodynamic responses in clinical environments.[20-24]

The breath-holding test (BHT) is an established physiological challenge that induces transient hypercapnia for the assessment of CVR. Rising arterial carbon dioxide tension during breath-holding (BH) results in cerebral arteriolar dilation and increased cerebral blood flow, which can be reliably captured using fNIRS derived hemoglobin signals. Compared with controlled carbon dioxide inhalation paradigms, the BHT is simpler to administer, well tolerated, and widely used as a screening tool for impaired vasomotor reserve.[25,26]

To date, longitudinal fNIRS-based investigations directly comparing CGRP monoclonal antibody therapy with conventional oral preventive treatments remain limited, and the relationship between clinical improvement and change in cerebrovascular hemodynamic responses has not been fully clarified. Therefore, this study aimed to longitudinally and descriptively compare fNIRS-derived cerebrovascular hemodynamic responses during the BHT between migraine patients treated with fremanezumab and those receiving conventional oral preventive medications at baseline and after 3 months of treatment.

MATERIALS AND METHODS

1. Study design and participants

This prospective observational study enrolled adult patients diagnosed with migraine without aura according to the International Classification of Headache Disorders, 3rd edition (ICHD-3). Patients with migraine with aura were excluded to minimize potential heterogeneity related to cortical spreading depolarization and its confounding effects on cerebrovascular hemodynamic responses. Both episodic migraine and chronic migraine patients were included in the study, and migraine subtype was not used

as a stratification factor at enrollment. This study was designed as an observational study. Treatment selection (anti-CGRP monoclonal antibody versus oral preventive medication) was determined clinically and not by random allocation.

Inclusion criteria were as follows: age ≥18 years; diagnosis of migraine without aura according to ICHD-3 criteria; eligibility for preventive migraine therapy with either a CGRP monoclonal antibody or a conventional oral preventive medication as determined by the treating neurologist; ability to comply with the BHT and fNIRS assessment protocol; and provision of written informed consent.

Exclusion criteria were as follows: migraine with aura or other primary headache disorders; prior cerebrovascular disease (ischemic or hemorrhagic stroke, transient ischemic attack, or significant intracranial arterial stenosis); major neurological disorders other than migraine (e.g., epilepsy, neurodegenerative disease); significant cardiovascular or respiratory disease that could interfere with CVR assessment or BH performance; use of medications known to substantially affect cerebral hemodynamics aside from prescribed preventive migraine treatments; and inability to complete baseline or follow-up fNIRS assessments.

Participants were allocated into two treatment groups: (1) CGRP monoclonal antibody group (12 patients treated with fremanezumab) and (2) oral preventive medication group (12 patients receiving conventional oral migraine preventive therapy). fNIRS assessments were performed at baseline prior to initiation of preventive treatment and at the 3-month follow-up. The study was approved by the Institutional Review Board of Hallym University (IRB No. 2023-09-017), and all participants provided written informed consent in accordance with the Declaration of Helsinki.

2. Functional near-infrared spectroscopy acquisition

Hemodynamic activity was recorded using a multichannel continuous-wave fNIRS system equipped with 24 laser sources and 32 photodetectors, yielding 48 measurement channels with a source–detector distance of 3 cm. Near-infrared light at 780 and 850 nm was delivered at a sampling rate of 8.138 Hz, with optical output maintained below 1 mW for safety.

Optical probes were secured to the forehead using a spring-mounted fixation system to minimize contact pressure, and rubber shielding at the probe interface was used to reduce ambient light interference. Detector gain and incident light intensity were calibrated prior to acquisition to optimize signal quality while accounting for inter-individual differences in scalp and skull properties. Data were transmitted wirelessly to the monitoring application via Wi-Fi.

Measurements were obtained over the prefrontal cortex, with FPz of the international 10–20 system as the anatomical anchor point for probe positioning. Estimated Montreal Neurological Institute coordinates and corresponding Brodmann areas for each channel are provided in the Supplementary Table 1 (available online).

3. Breath-holding test protocol

All participants underwent a standardized BHT consisting of three consecutive phases (Figure 1): (1) baseline resting phase, 30 seconds of spontaneous breathing; (2) BH phase, 30 seconds of voluntary BH; and (3) recovery (Rec) phase, 30 seconds of spontaneous breathing.

Participants were instructed to perform BH for approximately 30 seconds following normal expiration while avoiding deep inspiration to minimize Valsalva-related reductions in cerebral blood flow. During BH, increasing arterial carbon dioxide tension induces cerebral arteriolar dilation and increased cerebral blood volume, which are detectable through fNIRS derived hemoglobin signals. In accordance with previous literature, CVR was characterized using task related changes in oxygenated hemoglobin (HbO), HbR and total hemoglobin (HbT) during the BH and Rec phases.[26]

For BH–induced hemodynamic responses, the fNIRS signal was segmented into five consecutive 10-second intervals (resting, BH_A, BH_B, Rec_A, Rec_B). All segments were referenced to the resting interval to enable comparison of relative temporal trajectories of HbO, HbR, and HbT. Primary indices included the BH index (BH_B–BH_A) and Rec index (Rec_A–Rec_B), computed at baseline and 3 months and compared longitudinally to characterize potential alterations in CVR (Figure 2).

4. Signal preprocessing and feature extraction

Raw optical intensity signals were preprocessed using a standardized pipeline. A band-pass filter (0.005–0.20 Hz)

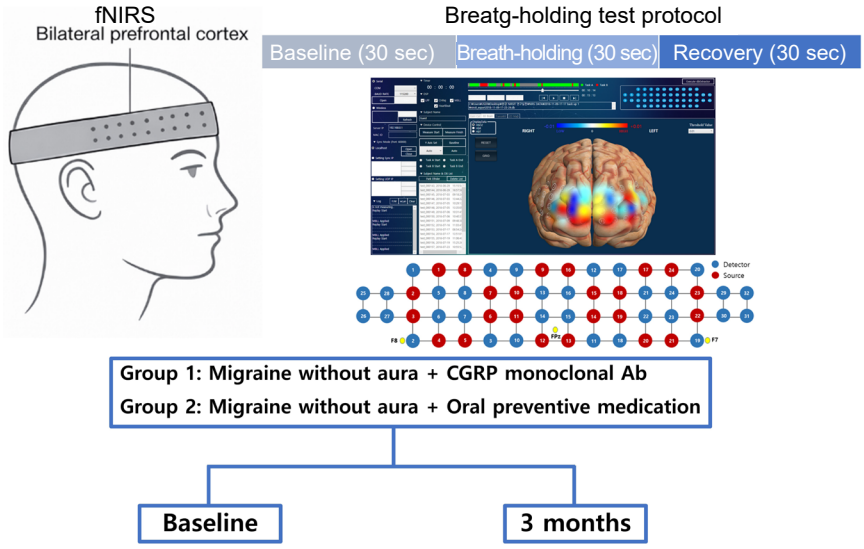


Figure 1. Experimental setup and breath-holding test protocol for fNIRS-based cerebrovascular reactivity assessment. fNIRS was applied over the bilateral prefrontal cortex to continuously measure oxygenated and total hemoglobin concentrations. The breath-holding test involved a 30-second baseline resting phase, followed by a 30-second breath-holding phase to induce hypercapnia, and a 30-second recovery phase. All participants underwent the same protocol at baseline and at 3 months.
fNIRS, functional near-infrared spectroscopy; CGRP, calcitonin gene-related peptide; Ab, antibody; Fpz, frontal pole, midline position; F7, left frontotemporal electrode; F8, right frontotemporal electrode.

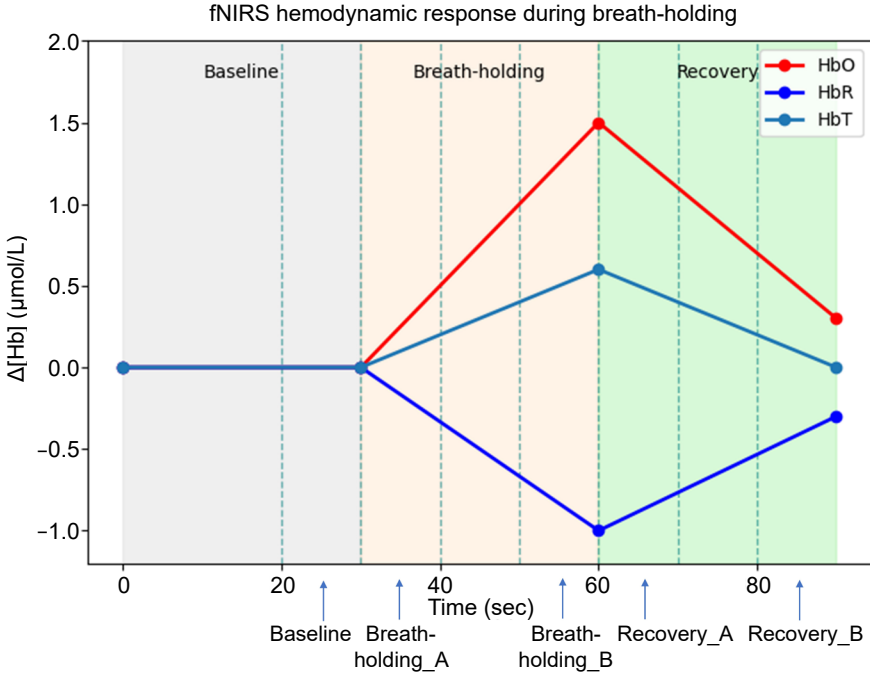


Figure 2. Conceptual schematic of fNIRS hemodynamic response patterns during resting, breath-holding, and recovery phases. This figure provides a conceptual illustration of typical hemodynamic response patterns measured by fNIRS during resting, breath-holding, and recovery phases. The schematic illustrates overall temporal trends and directional changes rather than quantitative study data used for statistical inference.
fNIRS, functional near-infrared spectroscopy; HbO, oxygenated hemoglobin; HbR, deoxygenated hemoglobin; HbT, total hemoglobin; Hb, hemoglobin.

was applied to attenuate slow drifts and high-frequency physiological noise. Motion artifacts were corrected using the temporal derivative distribution repair algorithm, and channels were excluded when the coefficient of variation exceeded 15%.

To further improve cortical signal quality, short-channel regression was applied using the mean signal from 8-mm short-separation channels to reduce superficial physiological contamination. Optical density signals were subsequently converted to concentration changes using the modified Beer–Lambert law (MBLL), with MBLL coefficients derived from Moaveni's calculation. Differential pathlength factors were not applied in order to preserve relative hemoglobin contrast values.

For each channel, block-averaged HbO, HbR, and HbT signals were extracted across the predefined task epochs. Primary cerebrovascular indices included the BH index (BH index=BH_B–BH_A) and the Rec index (Rec index=Rec_A–Rec_B), which were computed at baseline and again at 3 months to characterize longitudinal changes in hypercapnia-related hemodynamic responses.

5. Statistical analysis

Sample size adequacy was evaluated using a priori power analysis performed with G*Power 3.1. Between-group differences in continuous demographic variables were analyzed using independent samples t-tests, and categorical variables were compared using the chi-square test. Continuous data are reported as mean±standard deviation, and effect estimates are summarized as mean change scores (Δ). Within-group changes from baseline to 3 months were evaluated using paired t-tests, and between-group differences in Δ values were assessed using independent samples t-tests.

To determine whether longitudinal changes in fNIRS derived indices differed between treatment groups, a two-way repeated-measures ANOVA was performed with Group (CGRP vs. oral preventive) as the between subject factor and Time (baseline vs. 3 months) as the within subject factor. Post-hoc pairwise comparisons were conducted when significant interaction effects were present. Statistical significance was defined as $p<0.05$. Analyses were performed using SPSS version 21.0 (IBM Corp.).

The preprocessing and statistical analysis pipeline was adapted from our previously published methodology.[22]

6. Clinical and patient-reported outcome measures

Clinical and patient reported outcomes were assessed two times: baseline (prior to treatment initiation) and 3-month follow-up. The following headache-related and psychological symptom scales were administered at both time points: monthly headache days (day/mo), monthly acute medication days (day/mo), Headache Impact Test-6 (HIT-6), Migraine Disability Assessment (MIDAS), Generalized Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9). These measures were used to evaluate headache burden, functional disability, and mood symptoms associated with migraine.

HIT-6 is a widely used instrument that quantifies headache-related functional impact, with higher scores indicating greater headache-related disability. MIDAS assesses headache disability based on activity loss over the preceding 3 months, and scores are categorized into minimal, mild, moderate, and severe disability levels. GAD-7 and PHQ-9 were administered as screening measures for anxiety and depressive symptoms, respectively, with higher scores reflecting greater symptom severity.[27-30]

In addition, the Patient Global Impression of Change (PGIC) was administered only at the 3-month follow-up to assess patients' subjective perception of improvement following treatment. The PGIC is a 7-point scale in which higher ratings indicate greater perceived overall improvement.[31]

RESULTS

Baseline demographic characteristics did not differ significantly between the CGRP monoclonal antibody group and the oral preventive medication group. Age, sex distribution, height, body weight, and body mass index were comparable between-groups (all $p>0.05$) (Table 1).

At 3 months, monthly headache days numerically decreased in both groups; however, the within group changes did not reach statistical significance (CGRP: Δ=–2.00, p=0.26; oral: Δ=–1.50, p=0.48), and there was no significant between-group difference (p=0.85). Acute medication days were significantly reduced in the CGRP group (Δ=–7.00, p=0.03) but not in the oral group (Δ=–3.50, p=0.19), with no significant between-group difference (p=0.36). HIT-

6 and MIDAS scores improved in both groups; however, only the reduction in MIDAS was significant in the CGRP group (Δ=–21.25, p=0.02), while changes in the oral group were not significant (HIT-6: p=0.05; MIDAS: p=0.11), and no between-group differences were observed (both p=0.55). GAD-7 and PHQ-9 changes were modest and non-significant in both groups (all p>0.05). PGIC scores at 3 months were numerically higher in the CGRP group than in the oral group (4.50 vs. 3.42), without a significant between-group difference (p=0.15) (Table 2).

During the BH phase, both the CGRP monoclonal antibody group and the oral preventive medication group showed numerical increases in HbO across multiple prefrontal channels. In channel 06, HbO increased from 0.003 at baseline to 0.117 at the end of BH in the CGRP group and from –0.011 to 0.006 in the oral preventive medication group. During the Rec phase, HbO values in both groups numerically decreased toward pre-task levels, reaching 0.033 in the CGRP group and 0.022 in the oral preventive medication group by the end of Rec. Similar patterns were observed across the majority of channels, although the magnitude of change varied by channel and time point (Figure 3).

Two-way ANOVA revealed no significant group×time interaction effects across channels after correction for multiple comparisons for the HbO-based BH index (Table 3). Although channel 06 showed a nominally significant interaction at the uncorrected level (F(1,16)=8.448, p=0.010), this effect did not remain significant after family-wise error or false discovery rate correction (both corrected p=0.155), and no other channels demonstrated significant interaction effects.

Post hoc analyses focusing on channel 06 (Figure 4) demonstrated a significant difference between the CGRP group at baseline and the oral treatment group at 3 months (mean difference=0.169, p<0.001), which remained significant after Bonferroni correction. In contrast, the within group change from baseline to 3 months in the oral treatment group was significant only at the uncorrected level (mean difference=–0.069, p=0.029) and did not remain significant after correction for multiple comparisons.

Analyses of HbR- and HbT-based BH indices showed no significant group×time interaction effects after correction for multiple comparisons, with only nominal uncorrected effects in a few channels. Detailed results are presented in the Supplementary Tables 2, 3 (available online).

For the HbO-based Rec index, two-way ANOVA identified no significant treatment×time interaction effects across channels after correction for multiple comparisons (Table 4). Channel 10 showed a significant interaction at the uncorrected level (F(1,20)=8.242, p=0.009); however, this effect did not persist after family-wise error or false discovery rate correction (both corrected p=0.142), and no

Table 1. Baseline demographic characteristics of the CGRP mAb group and oral preventive medication group

Variable	G1 (CGRP mAb)	G2 (oral)	p-value
Age (yr)	37.92±10.53	45.92±12.73	0.11
Sex (M/F)	1/11	2/10	>0.99
Height (cm)	159.42±6.76	162.64±9.35	0.35
Weight (kg)	59.79±14.78	66.82±19.41	0.34
BMI (kg/m^2)	23.47±5.24	25.14±6.31	0.50

Values are presented as mean±standard deviation or number only.
CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; G1, group 1; G2, group 2; M, male; F, female; BMI, body mass index.

Table 2. Changes in clinical outcomes from baseline to 3M in both treatment groups

Outcome	G1				G2				p-value (between Δ)
	Base	3M	Δ G1	p-value	Base	3M	Δ G2	p-value	
Headache days	10.58	8.58	2.00	0.26	9.58	8.08	1.50	0.48	0.85
Medication days	11.67	4.67	7.00	0.03*	9.25	5.75	3.50	0.19	0.36
HIT-6	60.83	58.50	2.33	0.44	63.58	59.08	4.50	0.05	0.55
MIDAS	38.83	17.58	21.25	0.02*	31.92	17.58	14.33	0.11	0.55
GAD-7	2.75	2.92	–0.17	0.92	6.42	5.33	1.08	0.29	0.50
PHQ-9	5.25	5.42	–0.17	0.94	9.42	8.00	1.42	0.14	0.49
PGIC (3M)	-	4.50	-	-	-	3.42	-	-	0.15

Values are presented as mean only. Asterisk indicates a statistically significant (*p<0.05).
3M, 3 months; G1, group 1; G2, group 2; HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment; GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; PGIC, Patient Global Impression of Change.

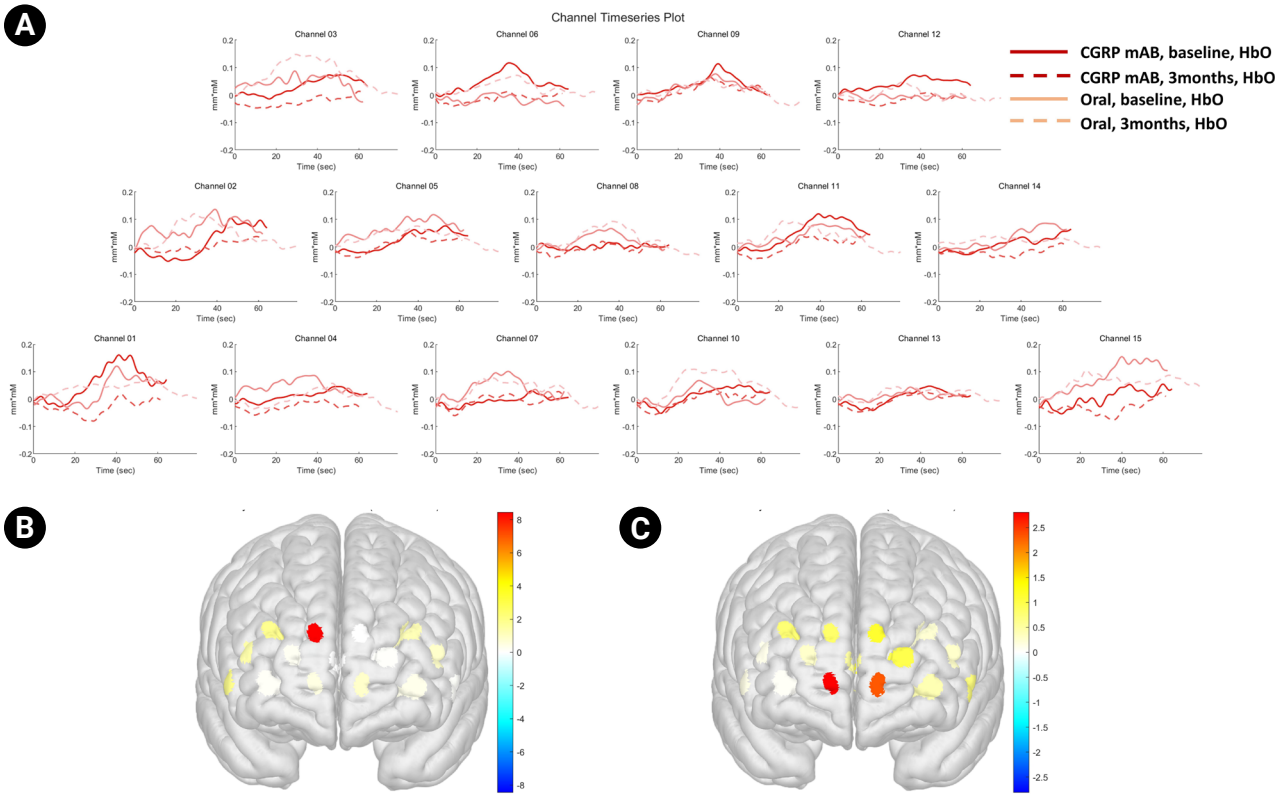
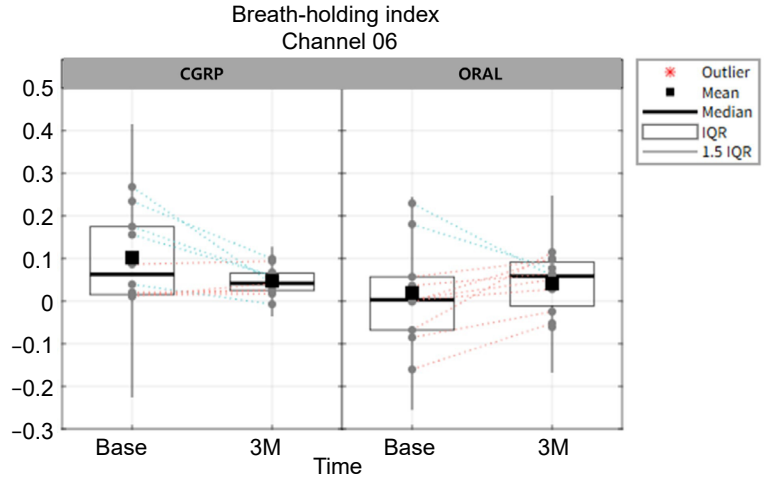


Figure 3. (A) HbO time series during the breath-holding test across prefrontal channels in the CGRP and oral preventive groups at baseline and at 3 months. Solid lines indicate baseline recordings, and dashed lines indicate 3-month follow-up recordings. (B, C) Three-dimensional maps showing the mean HbO concentration at 3 months in (B) the CGRP monoclonal antibody group and (C) the oral preventive medication group.
CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; HbO, oxygenated hemoglobin.

Table 3. Two-way ANOVA results for the HbO-based breath-holding index

Channel	F-value	df1	df2	p-value	p-value (FWE)	p-value (FDR)
01	1.880	1	20	0.186	>0.99	0.774
02	1.416	1	15	0.252	>0.99	0.774
03	1.874	1	14	0.193	>0.99	0.774
04	0.103	1	18	0.752	>0.99	0.908
05	0.167	1	18	0.687	>0.99	0.908
06	8.448	1	16	0.010*	0.155	0.155
07	0.475	1	19	0.499	>0.99	0.908
08	0.010	1	14	0.924	>0.99	0.924
09	0.028	1	19	0.869	>0.99	0.924
10	0.873	1	20	0.361	>0.99	0.774
11	0.075	1	20	0.787	>0.99	0.908
12	1.197	1	18	0.288	>0.99	0.774
13	0.316	1	16	0.582	>0.99	0.908
14	0.890	1	18	0.358	>0.99	0.774
15	0.081	1	13	0.781	>0.99	0.908

Two-way ANOVA was performed to evaluate the treatment×time (baseline vs. 3-month follow-up) interaction of the HbO-based breath-holding index across channels. p-values were corrected for multiple comparisons using FWE and FDR methods. Asterisk indicates a statistically significant (*p<0.05; uncorrected).
ANOVA, analysis of variance; HbO, oxygenated hemoglobin; df, degrees of freedom; FWE, family-wise error; FDR, false discovery rate.



Post hoc comparisons for the treatment×time interaction in Channel 06 based on the HbO breath-holding index

Comparison	Mean				p (uncorrected)	p (Tukey)	p (Bonferroni)
	Difference	SE	t	df			
CGRP_Base vs. CGRP_3M	0.049	0.029	1.713	16	0.106	0.349	0.636
CGRP_Base vs. Oral_Base	0.070	0.043	1.642	16	0.120	0.384	0.720
CGRP_Base vs. Oral_3M	0.169	0.032	5.215	16	<0.001***	<0.001***	<0.001***
CGRP_3M vs. Oral_Base	0.051	0.032	1.587	16	0.132	0.413	0.792
CGRP_3M vs. Oral_3M	−0.047	0.031	−1.518	16	0.148	0.450	0.891
Oral_Base vs. Oral_3M	−0.069	0.029	−2.397	16	0.029*	0.118	0.174

Figure 4. Treatment×time effects on the HbO-based breath-holding index on Channel 6. Tukey-adjusted p-values control the FWE rate for a family of four comparisons. Bonferroni-adjusted p-values control the FWE rate for a family of six comparisons. Green dotted line: decreasing within subject change from Base to 3M; orange dotted line: increasing within subject change from Base to 3M. Asterisk indicates a statistically significant (*p<0.05; ***p<0.001).
CGRP, calcitonin gene-related peptide; Base, baseline; 3M, 3 months; IQR, interquartile range; HbO, oxygenated hemoglobin; SE, standard error; df, degrees of freedom; FWE, family-wise error.

Table 4. Two-way ANOVA results for the HbO-based recovery index

Channel	F-value	df1	df2	p-value	p-value (FWE)	p-value (FDR)
01	1.219	1	17	0.285	>0.99	0.512
02	0.004	1	15	0.948	>0.99	0.948
03	2.378	1	16	0.143	>0.99	0.478
04	0.555	1	19	0.466	>0.99	0.635
05	0.949	1	20	0.342	>0.99	0.512
06	2.604	1	19	0.123	>0.99	0.478
07	2.355	1	22	0.139	>0.99	0.478
08	0.346	1	16	0.565	>0.99	0.706
09	2.165	1	17	0.159	>0.99	0.478
10	8.242	1	20	0.009*	0.142	0.142
11	0.241	1	21	0.629	>0.99	0.725
12	1.148	1	17	0.299	>0.99	0.512
13	1.412	1	18	0.250	>0.99	0.512
14	0.173	1	17	0.683	>0.99	0.732
15	0.974	1	13	0.342	>0.99	0.512

Two-way ANOVA was performed to evaluate the treatment×time (baseline vs. 3-month follow-up) interaction for the HbO recovery index across channels. p-values were additionally corrected for multiple comparisons using FWE and FDR methods. Asterisk indicates a statistically significant (*p<0.05; uncorrected).
ANOVA, analysis of variance; HbO, oxygenated hemoglobin; df, degrees of freedom; FWE, family-wise error; FDR, false discovery rate.

other channels showed significant interaction effects.

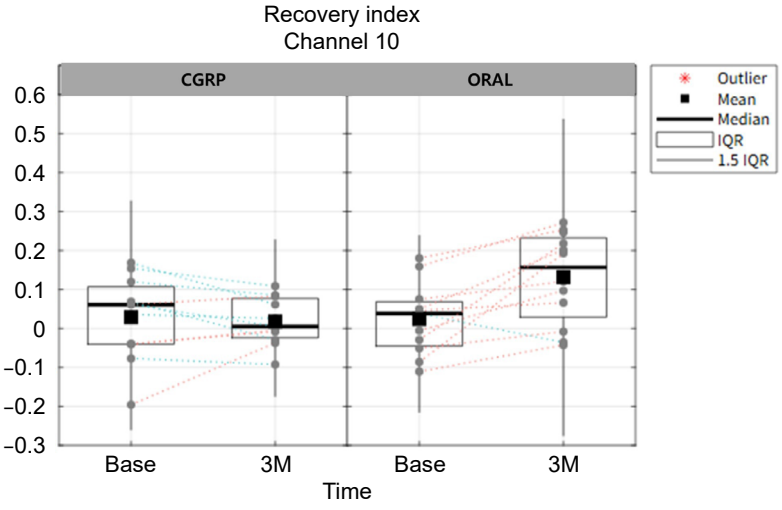
Post hoc analyses in channel 10 (Figure 5) revealed a significant difference between the CGRP group at baseline and the oral treatment group at 3 months (mean difference=0.150, p=0.001), which remained significant after Bonferroni correction (p=0.007). Additionally, a significant within group change was observed in the oral treatment group from baseline to 3 months (mean difference=–0.097, p=0.002), which also remained significant after Bonferroni correction (p=0.010).

Analyses of HbR and HbT based Rec indices revealed no significant treatment×time interaction effects after multiple comparison correction; detailed results are reported in the Supplementary Tables 4, 5 (available online).

DISCUSSION

This longitudinal fNIRS study examined whether clinical improvement following migraine preventive therapy is accompanied by changes in CVR during a hypercapnic challenge. Although both the CGRP monoclonal antibody group and the oral preventive medication group demonstrated clinically meaningful improvements over 3 months, these benefits were not uniformly associated with normalization of cerebrovascular hemodynamic responses. This dissociation suggests that symptomatic improvement in migraine may occur, at least in part, independently of restoration of altered CVR.

Cerebral blood flow is tightly regulated by arterial carbon dioxide tension, and within a physiologically relevant range, variation in pCO_2 produces dose-dependent vasodilatory or vasoconstrictive responses. The resulting



Post hoc comparisons for the treatment×time interaction in Channel 10 based on the HbO recovery index

Comparison	Mean				p (uncorrected)	p (Tukey)	p (Bonferroni)
	Difference	SE	t	df			
CGRP_Base vs. CGRP_3M	0.011	0.027	0.414	20	0.683	0.975	>0.99
CGRP_Base vs. Oral_Base	0.005	0.043	0.108	20	0.915	>0.99	>0.99
CGRP_Base vs. Oral_3M	0.150	0.040	3.798	20	0.001**	0.006**	0.007**
CGRP_3M vs. Oral_Base	0.042	0.040	1.064	20	0.300	0.715	>0.99
CGRP_3M vs. Oral_3M	–0.103	0.039	–2.629	20	0.016*	0.070	0.096
Oral_Base vs. Oral_3M	–0.097	0.027	–3.646	20	0.002**	0.008**	0.010**

Figure 5. Treatment×time effects on the HbO-based recovery index on Channel 10. Tukey-adjusted p-values control the FWE rate for a family of four comparisons. Bonferroni-adjusted p-values control the FWE rate for a family of six comparisons. Green dotted line: decreasing within subject change from Base to 3M; orange dotted line: increasing within subject change from Base to 3M. Asterisk indicates a statistically significant (*p<0.05; **p<0.01).
CGRP, calcitonin gene-related peptide; Base, baseline; 3M, 3 months; IQR, interquartile range; HbO, oxygenated hemoglobin; SE, standard error; df, degrees of freedom; FWE, family-wise error.

sigmoidal relationship reflects the degree of preserved vasomotor reactivity within the remaining autoregulatory reserve of the cerebrovascular system.[14] In this physiological context, the BHT provides a transient hypercapnic stimulus suitable for evaluating vasodilatory capacity across resting, BH, and Rec phases. In individuals with preserved vasomotor reserve, rising pCO_2 during BH is expected to induce arteriolar dilation and increases in HbO and HbT, whereas in those with reduced reserve, hypercapnia-induced increases may be attenuated or plateaued, reflecting limited residual dilatory capacity.[26,32]

In our cohort, the CGRP monoclonal antibody group showed a longitudinal decrease in both the BH and Rec indices, whereas the oral preventive medication group demonstrated an opposite pattern, with an increase in these indices from baseline to 3 months. These divergent temporal trajectories suggest that cerebrovascular responses may evolve differently over time between the two treatment groups. However, we caution against inferring a direct mechanistic effect of CGRP-targeted therapy on CVR from these findings alone.[33] The attenuation of the CO_2-driven hemodynamic response in the CGRP group may reflect modulation of late-phase vasodilatory dynamics, variability in vasomotor reserve, or other unmeasured physiological or behavioral factors.[34,35] Whether this pattern represents attenuation of excessive vasoreactivity or a relative reduction in cerebrovascular reserve remains uncertain and warrants confirmation in larger, mechanistically oriented studies. Accordingly, the present findings should be interpreted primarily in terms of longitudinal change patterns rather than absolute CVR values at individual time points.

From a clinical perspective, these findings imply that improvement in migraine burden may not necessarily require concurrent normalization of CVR. Nociceptive network modulation and cerebrovascular autoregulatory adaptation may therefore represent partially independent physiological domains. Accordingly, fNIRS-based cerebrovascular indices should be interpreted as complementary rather than surrogate markers of treatment response, particularly within short term therapeutic windows.[36-38]

One plausible interpretation is that CGRP monoclonal antibody therapy primarily exerts therapeutic benefit through modulation of trigeminovascular nociceptive signaling rather than direct correction of cerebrovascular autoregulatory dysfunction.[1] CGRP blockade may effectively suppress migraine attacks without immediately normalizing interictal neurovascular abnormalities. Alternatively, cerebrovascular adaptations may require longer treatment duration or cumulative exposure before measurable changes in vasomotor responsiveness emerge. This interpretation aligns with prior reports indicating that vascular and perfusion abnormalities may persist interictally despite clinical improvement.[13,39]

It is also possible that distinct migraine phenotypes exist some characterized predominantly by nociceptive network dysregulation and others by greater cerebrovascular dysautoregulation. Future studies incorporating subgroup- or responder-stratified analyses, extended longitudinal observation, and multimodal vascular assessment will be required to clarify these relationships and determine whether CVR trajectories carry prognostic or mechanistic relevance in migraine.[16]

From a methodological standpoint, the BHT was used as a practical hypercapnic challenge for fNIRS-based assessment of cerebrovascular reactivity. Although controlled CO_2 inhalation offers a more standardized stimulus, it requires specialized equipment and monitoring, which limits feasibility for routine or longitudinal studies. By contrast, the BHT induces hypercapnia with minimal procedural burden and allows repeated assessments. Prior reports showing good correspondence between BH derived and CO_2-based CVR measures support its suitability as a pragmatic approach for longitudinal evaluation, despite inter-individual variability in BH capacity.[6,25,40]

In the present study, fNIRS measurements were confined to the prefrontal cortex. Although this region is not traditionally regarded as a primary nociceptive hub, it plays an important role in autonomic regulation and cognitive-affective integration of pain, and it has demonstrated robust CVR to hypercapnic challenge in prior fNIRS studies.[41] Therefore, the present measurements likely capture a meaningful component of cortical vascular regulation relevant to migraine pathophysiology, although additional cortical and subcortical regions may contribute to cerebrovascular adaptation in ways not captured in our dataset.[4]

Several limitations should be acknowledged. Episodic and chronic migraine patients were analyzed together without stratification by migraine subtype. Given the known differences in disease severity between these subtypes,

this heterogeneity may have influenced the observed treatment-related changes. Because treatment allocation was not randomized, potential confounding by indication cannot be excluded. The relatively small sample size may have limited statistical power to detect subtle between-group differences in cerebrovascular responses. The recording montage was restricted to the prefrontal cortex and may not reflect hemodynamic changes in deeper or posterior brain regions. Finally, the 3-month follow-up period may be insufficient to capture delayed or progressive cerebrovascular adaptations; given that vascular remodeling and tone regulation may occur on longer temporal scales than symptomatic improvement, extended longitudinal observation will be essential in future work. Studies incorporating larger cohorts, longer treatment exposure, expanded cortical coverage, and multimodal vascular assessment will be necessary to further elucidate the temporal relationship between clinical improvement and CVR in migraine.

AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: DAY, YHK; Data curation: DAY, YHK; Formal analysis: JKC, YHK; Investigation: DAY, YHK; Methodology: YHK; Project administration: YHK; Supervision: YHK; Validation: JKC, YHK; Writing–original draft: DAY, YHK; Writing–review & editing: JKC, YHK.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING STATEMENT

This work was supported by the Korean Headache Society Research Grant (2022).

ACKNOWLEDGMENTS

Not applicable.

SUPPLEMENTARY MATERIAL

Supplementary materials are available from https://doi.org/10.62087/hpr.2025.0029.

REFERENCES

1. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. Physiol Rev 2017;97:553-622.
2. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol 2019;18:795-804.
3. Dodick DW. A phase-by-phase review of migraine pathophysiology. Headache 2018;58 Suppl 1:4-16.
4. Akin A, Bilensoy D. Cerebrovascular reactivity to hypercapnia in migraine patients measured with near-infrared spectroscopy. Brain Res 2006;1107:206-214.
5. Kastrup A, Krüger G, Neumann-Haefelin T, Moseley ME. Assessment of cerebrovascular reactivity with functional magnetic resonance imaging: comparison of CO(2) and breath holding. Magn Reson Imaging 2001;19:13-20.
6. Tancredi FB, Hoge RD. Comparison of cerebral vascular reactivity measures obtained using breath-holding and CO_2 inhalation. J Cereb Blood Flow Metab 2013;33:1066-1074.
7. Cho SJ. Toward precision migraine care: genetics, symptoms, and big-data-driven approaches. Headache Pain Res 2025;26:171-172.
8. Wattiez AS, Sowers LP, Russo AF. Calcitonin gene-related peptide (CGRP): role in migraine pathophysiology and therapeutic targeting. Expert Opin Ther Targets 2020;24:91-100.
9. Iyengar S, Johnson KW, Ossipov MH, Aurora SK. CGRP and the trigeminal system in migraine. Headache 2019;59:659-681.
10. Eun MY, Jung JM, Choi JC. A practical approach to headache in Moyamoya disease. Headache Pain Res 2025;26:173-183.
11. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med 2017;377:2113-2122.
12. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA 2018;319:1999-2008.
13. Carter SC, Cucchiara B, Reehal N, Hamilton K, Kaiser EA, Favilla CG. Effect of CGRP inhibitors on interictal cerebral hemodynamics in individuals with migraine. Front Neurol 2024;15:1399792.

14. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. J Physiol 2014;592:841-859.
15. Battisti-Charbonney A, Fisher J, Duffin J. The cerebrovascular response to carbon dioxide in humans. J Physiol 2011;589:3039-3048.
16. Dzator JS, Howe PR, Wong RH. Profiling cerebrovascular function in migraine: a systematic review and meta-analysis. J Cereb Blood Flow Metab 2021;41:919-944.
17. Silvestrini M, Vernieri F, Pasqualetti P, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA 2000;283:2122-2127.
18. Afridi SK, Giffin NJ, Kaube H, et al. A positron emission tomographic study in spontaneous migraine. Arch Neurol 2005;62:1270-1275.
19. Cao Y, Aurora SK, Nagesh V, Patel SC, Welch KM. Functional MRI-BOLD of brainstem structures during visually triggered migraine. Neurology 2002;59:72-78.
20. Zhao YN, Han PP, Zhang XY, Bi X. Applications of functional near-infrared spectroscopy (fNIRS) neuroimaging during rehabilitation following stroke: a review. Med Sci Monit 2024;30:e943785.
21. Kim YH, Paik SH, Kim Y, et al. Clinical application of functional near-infrared spectroscopy for burn assessment. Front Bioeng Biotechnol 2023;11:1127563.
22. Kim YH, Kim Y, Yoon J, et al. Frontal lobe hemodynamics detected by functional near-infrared spectroscopy during head-up tilt table tests in patients with electrical burns. Front Hum Neurosci 2022;16:986230.
23. Kim YH, Phillips VZ, Paik SH, Jeon NJ, Kim BM, Kim BJ. Prefrontal hemodynamic changes measured using near-infrared spectroscopy during the Valsalva maneuver in patients with orthostatic intolerance. Neurophotonics 2018;5:015002.
24. Kim YH, Paik SH, Phillips VZ, Jeon NJ, Kim BJ, Kim BM. Cerebral perfusion monitoring using near-infrared spectroscopy during head-up tilt table test in patients with orthostatic intolerance. Front Hum Neurosci 2019;13:55.
25. Chan ST, Evans KC, Song TY, et al. Cerebrovascular reactivity assessment with O2-CO2 exchange ratio under brief breath hold challenge. PLoS One 2020;15:e0225915.
26. Karunakaran KD, Ji K, Chen DY, et al. Relationship between age and cerebral hemodynamic response to breath holding: a functional near-infrared spectroscopy study. Brain Topogr 2021;34:154-166.
27. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. Qual Life Res 2003;12:963-974.
28. Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. Neurology 2001;56:S20-S28.
29. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-1097.
30. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606-613.
31. Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. J Manipulative Physiol Ther 2004;27:26-35.
32. Molinari F, Liboni W, Grippi G, Negri E. Relationship between oxygen supply and cerebral blood flow assessed by transcranial Doppler and near-infrared spectroscopy in healthy subjects during breath-holding. J Neuroeng Rehabil 2006;3:16.
33. Altamura C, Viticchi G, Fallacara A, et al. Erenumab does not alter cerebral hemodynamics and endothelial function in migraine without aura. Cephalalgia 2021;41:90-98.
34. Russo A, Silvestro M, Scotto di Clemente F, et al. Multidimensional assessment of the effects of erenumab in chronic migraine patients with previous unsuccessful preventive treatments: a comprehensive real-world experience. J Headache Pain 2020;21:69.
35. Ayata C, Lauritzen M. Spreading depression, spreading depolarizations, and the cerebral vasculature. Physiol Rev 2015;95:953-993.
36. Ferrari MD, Goadsby PJ, Burstein R, et al. Migraine. Nat Rev Dis Primers 2022;8:2.
37. Akin A, Bilensoy D, Emir UE, Gülsoy M, Candansayar S, Bolay H. Cerebrovascular dynamics in patients with migraine: near-infrared spectroscopy study. Neurosci Lett 2006;400:86-91.
38. Vitt JR, Loper NE, Mainali S. Multimodal and autoregulation monitoring in the neurointensive care unit. Front Neurol 2023;14:1155986.
39. Bsteh G, Marik W, Krajnc N, et al. MRI features of idiopathic intracranial hypertension are not prognostic of visual and headache outcome. J Headache Pain 2023;24:97.
40. Pinto J, Bright MG, Bulte DP, Figueiredo P. Cerebrovascular reactivity mapping without gas challenges: a methodological guide. Front Physiol 2021;11:608475.
41. Du J, Shi P, Fang F, Yu H. Cerebral cortical hemodynamic metrics to aid in assessing pain levels? A pilot study of functional near-infrared spectroscopy. Front Neurosci 2023;17:1136820.

Original Article

Headache Pain Res 2026;27(1):64-70
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2025.0021

Headache and Pain Research

Adult-Onset versus Pediatric-Onset Episodic Cluster Headaches: Results from the Korean Cluster Headache Registry

Pil-Wook Chung[1], Byung-Su Kim[2], Jeong-Wook Park[3], Jong-Hee Sohn[4], Mi Ji Lee[5], Byung-Kun Kim[6], Min Kyung Chu[7], Tae-Jin Song[8], Soo-Kyoung Kim[9], Heui-Soo Moon[1], Kyungmi Oh[10], Soo-Jin Cho[11]

For further information on the authors' affiliations, see **Additional information**.

Abstract

Purpose: This study aimed to compare clinical characteristics between pediatric-onset and adult-onset cluster headache (CH) using data from the Korean Cluster Headache Registry, a nationwide, prospective, multicenter registry.

Methods: This cross-sectional observational study analyzed data collected over a 4-year period from a prospective multicenter registry. A total of 337 patients aged ≥19 years with episodic CH were included. Participants were classified as having pediatric-onset CH (onset≤18 years) or adult-onset CH (onset>18 years). Demographic and clinical features, smoking status, and psychiatric comorbidities were compared between groups.

Results: Pediatric-onset CH was reported in 24.6% of patients (n=83). The diagnostic delay was significantly longer in the pediatric-onset group compared with the adult-onset group (10.1 years vs. 6.2 years, p<0.001). Patients with pediatric-onset CH experienced more severe headache attacks (numerical rating scale 9.2 vs. 8.9, p=0.025), although attack duration, frequency, and other clinical features were similar between groups. Smoking exposure was lower in the pediatric-onset group, suggesting potential differences in environmental risk factors. No significant differences were observed in psychiatric comorbidity or headache-related disability.

Conclusion: Pediatric-onset CH is relatively common and shares most clinical features with adult-onset CH, apart from greater attack severity and lower smoking exposure. The longer diagnostic delay in pediatric-onset cases highlights the need for improved awareness and earlier recognition. Further research is warranted to elucidate the underlying pathophysiological mechanisms and long-term outcomes in pediatric-onset CH.

Keywords: Cluster headache, Delayed diagnosis, Pediatrics

Received: September 30, 2025; **Revised:** November 5, 2025; **Accepted:** November 7, 2025

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

INTRODUCTION

Cluster headache (CH) is an excruciating form of primary headache disorder that is characterized by recurrent unilateral headache attacks accompanied by ipsilateral autonomic features.[1,2] Salient features of CH are its young male predominance, circadian rhythmicity, and trigeminal autonomic features. Although widely varied, CH is prevalent in young adult period with age at onset of CH typically between 20 and 40 years, and suggested to be rare among children. However, recent epidemiologic studies based on self-administered survey showed that 16%–35% of people with CH reported their initial CH attack before the age of 20 years, suggesting pediatric-onset might be underreported.[3,4] Clinical features of pediatric-onset CH are similar to adult-onset cases, but diagnostic delay was more frequently reported in pediatric-onset CH, though, there are few studies regarding clinical features of pediatric-onset CH, especially in Asian population.[5-7] The aim of this study was to identify different features between pediatric-onset and adult-onset CH using data from the Korean Cluster Headache Registry (KCHR), which prospectively enrolled patients with CH.

MATERIALS AND METHODS

1. Ethics approval and consent to participate

The study protocol and informed consent form were approved by the institutional review board at each hospital (HDT 2016-09-39). Written informed consent was obtained from all participants before they were enrolled in this study. This study was conducted in accordance with the principles of the Declaration of Helsinki.

2. Patients

This study was conducted using data from the KCHR. The KCHR is a prospective, multicenter registry that includes patients with consecutive CH aged ≥19 years across South Korea. Patients were enrolled over 4 years (September 2016 to December 2020) from 15 university hospitals (nine tertiary and six secondary referral centers) and two secondary referral general hospitals. The KCHR protocol has been published previously.[8,9] All participants were evaluated by board-certified neurologists in each center and CH was diagnosed using the third edition, beta version of the International Classification of Headache Disorders (ICHD-3b) or the third edition of the ICHD (ICHD-3).[10,11] Of the enrolled patients, only patients meeting ICHD-3 criteria for episodic CH were included in this study. Patients were excluded for this analysis if their diagnosis did not meet the ICHD-3 criteria for episodic CH (e.g., chronic CH, probable CH, or first CH) or the patient had missing data.

3. Clinical information

Data obtained and used in the study included the following: demographic factors, present age, age at onset, headache characteristics, seasonal and diurnal rhythmicity, and psychiatric status. Clinical information regarding current headache episodes included the severity, duration, and frequency of headache attacks, and diurnal rhythmicity. The previous history of CH included the onset age of CH, duration of CH disease, total number of cluster bouts, and pattern of seasonal periodicity. The personal history of cigarette smoking was obtained and used to classify patients into ever-smokers and never-smokers. Ever-smoker patients were further classified into current and former smokers.

4. Statistical analysis

Demographics and clinical features were compared between pediatric-onset and adult-onset patients. Pediatric-onset was defined as onset age 18 years or less, and adult-onset was defined as onset age more than 18 years. The two-sample t-test were used to compare the mean values between pediatric-onset and adult-onset cases. The chi-square test or Fisher's exact test was used to compare categorical variables. Probability values of $p<0.05$ were considered indicative of statistical significance. All analyses were performed using the Statistical Package for the Social Sciences (version 29.0; IBM Corp.).

RESULTS

The KCHR is a prospective, multicenter registry that enrolled patients with CH aged ≥19 years. Among the 463 patients identified as having CH in the KCHR, 337 met

the criteria for episodic CH according to the ICHD-3. Of the remaining 126 patients, 19 patients were diagnosed with chronic CH, 45 were diagnosed as probable CH, and the remaining 62 presented with the first CH period and neither categorized as episodic nor chronic CH. Therefore, 337 patients with episodic CH were included in this analysis (Figure 1). The age at enrollment was higher in the adult-onset CH group compared to the pediatric-onset CH group (39.4±9.2 years vs. 29.6±7.4 years). In the pediatric-onset CH group, 15 (18.1%) were female, and in the adult-onset group, 40 (15.8%) were female. There was no statistically significant difference in the sex ratio between pediatric- and adult-onset CH (Table 1). A total of 151 patients (44.8%) were current smoker, and 204 patients (60.5%) were ever-smoker (comprising current and ex-smokers). The prevalence of smoking differed significantly between pediatric and adult-onset group. Twenty-three (27.7%) were current smokers in pediatric-onset group and 128 (50.4%) were current smokers in adult-onset group (p<0.001). The proportion of ever-smokers was also lower in the pediatric-onset group than in the adult-onset group (41.0% vs. 66.9%, p<0.001) (Table 1).

Eighty-three (24.6%) participants reported an age of onset of 18 or younger (pediatric-onset), while 254 reported an age of onset after 19 years old. Disease history was compared between the pediatric-onset and adult-onset patients. The age at onset was 15.7±2.4 years (range, 9–18 years) in pediatric-onset patients and 29.5±9.1 years (range, 19–55 years) in adult-onset group. The time from onset to diagnosis of CH was prolonged in both groups, with pediatric-onset cases experiencing a notably greater delay in diagnosis (10.1±7.6 years [range, 0–31 years] vs.

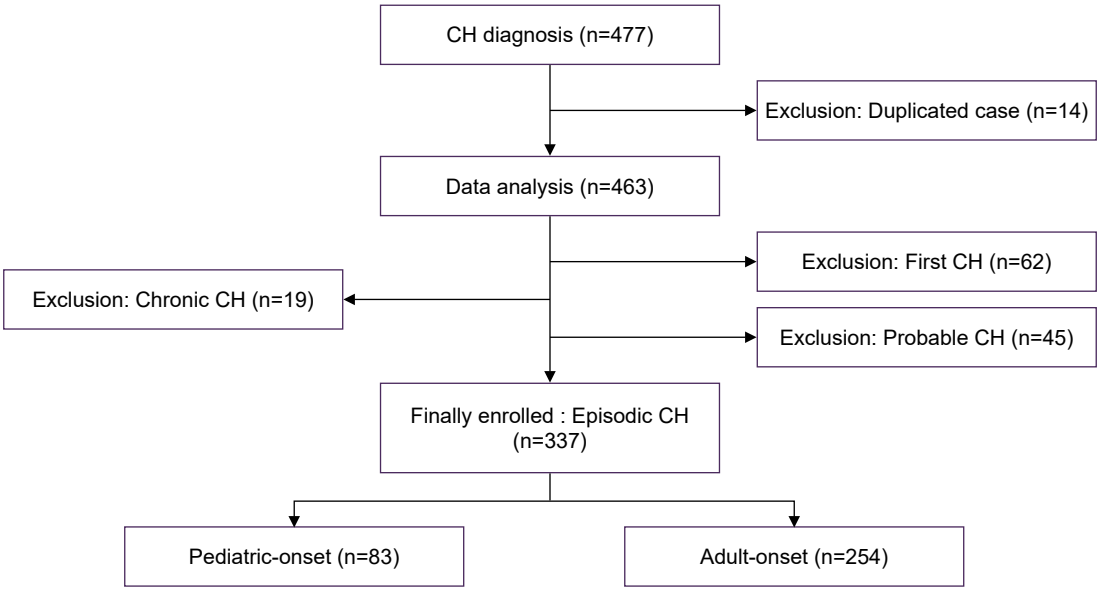


Figure 1. Patient enrollment flowchart.
CH, cluster headache.

Table 1. Demographic features between pediatric- and adult-onset cluster headaches

	All patients (n=337)	Pediatric-onset (n=83)†	Adult-onset (n=254)†	p-value
Age (yr)	37.0±9.8	29.6±7.4	39.4±9.2	<0.001
Female sex	55 (16.3)	15 (18.1)	40 (15.8)	0.619
Current smoker	151 (44.8)	23 (27.7)	128 (50.4)	<0.001
Ever-smoker*	204 (60.5)	34 (41.0)	170 (66.9)	<0.001
Alcohol drinking	213 (63.2)	46 (55.4)	167 (65.7)	0.09
Coexisting migraine	44 (13.1)	10 (12.0)	34 (13.4)	0.754

Values are presented as mean±standard deviation or number (%).
*Ever-smokers, current and ex-smokers combined; †Pediatric-onset was defined as onset age 18 years or less, and adult-onset was defined as onset age more than 18 years.

6.2±6.5 years [range, 0–32 years], p<0.001) (Table 2).

Headache characteristics were compared between pediatric- and adult-onset patients. Headache attack was more severe in pediatric-onset patients based on numerical rating scale (9.2±0.9 vs. 8.9±1.3, p=0.025). However, attack duration and daily attack frequency did not differ between the groups. There were no significant differences in bout frequency (mean number of bouts per year), duration of cluster period, diurnal rhythmicity, and seasonal propensity in both groups (Table 3). Depression scale assessed by 9-item Patient Health Questionnaire scale and anxiety scale based on 7-item Generalized Anxiety Disorder scale did not differ between pediatric and adult-onset CH. Headache-related disabilities, as determined by 6-item Headache Impact Test also did not differ (Table 3).

DISCUSSION

Main findings of present study were as follows: 1. Eighty-three out of 337 patients (24.6%) reported onset of CH in 18 years or younger, indicating that pediatric-onset CH is not uncommon. 2. Diagnostic delay of pediatric-onset CH is more severe than adult-onset CH. 3. Smoking exposure rate is lower than that of adult-onset case (all patients were evaluated in adult age). 4. Clinical features are generally similar to adult-onset CH, except more severe attack in pediatric-onset cases.

CH is a rare primary headache disorder with a prevalence of around 0.1% in general population.[12] It is generally known to occur most frequently in young adult males, and studies and reports are rare in pediatric patients. In this study, 24.6% (n=83) of 339 patients who met the criteria of episodic CH reported initial onset of CH during pediatric period (18-year or younger). Previous studies regarding

Table 2. Comparison of disease history and status

	All patients (n=337)	Pediatric-onset (n=83)*	Adult-onset (n=254)*	p-value
Onset age of CH disease (yr)	26.1±9.9	15.7±2.4	29.5±9.1	<0.001
Duration of CH disease (yr)	10.9±7.2	13.9±7.6	9.9±6.8	<0.001
Diagnostic delay (yr)	7.2±6.9	10.1±7.6	6.2±6.5	<0.001
Lifetime bout occurrence (n)	9.7±10.8	14.9±17.6	8.0±6.5	<0.001
Bout frequency (times/yr)	1.1±2.3	1.2±1.4	1.1±2.5	0.864

Values are presented as mean±standard deviation.
CH, cluster headache.
*Pediatric-onset was defined as onset age 18 years or less, and adult-onset was defined as onset age more than 18 years.

Table 3. CH features and psychiatric status

	All patients (n=337)	Pediatric-onset (n=83)*	Adult-onset (n=254)*	p-value
CH characteristics				
Attack severity (0–10 NRS)	9.0±1.2	9.2±0.9	8.9±1.3	0.025
Attack frequency (times/day)	2.0±2.1	1.7±1.3	2.1±2.2	0.108
Attack duration (min)	96.2±56.4	101.4±47.1	94.5±59.1	0.33
Duration of bout (wk)	6.2±5.3	6.6±7.1	6.1±4.6	0.401
Diurnal rhythmicity	209 (62.0)	48 (57.8)	161 (63.4)	0.138
Seasonal propensity	182 (54.0)	45 (54.2)	137 (53.9)	0.735
Psychiatric status				
GAD-7 score	8.1±6.0	7.5±6.1	8.3±6.0	0.292
PHQ-9 score	7.8±6.6	7.0±6.8	8.1±6.5	0.174
Suicidal ideation	79 (23.4)	22 (26.5)	57 (22.4)	0.747
Suicide attempt	3 (0.9)	1 (1.2)	2 (0.8)	0.757
HIT-6 score	69.4±7.8	70.1±7.0	69.1±8.0	0.322

Values are presented as mean±standard deviation or number (%).
CH, cluster headache; NRS, numerical rating scale; GAD-7, 7-item Generalized Anxiety Disorder scale; PHQ-9, 9-item Patient Health Questionnaire scale; HIT-6, 6-item Headache Impact Test.
*Pediatric-onset was defined as onset age 18 years or less, and adult-onset was defined as onset age more than 18 years.

pediatric-onset CH and/or pediatric CH is scarce and mostly based on case series or single clinic observations, therefore, epidemiologic data regarding pediatric CH is still elusive.[6,12] An Italian multicenter study reported that out of 6,629 childhood headache patients, 3 were diagnosed with CH, suggesting 1-year prevalence of childhood CH at 0.03%.[13] In United States CH survey study, 35% of 1,134 patients reported CH began at 20 years or younger.[3] International study using self-administered survey showed pediatric-onset (<18 years old) was found in 27.5% (341/1,583) of participants.[4] Both studies have a limitation of questionnaire or survey-based method of CH diagnosis. A previous headache clinic-based study reported that 16% of CH patients experienced early onset (before age of 20).[14] In contrast, the present study, which utilized a nationwide prospective registry, found that 24.6% of Korean participants with episodic CH reported an onset of CH at 18 years of age or younger. Although the age criteria of pediatric-onset CH varied among studies, the proportion of pediatric-onset cases in the present study is generally consistent with findings from Western or international research. Taken together, these results suggest that CH frequently begins during pediatric years.

Although clinical features of CH is characteristic and easily recognizable, there is no reliable biomarker available for its diagnosis. Therefore, early diagnosis of CH remains a challenge because many patients with CH experience delayed diagnosis or misdiagnosis.[15,16] Given the severe pain associated with CH attacks, such delays or misdiagnoses could have a significant impact on both patients and society as a whole. Our study demonstrated that diagnostic delay was more severe in pediatric-onset patients. Diagnostic delay was 10.1 years in pediatric cases, compared to 6.2 years in adult-onset CH patients. Our result confirms previous studies, which suggested younger age at onset as a factor for diagnostic delay of CH.[7,14,17,18] International CH questionnaire study found only 15.2% of participants with pediatric-onset were diagnosed before the age of 18.[4] The reasons for more delay in pediatric cases are unclear. Pediatric CH might be more difficult to diagnose because features of migraine are often frequently found in pediatric CH.[7] Furthermore, pediatric migraine attack can be as short as 2 hours, and overlap in attack duration between migraine and CH in child could make diagnosis even more difficult.[5] Studies have indicated that the duration of CH attacks in children may fall below the lower limit observed in typical CH attacks.[7] Pediatric headache specialist are fewer than adult headache specialist, therefore, lack of access to physician might be another reason for diagnostic delay.[4]

Clinical features of pediatric-onset CH was similar to adult-onset cases in this study, except for slightly more severe headache attack in pediatric-onset CH (9.2±0.9 vs. 8.9±1.3, p=0.025). However, headache feature analysis was based on current CH attacks (all patients enrolled after 19 years old) and we could not identify whether headache features changed from their original headache features in pediatric ages. Clinical and autonomic features of early onset CH were similar to adult-onset CH in other reports.[16,19,20] Pediatric-onset patients display the full range of each criterion for CH in a previous systematic review.[5] Cranial autonomic features and restlessness occur at a lower rate in pediatric cases, while migraine features such as nausea, photophobia, and phonophobia were found similarly to adult-onset patients.[5]

Although pathophysiologic associations are unknown, epidemiologic studies have shown that cigarette smoking is closely associated with CH.[21-23] Previous study has even suggested that secondary smoke exposure during childhood may be related to the subsequent development of CH.[24] Our study found that patients with pediatric-onset CH were less frequently exposed to smoking. Proportion of current smoker and ever-smoker in pediatric-onset cases were lower than those of adult-onset CH in this study. In line with our study, other studies demonstrated that CH not exposed to smoking were more likely to develop CH at a lower age than exposed patients.[25,26] Lower smoking exposure in pediatric-onset cases suggests a genetic or biology-based etiology in pediatric-onset CH, while higher smoking rate in adult-onset CH is suggestive of the smoking-related environmental etiology in adult-onset patients.[25,27] However, a lower age at CH onset could cause patients to avoid smoking habit, so the influence of smoking before and after the onset of CH needs to be investigated further.[27] Nonetheless, the relationship between smoking exposure and CH warrant cautious interpretation. Age, sex, and cultural background could markedly confound the smoking habitus. In particular, the significantly higher mean age in the adult-onset CH group may have provided greater opportunity for smoking exposure in the adult-onset participants in our cohort. Accordingly, until additional

validation is conducted, our findings should be considered preliminary and hypothesis-generating.

There are several limitations in the present study. First, the patients included in this study were individuals whose headache onset occurred during childhood or adolescence, but who were evaluated during adulthood. Some clinical features of pediatric CH can only be accurately assessed through direct observation during the pediatric period, and, as a result, recall bias may have affected our findings. Although long-term, prospective studies following CH from childhood into adulthood would provide the most reliable data, conducting such research is challenging due to the rarity of CH and the difficulties associated with its diagnosis in pediatric populations. Second, in this study, we did not investigate the differences of treatment responses between pediatric and adult-onset CH. Third, the participants in this study consisted only of Korean patients referred to a secondary or tertiary hospital, and so the results might not be generalizable to all patients with CH, especially those with milder forms of the disorder or other ethnicity. Lastly, our analysis was limited to patients with episodic CH, excluding those with chronic CH or probable CH. Chronic CH was very rare in our cohort, representing only 4.1% (19/463) of the entire sample. Since episodic CH is the most typical and prevalent form, focusing on strictly defined episodic CH may be more valuable for identifying the characteristics of pediatric-onset CH. Nevertheless, further research is warranted to investigate chronic CH and the long-term changes over time in patients with pediatric-onset CH.

ADDITIONAL INFORMATION

[1]Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[2]Department of Neurology, Ewha Womans University Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea
[3]Department of Neurology, Uijeongbu St. Mary's Hospital, Uijeongbu, Republic of Korea
[4]Department of Neurology, Chuncheon Sacred Heart Hospital, Hallym University College of Medicine, Chuncheon, Republic of Korea
[5]Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea
[6]Department of Neurology, Nowon Eulji Medical Center, Eulji University, Seoul, Republic of Korea
[7]Department of Neurology, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea
[8]Department of Neurology, Ewha Womans University School of Medicine, Seoul, Republic of Korea
[9]Department of Neurology, Gyeongsang National University College of Medicine, Jinju, Republic of Korea
[10]Department of Neurology, Korea University College of Medicine, Seoul, Republic of Korea
[11]Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine, Hwaseong, Republic of Korea

AVAILABILITY OF DATA AND MATERIAL

The data presented in this study are available upon reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: PWC, BSK, SJC; Data curation: PWC, BSK, MJL, BKK, MKC, TJS, SKK, HSM, KO, SJC; Formal analysis: BSK, JWP; Investigation: PWC, JHS, TJS, SJC; Methodology: BSK, HSM, KO; Writing–original draft: PWC, SJC; Writing–review & editing: BSK, JWP, JHS, MJL, BKK, MKC, TJS, SKK, HSM, KO, SJC.

CONFLICT OF INTEREST

Soo-Kyoung Kim is the Deputy Editor of *Headache and Pain Research* and was not involved in the review process of this article.
Kyungmi Oh is the Associate Editor of *Headache and Pain Research* and was not involved in the review process of this article.
Soo-Jin Cho is the Editor-in-Chief of *Headache and Pain Research* and was not involved in the review process of this article.
All authors have no other conflicts of interest to declare.

FUNDING STATEMENT

Not applicable.

ACKNOWLEDGMENTS

Not applicable.

REFERENCES

1. Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. Lancet Neurol 2002;1:251-257.
2. Kim M, Yu JK, Kim YH. Update on cluster headaches: from genetic to novel therapeutic approaches. Headache Pain Res 2024;25:42-53.
3. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. Headache 2012;52:99-113.
4. Schor LI, Pearson SM, Shapiro RE, Zhang W, Miao H, Burish MJ. Cluster headache epidemiology including pediatric onset, sex, and ICHD criteria: results from the International Cluster Headache Questionnaire. Headache 2021;61:1511-1520.
5. Ghosh A, Silva E, Burish MJ. Pediatric-onset trigeminal autonomic cephalalgias: a systematic review and meta-analysis. Cephalalgia 2021;41:1382-1395.
6. Petersen AS, Lund N, Goadsby PJ, et al. Recent advances in diagnosing, managing, and understanding the pathophysiology of cluster headache. Lancet Neurol 2024;23:712-724.
7. Taga A, Manzoni GC, Russo M, Paglia MV, Torelli P. Childhood-onset cluster headache: observations from a personal case-series and review of the literature. Headache 2018;58:443-454.
8. Cho S, Cho SJ, Lee MJ, et al. Clinical characteristics of pre-attack symptoms in cluster headache: a large series of Korean patients. Cephalalgia 2021;41:227-236.
9. Chung PW, Lee MJ, Park JW, et al. Differences of cluster headache on the basis of sex in the Korean Cluster Headache Registry. Headache 2019;59:1722-1730.
10. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
11. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2013;33:1-211.
12. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. Cephalalgia 2008;28:614-618.
13. Gallai B, Mazzotta G, Floridi F, et al. Cluster headache in childhood and adolescence: one-year prevalence in an out-patient population. J Headache Pain 2003;4:132-137.
14. Zidverc-Trajkovic J, Markovic K, Radojicic A, Podgorac A, Sternic N. Cluster headache: is age of onset important for clinical presentation? Cephalalgia 2014;34:664-670.
15. Kim BS, Chung PW, Kim BK, et al. Diagnostic delay and its predictors in cluster headache. Front Neurol 2022;13:827734.
16. Van Obberghen EK, Fabre R, Lanteri-Minet M. Cluster headache diagnostic delay and its predictors: a systematic review with a meta-analysis. J Headache Pain 2025;26:71.
17. van Vliet JA, Eekers PJ, Haan J, Ferrari MD; Dutch RUSSH Study Group. Features involved in the diagnostic delay of cluster headache. J Neurol Neurosurg Psychiatry 2003;74:1123-1125.
18. Buture A, Ahmed F, Dikomitis L, Boland JW. Systematic literature review on the delays in the diagnosis and misdiagnosis of cluster headache. Neurol Sci 2019;40:25-39.
19. Maytal J, Lipton RB, Solomon S, Shinnar S. Childhood onset cluster headaches. Headache 1992;32:275-279.
20. Bastos SNMAN, Barbosa BLF, Silva SF, et al. Cluster headache in children and adolescents: a systematic review of case reports. Dev Med Child Neurol 2021;63:1155-1160.
21. Levi R, Edman GV, Ekbom K, Waldenlind E. Episodic cluster headache. II: high tobacco and alcohol consumption in males. Headache 1992;32:184-187.
22. Manzoni GC, Terzano MG, Bono G, Micieli G, Martucci N, Nappi G. Cluster headache: clinical findings in 180 patients. Cephalalgia 1983;3:21-30.
23. Lund N, Petersen A, Snoer A, Jensen RH, Barloese M. Cluster headache is associated with unhealthy lifestyle and lifestyle-related comorbid diseases: results from the Danish cluster headache survey. Cephalalgia 2019;39:254-263.
24. Rozen TD. Cluster headache as the result of secondhand cigarette smoke exposure during childhood. Headache 2010;50:130-132.
25. Rozen TD. Cluster headache clinical phenotypes: tobacco nonexposed (never smoker and no parental secondary smoke exposure as a child) versus tobacco-exposed: results from the United States Cluster Headache Survey. Headache 2018;58:688-699.
26. Steinberg A, Fourier C, Ran C, Waldenlind E, Sjöstrand C, Belin AC. Cluster headache: clinical pattern and a new severity scale in a Swedish cohort. Cephalalgia 2018;38:1286-1295.
27. Chung PW, Kim BS, Park JW, et al. Smoking history and clinical features of cluster headache: results from the Korean Cluster Headache Registry. J Clin Neurol 2021;17:229-235.

Letter to the Editor

Headache Pain Res 2026;27(1):71-71
pISSN: 3022-9057 · eISSN: 3022-4764
https://doi.org/10.62087/hpr.2026.0001

Headache and Pain Research

The honored list of reviewer in 2025

We greatly appreciate your insightful contribution as a reviewer for *Headache and Pain Research* in 2025.

Top Reviewer

Hye Jeong Lee, Korea

Outstanding Reviewers

Woo-Seok Ha, Korea
Jiyoung Kim, Korea

Reviewers

Myoung-Jin Cha, Korea
Soo-Jin Cho, Korea
Soohyun Cho, Korea
Min Kyung Chu, Korea
Pil-Wook Chung, Korea
Gianluca Coppola, Italy
Young Eun Gil, Korea
Yooha Hong, Korea
Keiko Ihara, Japan
Hee-Jin Im, Korea
Ryotaro Ishii, Japan
Jin-Ju Kang, Korea
Mikyoung Kang, Korea
Byung Kun Kim, Korea
Byung-Su Kim, Korea
Joonho Kim, Korea
Soo-Kyoung Kim, Korea
Yoo Hwan Kim, Korea
Miji Lee, Korea
Seung Han Lee, Korea
Wonwoo Lee, Korea
Yun Jin Lee, Korea
Yu-Hsiang Ling, Taiwan
Otgonbayar Luvsannorov, Mongolia
Ji-hoon Na, Korea
Sun-Young Oh, Korea
Hong-Kyun Park, Korea
Jeong Wook Park, Korea
KwangYeol Park, Korea
Sanghyo Ryu, Korea
Jong-Hee Sohn, Korea
Tae-Jin Song, Korea
Yonggang Wang, China
Jungyon Yum, Korea

Instructions for authors

Headache and Pain Research

CONTACT INFORMATION

Headache and Pain Research **Editorial Office**
68 Hangeulbiseok-ro, Nowon-gu, Seoul 01830, Republic of Korea
Tel: +82-2-974-8606, Fax: +82-2-974-7785
E-mail: office@e-hpr.org

Editor-in-Chief: Soo-Jin Cho, M.D., Ph.D.
Department of Neurology, Dongtan Sacred Heart Hospital, Hallym University College of Medicine
Tel: +82-31-8086-2310, Fax: +82-31-8086-2317
E-mail: kheadache2014@gmail.com

GENERAL INFORMATION

Headache and Pain Research is the official Open Access Journal of Korean Headache Society. The journal published articles are freely and permanently accessible online immediately upon publication, without any subscription charges or registration barriers. The journal reports on basic and clinical investigations related to migraine, cluster headache, tension-type headache, intracranial hypotension, intracranial hypertension, reversible cerebral vasoconstriction syndrome, and other primary or secondary headache disorders. It also covers pediatric headache, temporomadibular disorder and orofaical pain, as well as headache and pain-related dizziness, psychological and cognitive problems, epidemiology, and big data. It publishes original articles, review articles, clinical trials, case reports, perspectives, letters to the editor, and editorials.

Headache and Pain Research follows Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (https://www.icmje.org/icmje-recommendations.pdf) from the International Committee of Medical Journal Editors (ICMJE) if not otherwise described below. Authors will be asked to confirm their compliance with the journal's policies and guidelines during manuscript submission on the web page, and each author will be asked to submit a signed "Authorship Responsibility, Conflicts of Interest, and Copyright Transfer/Publishing Agreement" (available at Instructions & Forms at https://e-hpr.org/authors/authors.php) prior to acceptance of their manuscript.

PUBLICATION AND RESEARCH ETHICS

The journal adheres to the ethical guidelines for research and publication described in the Guidelines on Good Publication (https://publicationethics.org/guidance/Guidelines) and the Good Publication Practice Guidelines for Medical Journals (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13).

Statement of Human and Animal Rights and Informed Consent

Any investigations involving humans and animals should be approved by the Institutional Review Board and Institutional Animal Care and Use Committee, respectively, of the institution where the study took place. *Headache and Pain Research* will not consider any studies involving humans or animals without the appropriate approval. Informed consent should be obtained, unless waived by the institutional review board, from patients who participated in clinical investigations. Human subjects should not be identifiable, such that patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. If experiments involve animals, the research should be based on national or institutional guidelines for animal care and use. *Headache and Pain Research* can request an approval by the institutional review board or institutional animal care and use committee for the other types of articles when necessary. The content of each article is the responsibility of the authors and not of *Headache and Pain Research*.

Authorship and Author's Responsibility

The corresponding author takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process, and typically ensures that all the journal's administrative requirements,

such as providing details of authorship, ethics committee approval, clinical trial registration documentation, and gathering conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors. The corresponding author should be available throughout the submission and peer review process to respond to editorial queries in a timely way, and should be available after publication to respond to critiques of the work and cooperate with any requests from the journal for data or additional information should questions about the paper arise after publication. Authors are responsible for the whole content of each article. Co-authorship should be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

If any persons who do not meet above 4 criteria, they may be listed as contributors in Acknowledgments section. There is no limit to the number of authors, and in principle, only one author should contact the editorial board. In the case of multi-center or multi-disciplinary research, up to two corresponding authors are allowed. *Headache and Pain Research* does not allow adding authors or changing the first or the corresponding authors once its decision of 'Accept as it is' is made. If any author wishes to be removed from the byline, he or she should submit a letter signed by the author, as well as all other authors, indicating his or her wish to be deleted from the list of authors. Any change in the name order in the byline requires a letter signed by all authors indicting agreement with the same.

Conflict of Interest

The authors should disclose all potential conflicts of interest including any research funding, other financial support, and material support for the work. The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. If there is a disclosure, the editors, reviewers, and reader can approach the manuscripts after understanding the situation.

Originality and Duplicate Publication

Manuscripts under review or published by other journals will not be accepted for publication in *Headache and Pain Research*, and articles published in this journal are not allowed to be reproduced in whole or in part in any type of publication without permission of the Editorial Board. Figures and tables can be used freely if original source is verified according to Creative Commons Non-Commercial License. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access. Regarding duplicate publication, plagiarism, and other problems related to publication ethics, "Good Publication Practice Guidelines for Medical Journals" (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=7) should be followed.

Secondary Publication

It is possible to republish manuscripts if the manuscripts satisfy the conditions of acceptable secondary publication of the Recommendations by ICMJE (https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html#three) as followings: Certain types of articles, such as guidelines produced by governmental agencies and professional organizations, may need to reach the widest possible audience. In such instances, editors sometimes deliberately publish material that is also being published in other journals, with the agreement of the authors and the editors of those journals. Secondary publication for various other reasons, in the same or another language, especially in other countries, is justifiable and can be beneficial provided that the following conditions are met. (1) The authors have received approval from the editors of both journals (the editor concerned with secondary publication must have access to the primary version). (2) The priority of the primary publication is respected by a publication interval negotiated by both editors with the authors. (3) The paper for secondary publication is intended for a different group of readers; an abbreviated version could be sufficient. (4) The secondary version faithfully reflects the authors, data, and interpretations of the primary version. (5) The secondary version informs readers, peers, and documenting agencies that the paper has been published in whole or in part elsewhere—for example, with a note that might read, "This article is based on a study first re-

ported in the [journal title, with full reference]"—and the secondary version cites the primary reference. (6) The title of the secondary publication should indicate that it is a secondary publication (complete or abridged republication or translation) of a primary publication.

Process to Manage the Research and Publication Misconduct

When the Journal faces suspected cases of research and publication misconduct such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, undisclosed conflict of interest, ethical problem with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and etc., The resolving process will be followed by flowchart provided by the COPE (https://publicationethics.org/guidance/Flowcharts). The discussion and decision on the suspected cases are done by Editorial Board.

Registration of Clinical Trial Research

Any research that deals with a clinical trial should be registered with a primary national clinical trial registration site such as Korea Clinical Research Information Service (CRiS, https://cris.nih.go.kr), other primary national registry sites accredited by World Health Organization (https://www.who.int/clinical-trials-registry-platform/network/primary-registries) or ClinicalTrial.gov (https://clinicaltrials.gov), a service of the US National Institutes of Health.

Data Sharing Statement

Headache and Pain Research accepts the ICMJE Recommendations for data sharing statement policy (https://icmje.org/icmje-recommendations.pdf). Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in JKMS vol. 32, no. 7:1051-1053 (https://doi.org/10.3346/jkms.2017.32.7.1051).

Use of generative AI-assisted technologies

• Permitted Use of Generative AI

Authors may use generative AI tools (e.g., ChatGPT, Gemini, Claude) during manuscript preparation only for limited purposes, provided that such use is transparently disclosed and the authors fully verify the outputs. Permitted uses include:

- Language polishing, grammar correction, and sentence restructuring.
- Literature summarization or assistance in drafting general background sections.
- Code syntax suggestions (e.g., R or Python formatting), but **not for performing actual statistical analyses or drawing inferences.**

*** Use of generative AI tools to conduct statistical analysis, produce statistical results, or assist in data interpretation is strictly prohibited due to concerns about reproducibility, reliability, and the risk of fabricated outputs (hallucinations).**

• Prohibited Use of Generative AI

Authors are strictly prohibited from:

- Generating original scientific content, results, tables, or data interpretation using AI tools.
- Using AI for statistical modeling, inferential analysis, or drawing conclusions from data.
- Listing AI tools as an author or co-author under any circumstances.
- Including unverifiable or AI-fabricated citations, references, or findings.

• Required Disclosure

Any use of generative AI tools must be clearly described in the manuscript, preferably in the "Methods," "Acknowledgments," or "Author Contributions" section. The disclosure must include:

- The name and version of the AI tool used (e.g., ChatGPT-4, Claude 3.5).
- The purpose and scope of use (e.g., English grammar correction, code suggestion).
- The date of AI use.
- A statement confirming that the authors have independently reviewed and verified all AI-generated content.

Example disclosure:

"This manuscript was prepared with the assistance of ChatGPT-4 (OpenAI), used on June 15, 2025, for grammar and language refinement. All content generated with AI assistance was independently verified by the authors."

• Authorship and Accountability

AI tools cannot be credited as authors.

All listed authors are responsible for the accuracy, integrity, and originality of the submitted manuscript, including any content generated with AI assistance.

The use of AI does not exempt authors from ethical, scientific, or legal responsibility.

• Use of AI in Peer Review

Reviewers may use AI tools to assist in summarizing manuscripts, but must not rely on them for forming scientific judgments or final recommendations.

If AI tools are used, reviewers must disclose the use and describe the scope briefly in their review comments.

• Ethics and Transparency

Any misuse of AI tools that results in fabricated, manipulated, or misleading scientific content will be considered a serious breach of publication ethics.

Undisclosed use of AI tools may lead to manuscript rejection, retraction, or a ban on future submissions.

• Policy Review and Updates

This policy will be reviewed and revised periodically to reflect advances in generative AI technology and publication ethics.

Editorial Responsibilities

Editorial board will continuously work for monitoring/safeguarding publication ethics: guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standard; publishing corrections, clarifications, retractions and apologies when needed; no plagiarism, no fraudulent data. Editors are always keeping following responsibilities: responsibility and authority to rejected/ accept article; no conflict of interest respect to articles they reject/ accept; acceptance of a paper when reasonably certain; promoting publication of correction or retraction when errors are found; preservation of anonymity of reviewers.

COPYRIGHTS, OPEN ACCESS, OPEN DATA, ARCHIVING, AND DEPOSIT POLICY

Copyrights

The manuscript, when published, will become the property of the journal. Copyrights of all published materials are owned by the Korean Headache Society. All authors must sign the Transfer of Copyright Agreement when they submit their manuscript. Copyright transfer agreement form (https://e-hpr.org/authors/copyright_transfer_agreement.php).

Open Access Policy

Headache and Pain Research is an Open Access journal distributed under the terms of the Creative Commons Attribution Non-Commercial License (https://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. Author(s) do not need to be permitted for use of tables or figures published in *Headache and Pain Research* in other journals, books, or media for scholarly and educational purposes. This is in accordance with the Budapest Open Access Initiative definition of open access. It also follows the open access policy of PubMed Central at the United States National Library of Medicine (NLM) (https://www.ncbi.nlm.nih.gov/pmc/).

Open data policy

For clarification on result accuracy and reproducibility of the results, raw data or analysis data will be deposited to a public repository or *Headache and Pain Research* homepage after acceptance of the manuscript. If the data is already a public one, its URL site or sources should be disclosed. The data will not be made publicly available; if it is made available by special request to the corresponding author, this will be stated.

Archiving Policy

According to the deposit policy (self-archiving policy) of Sherpa/Romeo (https://www.sherpa.ac.uk), authors can archive preprint (i.e., pre-refereeing) or postprint (i.e., final draft post-refereeing). Authors can archive publisher's version/PDF.

GUIDELINES FOR MANUSCRIPT FORMATTING

1. General Guidelines

- The manuscript must be written in English.
- The manuscript should be organized in a single file, which starts with the title page, abstract and keywords, introduction, materials and methods, results, discussion, acknowledgments, statements on conflicts of interest, references, tables, and figure legends.
- The manuscript should use an 11- or 12-point font size and be double spaced on 21.0 cm × 29.7 cm (A4) paper with 3.0 cm margins at the top, bottom, and left margin. Left-aligned text should be used.
- The authors should not number the pages or the lines. The page and line numbers will automatically be generated

when the uploaded manuscript is converted to PDF format.

- Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parentheses should be used on first mention.
- When quoting from other sources, give a reference number after the author's name or at the end of the quotation.
- Authors should express all measurements in conventional units, using the International System (SI) of units.
  - Biological names of organisms: *Saccharomyces cerevisiae, E. coli*
  - Restriction enzymes and some enzymes: EcoRI, Taq polymerase
  - Names of genes: Src, C-H-ras, Myc
  - Latin words: in vivo, in vitro, in situ
  - Centrifugation force: 100,000 × *g*
- The names of the manufacturers of equipment and generic names should be given.
- For specific study designs, such as randomized control studies, studies of diagnostic accuracy, meta-analyses, observational studies, and nonrandomized studies, authors are encouraged to also consult the reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (https://www.equator-network.org) and the NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

Headache and Pain Research recommends compliance with some or all of the following guidelines.

- CONSORT for reporting of randomized controlled trials (http://www.consort-statement.org)
- STARD for reporting of diagnostic accuracy studies (http://www.stard-statement.org)
- STROBE for reporting of observational studies in epidemiology (http://www.strobe-statement.org)
- PRISMA for reporting of systematic reviews (http://www.prisma-statement.org)
- MOOSE for reporting of Meta-analyses of observational studies (https://jamanetwork.com/journals/jamasurgery/article-abstract/2778476)
- CARE for reporting of clinical cases (https://www.care-statement.org)
- AGREE for reporting clinical practice guidelines (http://www.agreetrust.org/resource-centre/agree-reporting-checklist/)
- ARRIVE for reporting of animal pre-clinical studies (https://arriveguidelines.org/arrive-guidelines)

- Please also refer to the most recent articles published in *Headache and Pain Research* for style.

2. Main Document

- The main document should contain the following components in a single Microsoft Word file, each component starting on a separate page: title page, abstract, main body, acknowledgments/statements on conflicts of interest, references, and figure legends.

2.1. Title Page

- Include the following items on the title page:
  - Title
  - Names, affiliations, and addresses of all authors
  - Contact information of the corresponding author
  - Type of manuscript
- Each author's full name, not initials, must be provided in the order of first name, middle name (if it exists), and last name for all participating authors, e.g., John (first name) Doe (last name).
- When authors from different institutions/addresses are included, the authors should be matched with their organizations by placing the relevant organization number in superscript after each author's name.
- The contact information of the corresponding author should include the mailing address and e-mail address.
- ORCID: Open researcher and contributor ID (ORCID) of all authors are recommended to be provided. To have ORCID, authors should register in the ORCID web site available from: https://orcid.org. Registration is free to every researcher in the world.

2.2. Abstract

- Reference citations should not be used in the abstract. Abbreviations should be minimized and, if used, must be defined within the abstract by the full term followed by its abbreviation in parentheses.
- The abstract should be concise, less than 250 words, and describe the subject of research concisely, in a paragraph. The abstract for an original article must be structured to include a Purpose, Methods, Results, and Conclusion as follows:

  Purpose: In one or two sentences, the specific purpose of the article and why it is worthy of attention should be indicated. The purpose stated here should be identical to the

one given in the title of the paper and the introduction.

Methods: The methods used to achieve the purpose explained in the first paragraph should be described succinctly, stating what was done and how bias was controlled, what data were collected, and how the data were analyzed.

Results: The findings of the methods described in the preceding paragraph are to be presented here, with specific data. All results should flow logically from the methods described.

Conclusion: In one or two sentences, the conclusion of the study should be stated. This should relate directly to the purpose of the paper, as defined in the first paragraph of the abstract.

- Unlike that for an Original Article, the abstract for review/case report consist of a single paragraph without separate sections. The most recently published articles should be consulted for style.
- Three to five keywords (index terms) should appear after the abstract. For the selection of keywords, refer to the list of Medical Subject Headings (MeSH, https://www.ncbi.nlm.nih.gov/mesh).

2.3. Main Body

2.3.1. Original Article

Original articles are papers containing results of basic and clinical investigations, which are sufficiently well documented to be acceptable to critical readers. The maximum length of a manuscript is 5,000 words (exclusive of the title page and abstract), 50 references (if the references exceed 50, authors can consult with the Editorial Office). A total of 8 figures or tables are allowed; additional tables and figures may be provided using the online data supplement system.

Introduction

- The introduction provides the research background and specific purpose or objectives, generally enough to inform the readers of the topic, and relevant findings of others are described. The hypothesis tested can be stated. The references should be as few and pertinent as possible.

Materials and Methods

- The first paragraph should address whether the study was conducted under an approval by the Institutional Review Board (with or without patient informed consent) and Institutional Animal Care and Use Committee of the institution where the study took place for any investigation involving humans and animals, respectively.
- The materials (or subjects), inclusion and exclusion criteria, research plan, and the methods used should all be described.
- Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.
- How the disease was confirmed and how subjectivity in observations was controlled should be explained in detail, if relevant.
- When experimental methodology is the main issue of the paper, the experimental process should be described in detail so as to make it possible for the reader to recreate the experiment as closely as possible.
- The methods of statistical analysis and criteria for statistical significance should be described.
- If the study includes reuse/overlap of materials previously published or under consideration for publication elsewhere, the reuse/overlap of study materials should be clearly stated.

Results

- The results of the paper should be described logically according to the Methods section.
- Tables and figures are recommended when they can present data more succinctly and clearly. Do not duplicate the content of tables or figures in the Results section.
- Briefly describe the core results related to the conclusion in the text when data are provided in tables or in figures.
- In the Results section, audio or video files are also welcomed. Supplementary results can be placed in the Appendix.

Discussion

- In the first part of the discussion, the main findings should be briefly summarized, then possible explanations for these findings should be explored, and these results should be compared and contrasted with the findings of other relevant studies.
- The results of previous relevant studies should not be men-

tioned repeatedly, but any concordance or discordance should be noted.
- The core findings and the conclusions derived from them should be emphasized according to the best available evidence.
- In the last part of the discussion, the limitations of the study, future research suggestions or plans, and the conclusion should all be described. If there was a research hypothesis in the introduction section, whether it was supported should be stated.

Conflict of Interest
- State any potential conflict of interest that could influence the authors' interpretation of the data, such as financial support from or connections to pharmaceutical companies, political pressure from interest groups, or academically related issues.

Acknowledgments and Author Contribution
- All persons who have made substantial contributions but have not met the criteria for author- ship are acknowledged here. All sources of funding applicable to the study should be explicitly stated here.
- What authors have done for the study should be described in this section. To qualify for authorship, all contributors must meet at least one of the seven core contributions by CRediT (conceptualization, methodology, software, validation, formal analysis, investigation, data curation), as well as at least one of the writing contributions (original draft preparation, review and editing). Contributions will be published with the final article, and they should accurately reflect contributions to the work. The submitting author is responsible for completing this information at submission, and it is expected that all authors will have reviewed, discussed, and agreed to their individual contributions ahead of this time.

References
- In the text, references should be cited using superscript Arabic numerals (e.g., [1], [2,3], [4-6]) and numbered in the order cited.
- In the references section, the references should be numbered and listed in the order of their appearance in the text.
- List all authors when there are six or fewer; for seven or more, list only the first three and add "et al."
- If an article has been published online but has not yet been given an issue or pages, the digital object identifier (DOI) should be supplied.
- Journal titles should be abbreviated in the style used in Medline.
- Other types of references not described below should follow "Samples of Formatted References for Authors of Journal Articles" (https://www.nlm.nih.gov/bsd/uniform_requirements.html).
- Unpublished data should not be cited in the reference list, but parenthetically in the text, for example: (Smith DJ, personal communication), (Smith DJ, unpublished data).
- The style and punctuation for journal articles, books, or book chapters should follow the format illustrated in the following examples:

- Journal article

  Na JH, Cho SJ, Moon JS, et al. Application and effectiveness of dietary therapy for pediatric migraine. *Headache Pain Res* 2023;1:14-19.
- Journal article published electronically ahead of print

  Mantegazza R, Wolfe GI, Muppidi S, et al. Post-intervention status in patients with refractory myasthenia gravis treated with eculizumab during REGAIN and its open-label extension. Neurology 2020 Nov 23 [Epub]. https://doi.org/10.1212/WNL.0000000000011207

- Conference paper

  Mark MH, Dickson DW, Schwarz KO, et al. Familial diffuse Lewy body disease. Presented at the 10th International Symposium on Parkinson's Disease; October 19, 1991.

- Forthcoming

  Tian D, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. Proc Natl Acad Sci USA. Forthcomming 2002.

- Book

  Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology, 4th ed. Mosby; 2002.

  Gilstrap LC 3rd, Cunningham FG, VanDorsten JP, editors. Operative obstetrics, 2nd ed. McGraw-Hill; 2002.

  Meltzer PS, Kallioniemi A, Trent JM. Chromosome Alterations in Human Solid Tumors. In: Vogelstein B, Kinzler KW, editors. The Genetic Basis of Human Cancer. McGraw-Hill; 2002. p. 93-113.

- Online book or Website

  Foley KM, Gelband H, editors. Improving palliative care for cancer [Internet]. National Academy Press; 2001 [cited 2002 Jul 9]. Available from: https://www.nap.edu/catalog/10149/improving-palliative-care-for-cancer

Tables

- The tables should start on a separate page. The tables should be numbered using Arabic numerals in the order in which they are cited in the text.
- The title of the table should be not sentences, but phrases or clauses, without periods.
- Footnotes should be indicated by *, †, ‡, §, ‖, ¶, **, ††, ‡‡, etc. Abbreviations should be defined in a footnote below each table.
- Written permission from the prior publisher should be obtained for the use of all previously published tables and copies of the permission letter should be submitted.
- The statistical significance of observed differences in the data should be indicated by the appropriate statistical analysis.

Figure Legends

- The figure legends should start on a separate page. Legends should be numbered in the order in which they are cited, using Arabic numerals.
- In case of the use of previously published figures, the original source must be revealed in the figure legend.

Figures

- Multiple figures mentioned in the text should be described as follows, e.g., Figures 1, 3.
- Labels/arrows should be of professional quality.
- All names and all other identifiers of the patient, authors, and authors' institutions should be removed from the figures.
- Color figures should be in RGB color mode and line drawings should be black on a white background.
- Written permission from the prior publisher should be obtained for the use of all previously published illustrations and copies of the permission letter should be submitted.

Video Clips

- Video clips can be submitted for placement on the journal website. All videos are subject to peer review and can be uploaded as supplementary materials.
- A video file submitted for consideration for publication should be in complete and final format and at as high a resolution as possible. Any editing of the video will be the responsibility of the author.
- *Headache and Pain Research* recommends Quicktime, AVI, MPEG, MP4, or RealMedia file formats of less than 5 minutes duration.
- A legend to accompany the video should be double-spaced in a separate file.
- All copyrights for video files after acceptance of the main article are automatically transferred to *Headache and Pain Research*.

Supplementary Data

- Supplementary data: If there are complementary materials that help the understanding of readers or if there is a large amount of data, these may be used as supplementary data. Supplementary data should be as concise as possible and must be related to the main conclusion of the paper. Supplementary data can include electronic files of high resolution images, background datasets, video materials, animations, and more. Supplementary data will be published online alongside the electronic version of the article. Video data files can be submitted in the same way as a figure or table by referring to the video or animation content. Since video and animation cannot be embedded in the print version, authors have to provide text for both the electronic and the print version for the portions of the article that refer to this content.

2.3.2. Review Article

- A review is generally published as a commissioned paper at the request of the editor(s).
- Review articles contain an Abstract, Introduction, Main text, and Summary (or Conclusion) followed by references, tables, and figure legends.
- A review article is a comprehensive scholarly review on a specific topic. It is not an exhibit of a series of cases.
- Neither new information nor personal opinions are to be included.
- An introduction that explains the scope of the paper is required, and headings should be used appropriately to separate and organize the text.
- Please send us a Presubmission Inquiry before writing a review article. All review articles undergo the same review process as other types of articles prior to acceptance. Reviews have no restrictions on word count or the number of figures and tables. However, authors should eliminate re-

dundancy, emphasize the central message, and provide only the data necessary to convey that message. The approximate length should be less than 5,000 words. There should be an unstructured abstract equal to or less than 250 words. References should not exceed 200 references.
- The most recent Review articles published in *Headache and Pain Research* should be consulted for further details on formatting.

2.3.3. Case Reports

- Case reports will be published only in exceptional circumstances, if they illustrate a rare occurrence of clinical importance. These manuscripts should be organized in the following sequence: title page, abstract and keywords, introduction, case report(s), discussion, acknowledgments, references, tables, figure legends, and figures. Case reports are limited to 2,000 words (excluding the abstract, references, tables, and legends), and references should not exceed 30. A maximum of 5 figures or tables are allowed.

2.3.4. Letter to the Editor

- Constructive criticism of a specific thesis published by *Headache and Pain Research* is welcome.
- Letters to the editor may be in response to a published article or a short, free-standing piece expressing an opinion. If the letters to the editor is in response to a published article, the Editor-in-Chief may choose to invite the article's authors to write a reply. No abstraction is required. The letter should be 1,000 words or less (excluding references and figure legends) with a maximum of 10 references. A maximum of 2 figures including tables is allowed.

2.3.5. Editorials

- Editorials are submitted or invited by the editor and should be commentaries on articles in the recent issues. Editorial topics could include active areas of research, fresh insights, and debates in all fields considered to be of interest to *Headache and Pain Research* readers. Editorials should not exceed 1,000 words, excluding references, tables, and figures. References should not exceed 10. A maximum of 3 figures including tables is allowed.

2.3.6. Perspective

- A perspective is a report of the authors' viewpoint on a specific subject of interest to our readers as a commissioned paper at the request of the editor(s).
- Little or no new original information is included, and there is limited literature analysis. A perspective is a report of the authors' viewpoint on a specific subject of interest to our readers as a commissioned paper at the request of the editor(s).

Table 1. Specification for publication types

Type of article	Abstract (word)	Text (word)[a)]	Reference	Table & figure
Original article	Structured, 250	5,000	50	8
Review article	250	5,000	200	Not limited
Case report	250	2,000	30	5
Letter to the editor	Not required	1,000	10	2
Editorial	Not required	1,000	10	3
Perspective	Not required	1,500	10	3

[a)]Excluding the title page, abstract, references, tables, and legends.

REVIEW PROCESS AND MANUSCRIPT DECISION

- The submitted manuscript will first be evaluated at the editorial office regarding the completeness of the submitted materials and their suitability to *Headache and Pain Research*. Modifications/corrections may be requested from the authors at this stage before starting the peer review.
- Submitted manuscripts will generally be reviewed by the editors, as well as two peer reviewers who are experts in the submitted subject matter and the peer reviewers will make suggestions to the editor(s).
- Authors may suggest preferred and non-preferred reviewers during manuscript submission. However, the ultimate selection of the reviewers will be determined by the editor(s).
- The authors can monitor the progress of the manuscript throughout the review process at the submission site (https://submit.e-hpr.org).
- Submitted manuscripts will be rendered one of the following decisions:

Accept: The manuscript is accepted for publication.

Minor Revisions: A revision needs to be submitted within the due date. Otherwise, the manuscript will be treated as a new submission.

Major Revisions: A revision needs to be submitted within the due date. Otherwise, the manuscript will be treated as a new submission.

Reject, Resubmission allowed: The authors are allowed to resubmit their work. However, it is effective only when they are able to respond to the various reviewer comments and make substantial changes to the study. The resubmitted manuscript will be treated as a new submission.

Reject, No further consideration: The paper will no longer be considered for publication.

- The decision to accept a manuscript is not based solely on the scientific validity and originality of the study content; other factors are considered, including the extent and importance of new information in the paper as compared with that in other papers being considered, the Journal's need to represent a wide range of topics, and the overall suitability for *Headache and Pain Research*.
- Decision letters usually, but not always, convey all factors considered for a particular decision. Occasionally, the comments to the authors may appear to be inconsistent with the editorial decision, which takes into consideration reviewers' comments to the editor, as well as the additional factors listed above.
- If the author(s) believe that the journal has rejected their article in error, perhaps because the reviewers have misunderstood its scientific content, an appeal may be submitted by e-mail to the editorial office (office@e-hpr.org). However, appeals are ineffective in most cases and are discouraged.

ELECTRONIC SUBMISSION OF MANUSCRIPT

Online Submission

- All manuscripts should be submitted online via the journal's website (https://submit.e-hpr.org) by the corresponding author. Once you have logged into your account, the on-line system will lead you through the submission process in a step-by-step orderly process. Submission instructions are available at the website. All articles submitted to the journal must comply with these instructions. Failure to do so will result in the return of the manuscript and, possibly, in delayed publication.
- Author's checklist: You will be first requested to confirm the Author's Checklist. Before submitting the new manuscript, please ensure every point listed in the Author's Check- list has been addressed.
- Document forms: Before you log into the online submission system, it is helpful to prepare the following documents as you will be asked to upload them during the electronic submission process.
  - Author statement forms
  - Cover letter: A Cover Letter must indicate the address, telephone and fax numbers, and E-mail address of the corresponding author. The cover letter accompanying the manuscript must specify the type of manuscript and include statements on ethical issues and conflicts of interest, and complete contact information for the corresponding author. The cover letter should include the following statement: "All authors have read and approved the submitted manuscript, the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part, except as an abstract (if relevant)."
  - English proof-reading (non-obligatory): Although it is not an obligatory demand, authors may show that their manuscript has been edited through English proofreading

Submission of Revised Manuscript

- Revision should be submitted within the due date of the decision. Otherwise, the manuscript will be treated as a new submission.
- Please carefully read and follow the instructions written here and those included in the manuscript decision e-mail.
- To start the submission of a revised manuscript, log in at https://submit.e-hpr.org. Click the "Manuscripts in Revision" queue in the "My Manuscripts" area. Then, find the submission you wish to start the revision process for and click on the "Create Revision" link for that manuscript.
- To continue with a revised manuscript that has yet to be submitted, click on the "Revised Manuscripts in Draft" queue in the "My Manuscripts" area. Find the submission you wish to continue with and then click on the "Continue Submission" button.
- Please submit a point-by-point response to the editor/reviewer comments by directly pasting it in the box provided in "View and Response to Decision Letter" page as well as by uploading the same as a Microsoft Word document file (DOC/DOCX) on the "File Upload" page
- Any changes in the authorship should be reported to the editor in the cover letter.
- For file uploading, if you have updated a file, please delete the original version and upload the revised file. To designate the order in which your files appear, use the dropdowns in

the "order" column on the "File Upload" page.
- For a revision, we require two copies of the Main Document. Each should be a Microsoft Word document. The FIRST COPY should represent the final "clean" copy of the manuscript. The SECOND "annotated" COPY should have changes tracked using the track changes function in Microsoft Word with marginal memos indicating changes (e.g., E-1 indicates a response to comment #1 of the Editor; R2-3 indicates a response to comment #3 of Reviewer #2).

MANUSCRIPTS ACCEPTED FOR PUBLICATION

Final Version

After a paper has been accepted for publication, the names and affiliations of authors should be double-checked, and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All symbols must be defined in the figure caption. If references, tables, or figures are moved, added, or deleted during the revision process, renumber them to reflect such changes so that all tables, references, and figures are cited in numeric order.

Manuscript Corrections

Before publication, the manuscript editor will correct the manuscript such that it meets the standard publication format. The author(s) must respond within 48 hours when the manuscript editor contacts the author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

Proofs

The corresponding author will receive page proofs for final checking, which should be corrected and returned within 48 hours. The authors must carefully check proofs to see that all errors are corrected and queries from editors answered. Keep a copy for your records.

Errata and Corrigenda

To correct errors in published articles, the corresponding author should contact the journal's Editorial Office with a detailed description of the proposed correction. Corrections that profoundly affect the interpretation or conclusions of the article will be reviewed by the editors. Corrections will be published as corrigenda (corrections of author's errors) or errata (corrections of publisher's errors) in a later issue of the journal.

ARTICLE-PROCESSING CHARGE

There are no author submission fees or other publication-related charges. All cost for the publication process is supported by the Publisher. Korean Headache Society is a so-called platinum open access journal which does not charge author fees.

Author Checklist

Headache and Pain Research

☐ Submit manuscripts as DOC or DOCX files. Double space all parts of the manuscript.

☐ The structured abstract should be no more than 250 words, and the abstract of the original article should be organizied as follows: Purpose, Methods, Results, and Conclusion.

☐ Include institutional review board approval, informed consent, and/or animal care committee approval for an original article or case reports.

☐ The tables and figures should start on a separate pages after references

☐ Digital figures must be at least 600 dpi and a 9-18 cm in width and height. Use JPG/JPEG/TIF/TIFF.

☐ Video clips should be less than 5 minutes duration for each.

☐ References should be cited using superscript Arabic numerals (e.g., 1, 2,3, 4-6) and numbered in the order in which they are cited.

☐ For previously published materials, send written permission to reprint any figure or any other applicable permissions.

☐ Please include the following components in the title pages (“not applicable” is a possible answer):
Abbreviations, Acknowledgements, Author contributions, Availability of data and material, Ethic approval and consent to participate, Conflict of interest, Funding statement, and ORCID (all authors)

☐ Provide copies of any material for which there is overlap with your manuscript (see Originality and Duplicate Publication)

Copyright transfer agreement

Headache and Pain Research

Manuscript title: _____

I hereby certify that I agreed to submit the manuscript entitled as above to *Headache and Pain Research* with the following statements:

- This manuscript is original and there is no copyright problem, defamation and privacy intrusion. Any legal or ethical damage should not be directed to the The Korean Headache Society due to this manuscript.
- All authors contributed to this manuscript actually and intellectually and have responsibility equally to this manuscript.
- This manuscript was not published or considered for publication to any other scientific journals in the world. It will not be submitted again to other journals without permission from Editor of *Headache and Pain Research* if it is accepted for publication.
- Copyright of this manuscript shall be transferred to the The Korean Headache Society if it is published in *Headache and Pain Research*. It means that if any persons including authors want to use the contents of this manuscript, they should cite the source and can use it for educational and research purpose according to Creative Commons Attribution License.
- All authors have provided a signature for copyright transfer agreement on this manuscript.

Conflict of Interest Disclosure Statement

List any potential conflicts of interests of this manuscript (any financial support or benefits have been received by the author(s) that could affect the work reported in the article) or indicate "The author(s) declared no conflict of interest."

Name of the author(s)	Date	Signature

수마트립탄†+나프록센나트륨

하나로 더 강력하게![2,3]

수벡스정

† **SUMATRIPTAN**, SUMATRIPTAN SUCCINATE;
§ **NAPROXEN**, NAPROXEN SODIUM

REFERENCES 1. 의약품안전나라, 의약품등 정보검색(검색어: 수벡스정). Available at https://nedrug.mfds.go.kr/searchDrug. Accessed on 29 of Jul, 2024, **2.** 대한두통학회, 편두통 진료지침 제2판, 2009 Nov, Available from: https://www.headache.or.kr/bbs/board.php?bo_table=3_5_1_1&wr_id=1, **3.** Brandes JL *et al.* Sumatriptan–naproxen for acute treatment of migraine: a randomized trial. *JAMA.* 2007 Apr 4;297(13):1443–54.

수벡스정 제품요약정보

[제품명] : 수벡스정 **[원료약품 및 그 분량]** 이 약 1정 중 유효성분: 수마트립탄숙신산염•119mg (수마트립탄으로서 85mg), 나프록센나트륨•500mg **[효능·효과]** 18세 이상의 성인 환자에서 전조증상을 수반하거나 수반하지 않는 편두통의 급성 치료 **[용법용량]** 이 약은 쪼개거나 씹거나 또는 부수지 말고 물과 함께 그대로 삼켜서 복용한다. 이 약은 편두통 예방 목적으로는 복용하지 않는다. ○ 성인 : 이 약의 권장 복용량은 1일 1정(수마트립탄 85mg/나프록센나트륨500mg)이다. 24시간 동안 최대 권장 용량은 2정을 초과해서는 안된다. 이 때, 투여 간격은 최소 2시간 간격을 두고 복용해야 한다. 최초 1정 투여 후 재투여에 대한 효과는 체계적으로 평가되지 않았다. 초기 투여가 효과가 없는 경우 재투여에 대한 효과는 확립되지 않았다. 30일 동안 평균 5회 이상의 편두통에 대한 이 약의 안전성은 확립되지 않았다. 이 약은 수마트립탄숙신산염의 최소 유효용량보다 높은 용량을 포함하고 있으므로 환자별로 높은 용량의 수마트립탄에 대한 유익성과 더 높은 이상반응의 위험성을 고려하여 이 약의 사용하여야 한다. 개별 환자 치료목적에 맞게 최소 유효용량을 최단기간 동안 사용해야 한다. ○ 신 장애 환자 : 이 약은 신부전 환자와 중증의 신 장애(크레아티닌 청소율 < 30 mL/min) 환자에게 투여해서는 안된다. 이 약은 경증~중등증의 신 장애 환자에서의 투여는 권장되지 않는다. ○ 간 장애 환자 : 이 약은 중등도~중증(Child-Pugh B and C) 간 장애 환자에게 투여해서는 안된다. 이 약은 경증의 간장애 환자에서의 투여는 권장되지 않는다. **[사용상의 주의사항]** 1. 다음 환자에는 투여하지 말 것 : 1) 수마트립탄, 나프록센 및 이 약의 구성성분에 과민증이 있는 환자 2) 설폰아미드에 과민반응 병력이 있는 환자(중략) 3) 아스피린이나 기타 비스테로이드성 소염진통제의 투여에 의하여 천식, 비염, 코의 용종, 두드러기, 알레르기 반응 또는 그 병력이 있는 환자 (중략) 4) 허혈성 관상동맥질환(중략), 심판막질환, 부정맥(특히 빈맥)의 중상, 징후 또는 그 병력이 있는 환자 또는 프린즈메탈 협심증을 포함한 관상동맥연축 병력이 있는 환자 5) 점재적인 심혈관 질환 환자(중략) 6) 관상동맥 우회로술(CABG)을 받기 전후의 환자 7) Wolff-Parkinson-White 증후군 또는 기타 심장 부전도 경로 장애가 있는 환자 8) 조절되지 않는 고혈압 환자, 중등도 또는 중증 고혈압 환자 9) 심한 심기능부전 환자 10) 뇌혈관성 우발증상(CVA), 뇌출중, 일시적인 허혈성 발작(TIA) 병력이 있는 환자 11) 편마비, 경련, 눈근육 경련 및 마비, 시각 장애를 동반한 편두통 또는 뇌저성 편두통 병력이 있는 환자 12) 말초혈관 질환 환자 13) 허혈성 장 질환, 염증성 장 질환 환자 14) 활동성 소화성 궤양, 활동성 장출혈 환자 15) 뇌혈관 출혈, 기타 출혈 질환 또는 심한 혈액이상 환자 16) 중등증 또는 중증 간장애 환자 17) 중증 신장애 환자 18) 고칼륨혈증 환자 19) 임부 또는 임신하고 있을 가능성이 있는 여성, 수유부 20) 18세 미만의 소아 및 청소년 21) 에르고티민 및 그 유도체 함유제제(methysergide 포함) 또는 다른 트립탄, 5-HT1 수용체 효능제를 복용하는 환자 22) MAO 억제제를 투여 중이거나 투여 중단 후 2주 이내의 환자, 선택성 5-HT 재흡수 억제제, 클로미프라민 또는 리튬을 투여 받고 있는 환자 **[제조자]** Halo Pharmaceutical Incorporated, 미국, 30 North Jefferson Road, Whippany, New Jersey 07981, USA **[소분제조자]** 에스케이케미칼(주) 충청북도 청주시 흥덕구 산단로 149 **[판매자]** 에스케이케미칼(주) 경기도 성남시 분당구 판교로 310

2023.10.30 개정

※처방하시기 전 제품설명서 전문을 참고하십시오. 최신 허가사항에 대한 정보는 '식품의약품안전처 의약품안전나라 (https://nedrug.mfds.go.kr/index)'에서 확인할 수 있습니다.

SVX-HA03-202408-02

SK 케미칼 Life Science Biz.

보건의료전문가용

공동판매원 환인제약

수입판매원 GSK

References 1. Naramig Prescribing Information. **2.** Ong JJY:Neurotherapeutics:2017;15:274–290. **3.** Ashcroft DM, Millson D. Pharmacoepidemiology and Drug Safey. 2004 Feb;13(2):73–82.

Integrated safety information[1]

1. 다음 환자에는 투여하지 말 것. 1) 이 약에 과민반응의 병력이 있는 환자 2) 허혈심장병 환자 3) 심근경색증 병력이 있는 환자 4) 프린츠메탈협심증/관상혈관경련 환자 5) 말초혈관병 또는 허혈심장병과 일치하는 증상/증후를 보이는 환자 6) 뇌혈관사고(CVA) 또는 일과성허혈발작(TIA)의 병력이 있는 환자 7) 조절되지 않는 고혈압 환자 8) 중증의 신장애(크레아티닌 청소율 <15 mL/분)또는 간장애(Child-Pugh grade C)환자 9) 다른 5-HT1 효능제 투여 후 24시간 이내인 환자 10) 편두통, 뇌기저 또는 안근마비 편두통 환자 11) 이 약은 유당을 함유하고 있으므로, 갈락토오스 불내성(galactose intolerance), Lapp 유당분해효소 결핍증(Lapp lactase deficiency) 또는 포도당-갈락토오스 흡수장애(glucose-galactose malabsorption) 등의 유전적인 문제가 있는 환자에게는 투여하면 안 된다. 2. 다음 환자에는 신중히 투여할 것. 설폰아미드에 과민반응을 나타내는 환자(이 약은 설폰아미드 성분을 함유하고 있다.) 3. 이상반응 이상반응은 기관 및 빈도별로 정리하였다. 발현빈도에 따라 매우 자주(≥ 1/10), 자주(≥ 1/100, <1/10), 때때로 (≥ 1/1,000, <1/100), 드물게(≥ 1/10,000, <1/1,000), 매우 드물게 (<1/10,000)로 구분하여 아래와 같이 나타내었다. 1) 임상시험에서 보고된 이상반응 이 약의 지르용량 임상시험에서 보고된 이상반응 빈도는 위약과 유사했다. (1) 신경계 : 통상 일시적인 자통이 자주 보고되었는데, 간혹 심한 경우도 있고 흉부 또는 인후부 등을 포함한 신체 일부분에 영향을 미칠 수 있다. 시각장애가 드물게 보고되었다. (2) 소화기계 : 구역과 구토가 자주 발생하였으나, 발생 빈도가 위약과 유사하거나 높았기 때문에 이 약과의 관련성은 명확하지 않다. (3)근골격계 : 때때로 일시적인 중압감이 보고되었는데, 간혹 심한 경우도 있고 흉부 또는 인후부 등을 포함한 신체 일부분에 영향을 미칠 수 있다. (4) 순환기계 : 서맥, 빈맥, 심계항진이 드물게 보고되었다. (5) 전신 및 투여부위 : 자주 피로, 권태, 이지럼, 졸음, 통증, 저림 및 열감, 때때로 압박감 또는 죄이는 듯한 느낌이 보고되었는데, 통상 일시적인 것으로 간혹 심한 경우도 있고 흉부 또는 인후부등을 포함한 신체 일부분에 영향을 미칠 수 있다.

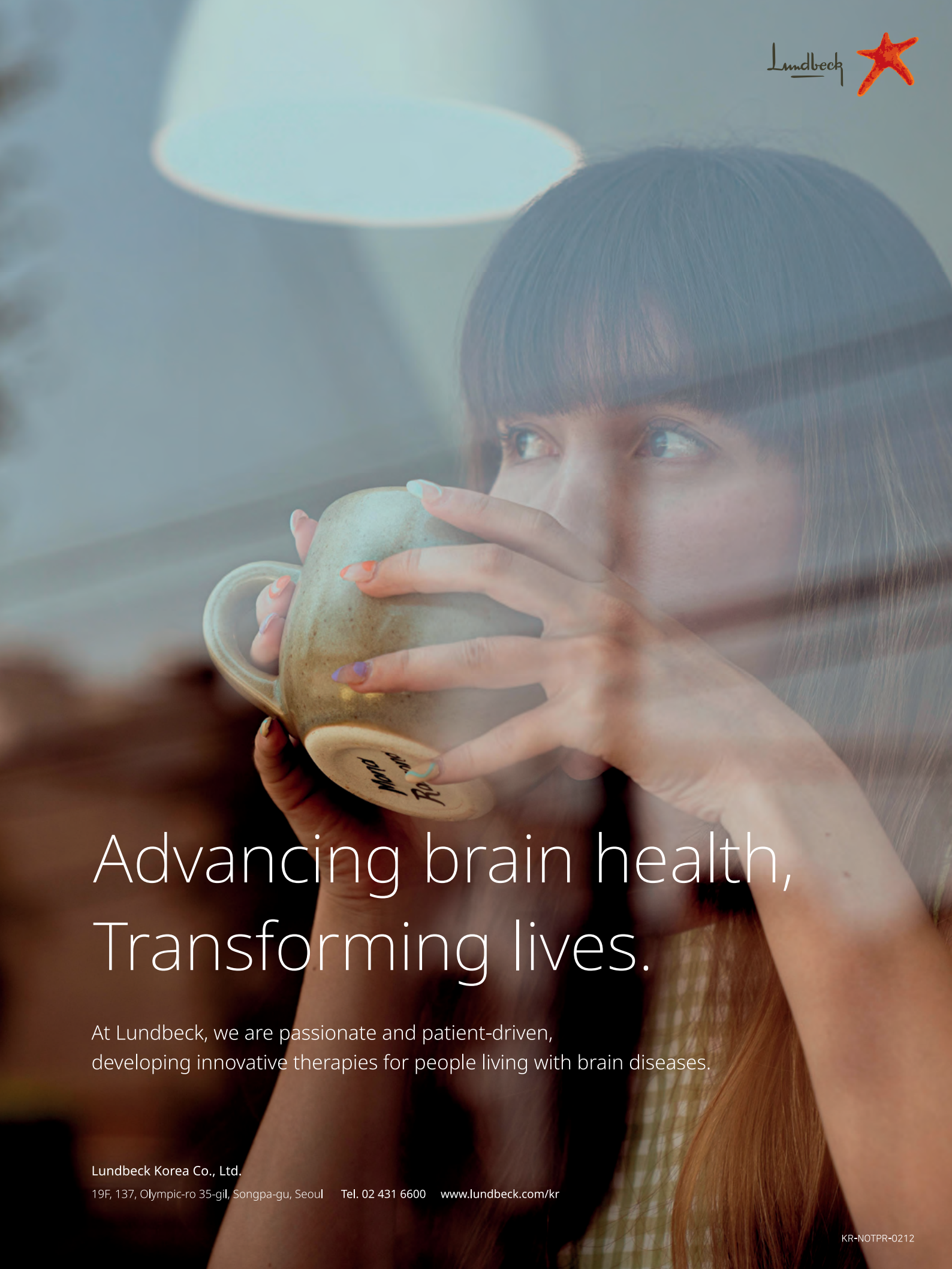
GSK제품 사용 중 발생한 이상사례(부작용)는 080-901-4100 또는 kr-medical.drug-safety@gsk.com으로 보고해 주시기 바랍니다. 최신 제품설명서 전문은 kr.gsk.com에서 확인하실 수 있습니다.

Product information
나라믹정2.5밀리그램(나라트립탄염산염)
처방하시기 전 QR 코드 또는 식품의약품안전처 의약품통합정보시스템 (https://nedrug.mfds.go.kr/)을 통해 상세제품정보를 참조하시기 바랍니다.

수입판매원 ㈜ 글락소스미스클라인, 서울특별시 용산구 한강대로 92, Tel. 080-901-4100
공동판매원 ㈜ 환인제약, 서울특별시 송파구 법원로 6길 11 환인빌딩 8-11층, Tel. 02-405-3000

PM-KR-NRT-ADVR-230001
Date of preparation: Nov 2023

NARAMIG (naratriptan)



Advancing brain health, Transforming lives.

At Lundbeck, we are passionate and patient-driven,
developing innovative therapies for people living with brain diseases.

Lundbeck Korea Co., Ltd.
19F, 137, Olympic-ro 35-gil, Songpa-gu, Seoul Tel. 02 431 6600 www.lundbeck.com/kr

KR-NOTPR-0212

JW 중외제약

효과를 높여보세요

당뇨병 걱정없이, 약효까지 강력하게!

강력한 이상지질혈증 솔루션

리바로젯®

효과성
- 복용 후 50% 이상 LDL-C 감소효과 입증 [1)]
- 저·중등위험군은 물론, 고위험군 이상으로 넓어진 치료범위 [2)]

안전성
- 당뇨병 안전성을 공인 받은 유일한 스타틴
- 32개국 당뇨병 안전성 공인 [3)]

1), 2) 리바로젯 3상 허가임상 결과 3) 32개 국가 현황 •유럽(13개국): 영국, 독일, 프랑스, 스페인, 이탈리아, 핀란드, 네덜란드, 스웨덴, 오스트리아, 아일랜드, 포르투갈, 그리스, 노르웨이 •동유럽(5개국): 러시아, 폴란드, 우크라이나, 조지아, 아르메니아 •동아시아(5개국): 싱가포르, 대만, 인도네시아, 말레이시아, 카자흐스탄 •중동(8개국): 사우디아라비아, UAE, 쿠웨이트, 카타르, 요르단, 오만, 레바논, 바레인 •아프리카(1개국): 모로코

전문의약품 | 의료전문가용 ILDONG

Sermion®

Nicergoline 5mg,10mg, 30mg

뇌경색 후유증에는

사미온®정 5,10

Nicergoline 5mg,10mg

치매증후군의
일차적 치료에는

사미온®정 30

Nicergoline 30mg

사미온정 5,10mg (Nicergoline 5mg,10mg)	[효능·효과] 뇌경색 후유증에 수반되는 만성뇌순환장애에 의한 의욕저하의 개선; 노인 동맥경화성 두통; 고혈압의 보조요법 [용법·용량] (성인) 니세르골린으로서 1회 5~10mg을 1일 2~3회 식전에 경구투여한다. 증상에 따라 적절히 증감한다.
사미온정 30mg (Nicergoline 30mg)	[효능·효과] 일차성 퇴행성 혈관치매 및 복합성치매와 관련된 다음 치매증후군의 일차적 치료 : 기억력 손상, 집중력장애, 판단력장애, 적극성 부족 [용법·용량] (성인) 니세르골린으로서 1일 1회 30mg을 식전에 경구투여한다. 이 용량에서 원하는 효과가 나타나지 않을 경우 60mg까지 증량할 수 있다. 증상이 호전 된 후 감량이 가능하다. 신장기능에 이상이 있는 환자의 경우 (혈청 creatinine >175μmol/L) (2mg/dL)는 감량하여 투여한다.

※ 자세한 사항은 제품설명서 전문 또는 식약처 의약품안전나라 홈페이지(http://nedrug.mfds.go.kr)를 참조하십시오.

Ref. 국내 식약처 허가사항 기준 (2023.08)

SER2308A1-2508
ID.2308