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More migraine-free days with only 4 injection days per year[1,2]

Reference 1. 의약품통합정보시스템 (http:\\nedrug.mfds.go.kr) 아조비 제품정보 **2.** Goadsby PJ, *et al. Neurology* 2020;95:e2487-2499

아조비프리필드시린지주(프레마네주맙, 유전자재조합) 아조비오토인젝터주(프레마네주맙, 유전자재조합) 전문의약품

[유효성분] 1프리필드시린지/1오토인젝터(1.5 밀리리터) 중 프레마네주맙(별규) 225밀리그램 **[효능효과]** 성인에서의 편두통의 예방 **[용법용량]** 이 약은 1회 225mg을 1개월 간격 또는 1회 675mg(225mg 3회 연속)을 3개월 간격으로 피하 주사한다. 투여간격을 변경할 경우 다음 예정일부터 새로운 투여 일정으로 투여한다. 이 약의 투여를 잊은 경우 가능한 한 빨리 투여한다. 이후 최종 투여 일자를 기준으로 이 약의 투여 일정을 정할 수 있다. **[수입자]** (하한독테바, 서울시 강남구 테헤란로 132 **자세한 품목허가 사항은 식품의약품안전처 의약품통합정보시스템 (http://nedrug.mfds.go.kr) 또는 제품의 첨부문서를 확인하여 주시기 바랍니다.** ☎소비자 상담전화(02-527-5506)

AJO-KR-00388 2212104

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, 최종 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. 중대하게나 중증의 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, 이용 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 선종히 투여할 것임 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 혈청 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

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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 headache and pain such as dizziness, psychological, and cognitive problems, and *Temporomadibular 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.

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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
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Tel: +82-2-6966-4930 Fax: +82-2-6966-4945 E-mail: support@m2-pi.com

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Headache and Pain Research

Toward Precision Migraine Care: Genetics, Symptoms, and Big-Data-Driven Approaches

Soo-Jin Cho

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

Migraine is an extremely common disease affecting approximately one billion people worldwide. Migraine-specific preventive treatments such as calcitonin gene-related peptide (CGRP) monoclonal antibodies, CGRP receptor antagonists, and the established botulinum toxin A therapy are now given higher priority than conventional treatments. However, delays in diagnosis and treatment remain substantial.[1] A deeper understanding of migraine is essential to improving patients' quality of life. The latest issue features in-depth research addressing multiple aspects of migraine.

One notable article is the systematic review "Genetic architecture of migraine: from broad insights to East Asian perspectives" by Kim and Chu.[2] According to this study, the estimated heritability of migraine ranges from 30% to 60%. This spectrum includes rare monogenic forms (*CACNA1A*, *ATP1A2*, *SCN1A*, *PRRT2*, *NOTCH3*, and *GLUT1*) as well as common polygenic migraine. Up to 181 migraine loci have been identified through genome-wide association studies. The molecular mechanisms underlying migraine pathogenesis may differ among ancestries. Genetic factors play a crucial role in migraine development, comparable in significance to hormonal influences.

As the saying goes, "if you don't suspect it, you won't find it." Therefore, recognizing migraine-associated symptoms is essential, particularly when evaluating patients presenting with dizziness. A narrative review of vestibular migraine estimated its annual prevalence at 1%–3%.[3] For acute management, triptans may be considered in selected cases of vestibular migraine despite previous failed trials. A systematic review found valproic acid and flunarizine to be effective, while CGRP monoclonal antibodies have shown promising results in certain trials.

Additionally, what about prodromal symptoms? One study reported that 74.7% of migraineurs experienced at least one premonitory symptom.[4] The most common were neck stiffness, followed by photophobia, fatigue, and phonophobia. These symptoms were often associated with cognitive impairment.

What further steps are needed for big data-based migraine research in the AI era to achieve valid conclusions? The article "Validity of migraine diagnoses in Korean National Health Insurance claims data" illustrates this potential. A retrospective review of the electronic medical records of 500 patients revealed that the positive predictive value (PPV) for a single claim was 74%. Accuracy increased markedly with three or more claims (PPV: 81.14%), particularly when combined with medication prescriptions (PPV: 94.96%; specificity: 85.37%).[5]

Precision medicine, incorporating machine learning and big data, may enable the prediction of individual treatment responses. For instance, beta blockers may be more effective in thin patients, whereas topiramate may be more effective in overweight individuals.[6] A multifaceted,

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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

patient-tailored approach to migraine research, as emphasized in *Headache and Pain Research*, may open new horizons for both clinicians and investigators.

AVAILABILITY OF DATA AND MATERIAL

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

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

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

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Review Article

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Headache and Pain Research

A Practical Approach to Headache in Moyamoya Disease

Mi-Yeon Eun[1,2], Jin-Man Jung[3], Jay Chol Choi[4]

[1]Department of Neurology, School of Medicine, Kyungpook National University, Daegu, Republic of Korea
[2]Department of Neurology, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea
[3]Department of Neurology, Korea University Ansan Hospital, Ansan, Republic of Korea
[4]Department of Neurology, Jeju National University Hospital, Jeju National University College of Medicine, Jeju, Republic of Korea

Moyamoya disease (MMD) is a progressive steno-occlusive cerebrovascular disorder of the intracranial internal carotid arteries characterized by fragile collateral vessel formation. Although ischemic and hemorrhagic strokes are the most widely recognized manifestations of MMD, headaches are common, often disabling, and remain underacknowledged. Epidemiological studies report headache in 17%–85% of MMD patients, with particularly high rates among pediatric patients. Clinically, headache phenotypes are diverse and include migraine-like headaches with or without aura, tension-type, cluster, and hemiplegic variants. These presentations often overlap with primary headache disorders, complicating the diagnosis and sometimes delaying the recognition of underlying MMD. The pathophysiology of MMD-related headaches is multifactorial, involving vascular stenosis, abnormal collateral circulation, altered hemodynamics, and neurogenic inflammation. Chronic hypoperfusion may lower the threshold for cortical spreading depression, contributing to migraine-like or aura-associated symptoms. Surgical revascularization has been reported to alleviate headaches in both pediatric and adult patients, but persistent or new headaches may occur postoperatively, and long-term outcomes remain inconsistent. Management often involves general analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs, but vasoconstrictive agents (e.g., triptans and ergotamines) should be avoided. Lasmiditan, a non-vasoconstrictive 5-HT1F agonist, may represent a safer option for acute treatment, while the efficacy of other pharmacological agents remains unclear due to limited evidence. In conclusion, headaches in MMD are not only a frequent source of disability but also a potential clinical marker of disease activity. Wider recognition of their epidemiology, phenotypes, and mechanisms may improve the diagnosis, guide individualized treatment, and ultimately enhance quality of life for patients.

Keywords: Cerebral revascularization, Headache, Migraine disorders, Moyamoya disease

INTRODUCTION

Moyamoya disease (MMD) is a rare, progressive cerebrovascular condition characterized by chronic stenosis or occlusion of the intracranial internal carotid arteries and the subsequent development of compensatory collateral vessels, creating a distinctive "puff of smoke" appearance on angiography.[1] Recent advances in genetics have shed new light on the pathogenesis of MMD. The *RNF213* gene, particularly the p.R4810K variant, has been identified as

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Correspondence: Jay Chol Choi, M.D., Ph.D.
Department of Neurology, Jeju National University College of Medicine, 15 Aran 13-gil, Jeju 63241, Republic of Korea
Tel: +82-64-754-8160, Fax: +82-64-717-1131, E-mail: jaychoi@jejunu.ac.kr

the major susceptibility gene in East Asian populations, with carriers showing a markedly increased risk of MMD development.[2] This variant is thought to affect vascular remodeling and angiogenesis, thereby predisposing to steno-occlusive changes of the intracranial arteries. In addition to *RNF213*, other genes such as *GUCY1A3* and *ACTA2* have been implicated in Moyamoya syndromes. Variants in *GUCY1A3*, which encodes a subunit of soluble guanylate cyclase, have been reported in families with Moyamoya angiopathy, while *ACTA2* variants, associated with vascular smooth muscle dysfunction, have been described in syndromic cases with aortic disease and cerebral arteriopathy.[3,4] Together, these discoveries not only enhance our understanding of disease mechanisms but may also inform diagnostic strategies, risk stratification, and future targeted therapies.

The clinical manifestations of MMD are diverse, with ischemic strokes and transient ischemic attacks (TIAs) being the most recognized symptoms. However, headaches represent a significant and often overlooked aspect of MMD and they can present with a wide spectrum of phenotypes, including migraine (with or without aura), tension-type headaches, and cluster headaches.[5,6]

These headaches frequently mimic primary headache disorders, complicating diagnosis and potentially delaying timely intervention. Beyond their symptomatic burden, headaches in MMD may signify underlying cerebral hypoperfusion or hemodynamic instability, underscoring their clinical importance. The pathophysiology of headaches in MMD involves complex interactions between vascular stenosis, neurogenic inflammation, and altered hemodynamics, which contribute to the diverse headache presentations observed in MMD.[5,6] This review aims to provide a comprehensive understanding of headaches in MMD by synthesizing current knowledge on their epidemiology, clinical characteristics, pathophysiology, and management strategies. By doing so, it seeks to offer practical insights for optimizing diagnosis and treatment, ultimately improving outcomes for patients with MMD.

EPIDEMIOLOGY OF HEADACHES IN MOYAMOYA DISEASE

Headaches constitute a prevalent yet frequently overlooked manifestation among individuals diagnosed with MMD. This narrative review synthesizes current evidence on headaches in MMD based on literature retrieved from major databases including PubMed and EMBASE. For epidemiological data (Table 1),[7-27] we included observational studies with sufficient sample size and clinical detail, while for clinical characteristics (Table 2),[5,28-37] representative case reports and case series were selected to illustrate the diversity of headache manifestations in MMD. A review of multiple observational studies indicates that the reported incidence of headache among patients with MMD ranges from 17% to 85%, with most studies documenting prevalence rates between 30% and 60%.[7-11] The substantial variability of headache prevalence is likely attributable to disparities in the demographic characteristics of study cohorts, research methodologies, and the diagnostic criteria utilized in various investigations (Table 1).

Although MMD shows a markedly higher prevalence in East Asian populations compared with Western cohorts, headache manifestations appear to be less strongly influenced by ethnicity. In Japan, reported headache prevalence ranges from 21% to 85%,[7,10,12-15] whereas studies from Korea indicate prevalence rates between 22% and 38%.[8,9,16] In American and European populations, the occurrence is lower than in Asian groups; however, headaches remain a notable symptom, particularly among pediatric patients (17% to 67%).[11,17-20]

MMD demonstrates a bimodal age distribution, with incidence peaks during childhood (the first decade of life) and adulthood (around 40 years). Headache is a frequently reported symptom across all age groups, though its prevalence and clinical significance may vary by age. In pediatric patients, headache is often the second most frequent symptom after motor deficits,[9,13] with prevalence ranging from 22% to 85% depending on study design, diagnostic criteria, and surgical status.[7-9,13,14,19,20] In adults, reported headache prevalence ranges from 17% to 67%.[11,15,17,21] While headache has been considered somewhat more common in pediatric MMD than in adults, the evidence for this remains mixed and inconsistent. Several factors may influence these reported differences, including variations in study methodology, differences in headache assessment and definition, and potential age-related differences in symptom reporting. Additionally, the higher frequency of revascularization surgery in pediatric populations may contribute to postoperative headaches, poten-

Table 1. Epidemiology and characteristics of headache associated with Moyamoya disease

Author (year)	Country	Study design	Total patients (n)	Age (yr)	Study population	Headache, n (%)	Migraine, n (%)	Migraine with aura, n (%)	Tension-type, n (%)	Other headache type, n (%)	Headache severity
Matsushima et al. (1990)[13]	Japan	Retrospective	81	10.4	Pediatric	22 (27.2)	N/A	N/A	N/A	N/A	N/A
Yu et al. (1991)[16]	Korea	Retrospective	38	6.3, 36.8†	Both	10 (26.3)	N/A	N/A	N/A	N/A	N/A
Battistella and Carollo (1997)[24]	Italy	Retrospective	34	13.5	Both	7 (20.6)	7 (100)	N/A	0	0	N/A
Seol et al. (2005)[8]	Korea	Retrospective	204	7	Pediatric	44 (21.6)	N/A	N/A	N/A	Morning HA 14 (31.8)	N/A
Kim et al. (2010)[9]	Korea	Retrospective	410	7.3	Pediatric	134 (32.7)	N/A	N/A	N/A	N/A	Severe headache
Okada et al. (2012)[12]	Japan	Retrospective	117	33	Both	25 (21.4)	N/A	N/A	N/A	N/A	Grade 1* 4 (16.0), Grade 2 13 (52.0), Grade 3 8/25 (32.0)
Hoshino et al. (2012)[25]	Japan	Retrospective	941	N/A	Both	56 (6.0)	N/A	N/A	N/A	N/A	N/A
Kawabori et al. (2013)[10]	Japan	Retrospective	29	10	Pediatric	11 (37.9)	N/A	N/A	N/A	N/A	Severe
Amlie-Lefond and Ellenbogen (2015)[20]	USA	Retrospective	54	7.5	Pediatric	28 (51.9)	6 (21.4)	1 (16.7%, hemiplegic migraine)	N/A	N/A	N/A
Bohara et al. (2015)[14]	Japan	Retrospective	10	8	Pediatric	8 (80.0)	N/A	N/A	N/A	N/A	N/A
Kraemer et al. (2017)[17]	Germany	Retrospective	55	37.6	Adult	37 (67.3)	17 (45.9)	10 (27.0)	10 (27.0)	Mixed 10 (27.0; migraine+TTHA)	NRS mean 3.2±1.3
Tho-Calvi et al. (2018)[19]	UK	Retrospective	88	5.1	Pediatric	50 (56.8)	N/A	N/A	N/A	N/A	N/A
Katano et al. (2019)[15]	Japan	Retrospective	68	49.8	Adult	33 (48.5)	N/A	N/A	N/A	N/A	Light 19 (57.6), moderate 12 (36.4), severe 3/33 (9.1)
Gao et al. (2020)[23]	China	Retrospective	119	34.4	Both	119 (100)	46 (38.7)	34 (73.9)	29 (24.4)	Mixed 44 (37.0; migraine+TTHA)	Severe 67 (56.3), VAS 5.9
Das et al. (2020)[22]	India	Retrospective	76	21.2	Both	28 (36.8)	N/A	N/A	N/A	N/A	N/A
Aihara et al. (2021)[7]	Japan	Retrospective	35	10.5	Pediatric	29/34 (85.3)	N/A	N/A	N/A	N/A	Moderate 9 (25.7), intractable 20 (57.1)
Sutton et al. (2022)[26]	USA	Retrospective	12	42	Adult	4 (33.3)	4 (100)	N/A	N/A	N/A	N/A
Das et al. (2022)[27]	India	Retrospective	6	23.7	Both	3 (50.0)	N/A	N/A	2 (33.3)	N/A	Mild to moderate
Teo et al. (2022)[18]	USA	Retrospective	769	32	Both	354 (46.0)	N/A	N/A	N/A	N/A	N/A
Vassilopoulou et al. (2023)[11]	Greece	Prospective	12	43.5	Adult	2 (16.7)	N/A	N/A	N/A	N/A	N/A
Gallego Moyano et al. (2024)[21]	Canada	Retrospective	59	47	Adult	41 (69.5)	N/A	N/A	N/A	N/A	VAS median 5

N/A, not available; Morning HA, morcing headache; TTHA, tension-type headache; NRS, Numerical Rating Scale; VAS, visual analogue scale.
*Grade 1, severe headache not requiring medication and/or rest; Grade 2, severe headache requiring medication (non-steroidal anti-inflammatory drugs and/or medication for migraine); and Grade 3, severe headache requiring medication and rest. †Mean age of pediatric and adult patients, respectively.

Table 2. Clinical characteristics and headache patterns in reported cases of MMD

Author (year)	Sex	Age (yr)	MMD	Headache type	Location	Severity	Combined symptoms	Neurological symptoms	Treatment	Outcome
Park-Matsumoto et al. (1999)[34]	Female	49	Bilateral	Migraine with aura	N/A	Severe	N/A	Cerebral infarction	N/A	Gradually improved, no recurrence
Aydin et al. (2003)[35]	Female	4	Bilateral	Migraine	N/A	Severe	Nausea, vomiting, photophobia	None	Nimodipine	Improved headache
Sewell et al. (2009)[28]	Male	34	Bilateral	Cluster headache	N/A	Severe	Rhinorrhea, lacrimation, ptosis	Left-sided RLS, left hand numbness	Revascularization	Improved after revascularization
Siddiqui et al. (2010)[29]	Female	10	Bilateral	Hemiplegic migraine	Left hemicranial	Moderate	Nausea, vomiting, photophobia	Left hemiparesis	NSAIDs, propranolol, prochlorperazine, nimodipine, aspirin	Gradually improved
Zach et al. (2010)[5]	Female	39	Bilateral	Migraine without aura, tension-type headache	Bilateral frontal	Moderate to severe	Photophobia, allodynia, nausea, light headedness	Tinnitus	NSAIDs, acetaminophen	N/A
Verdure et al. (2012)[31]	Female	13	Bilateral	Migraine without aura	N/A	N/A	N/A	TIA, left ACA territory infarction	N/A	N/A
Vuignier et al. (2014)[32]	Female	4	Right	N/A	Right frontal	N/A	Vomiting	Ischemic stroke	Revascularization	Improved headache after revascularization
Lee et al. (2014)[36]	Female	12	Bilateral	N/A	Bitemporal	Severe	Eyeball pain	TIA, dysarthria, right hemiparesis, numbness	NSAIDs, topiramate	Not effective
Diaz et al. (2014)[37]	Female	32	Left	Migraine	N/A	Intractable	Nausea, vomiting	N/A	Aspirin	N/A
Tozzi et al. (2015)[30]	Female	7	Bilateral	N/A	Frontal	N/A	N/A	Drop attacks, dysarthria, chorea, hemiparesis	Revascularization	Improved headache intensity and frequency (1 time/wk)
Khan et al. (2025)[33]	Male	65	Right	N/A	Right-sided	Severe	N/A	Left-sided numbness	Aspirin	Improved

MMD, Moyamoya disease; N/A, not available; RLS, left-to-right shunt; NSAIDs, non-steroidal anti-inflammatory drugs; TIA, transient ischemic attack; ACA, anterior cerebral artery.

tially affecting prevalence estimates. Interestingly, when examining patients with similar surgical exposure, Teo et al.[18] reported comparable headache rates in children (43%) and adults (47%), while studies by Das et al.[22] and Yu et al.[16] found higher headache prevalence in adults within the same cohort. These findings highlight the complexity of age-related headache patterns in MMD and underscore the need for additional well-designed prospective studies that account for surgical status, disease stage, and the use of standardized headache assessment tools to better clarify the true relationship between age and headache manifestations in this disease.

Gender differences in headache prevalence among patients with MMD have been less extensively studied and remain inconclusive. While some studies reported a higher prevalence of headache in males compared to females,[10,12] Katano et al.[15] found the opposite trend, with headaches more frequently reported in females (57%) than in males (32%). These conflicting results are noteworthy given the female predominance of MMD itself and the higher prevalence of primary headache disorders among females in the general population. Further investigation is needed to clarify these gender-specific patterns in MMD-associated headache.

Headache in MMD presents with three distinct temporal patterns: preceding MMD diagnosis, as an initial presenting symptom, and following diagnosis or revascularization surgery. Some patients experience recurrent headaches months to years prior to diagnosis, and the median interval from headache onset to MMD diagnosis is approximately 9.5 months (range, 0–192 months).[5] As an initial symptom, headache is reported in 7% to 33% of patients, particularly in pediatric cases.[9,13] Headache may also newly develop or persist after diagnosis, especially following revascularization surgery.[8,9,17,21] Among patients with preoperative headaches, 64%–100% report improvement following surgery, whereas 6%–16% of those without prior headache experience new-onset headaches postoperatively.[8-10,14,17,19,21] In line with this, the International Classification of Headache Disorders, 3rd edition (ICHD-3), formally recognizes "Headache attributed to Moyamoya disease" (code 6.8.2). This category applies to patients with a new or significantly changed headache in close temporal relation to MMD onset or progression, with radiological confirmation of the disease. These temporal patterns underscore the need to consider MMD in the differential diagnosis of new or refractory headaches, especially in younger patients, and highlight the importance of clinical history and neuroimaging in guiding timely diagnosis and tailored management.

CHARACTERISTICS OF HEADACHE IN MOYAMOYA DISEASE

The clinical features of headache in MMD are diverse and often resemble those of primary headache syndromes, but arise from distinct cerebrovascular mechanisms. Migraine-like presentations are particularly common, with several large observational studies reporting migraine prevalence ranging from 39% to 48% among MMD patients with headache.[17,23] A distinctive feature is the high prevalence of migrainous aura (27%–74%), with visual, sensory, motor, and speech disturbances reported. This is substantially higher than the 30% aura prevalence typically seen in primary migraine, suggesting that the underlying cerebrovascular pathology in MMD may facilitate cortical spreading depression and aura phenomena. Tension-type headaches affect approximately 25% of patients, while 8%–37% experience mixed headache patterns combining both migraine and tension-type features.[17,23] Cluster headache has been documented in rare cases, typically in male patients.[28] Hemiplegic migraine variants have also been reported in the literature, particularly in pediatric patients.[29]

The quality of pain in MMD-associated headaches varies widely. Case studies describe throbbing or pulsatile pain characteristic of migraine, as well as pressing or oppressive pain typical of tension-type headache (Table 2).[5,29,30] Occasionally, patients experience thunderclap headaches with sudden, severe onset, which may signal acute changes in cerebral hemodynamics or incipient ischemic events.[31]

The severity of headaches in MMD generally tends toward the moderate-to-severe range in case series.[5] Many observational studies that assessed headache prevalence used criteria emphasizing functional impairment, often classifying headaches as severe if they interfered with daily activities.[9,12,23] For instance, Aihara et al.[7] reported in a pediatric MMD cohort that 57% of patients experienced intractable headaches, while 26% reported moderate-intensity headaches, highlighting the significant burden of symptoms even in younger populations. These findings underscore the disabling nature of MMD-associated headache and its potential impact on quality of life, especially in cases resistant to conventional analgesic treatment.

The location of headache in MMD patients demonstrates considerable variability. Frontal and temporal regions are most commonly affected, with both unilateral and bilateral distributions frequently reported.[10,15,29,32] Importantly, headache laterality does not always consistently align with the side of vascular involvement, and the correspondence appears inconsistent across cases.[29] This suggests that pain generation in MMD likely reflects broader hemodynamic or neurogenic mechanisms rather than focal vascular stenosis alone. Duration patterns also vary widely, ranging from several hours to multiple days, with most cases reporting headache episodes lasting less than 24 hours.

Associated symptoms frequently accompany headaches in MMD, enhancing their similarity to primary headache disorders. Nausea and vomiting are common accompanying symptoms, reported in multiple observational and case studies.[8,21] Photophobia, phonophobia, and occasionally allodynia are also reported, further mimicking the symptom profile of primary migraine.[5,21] In patients with cluster-like presentations, ipsilateral autonomic features such as lacrimation, rhinorrhea, and ptosis may occur, though

these appear to be relatively rare.[28]

A distinctive feature of headache in MMD is its frequent association with neurological symptoms, either concurrent with headache episodes or as separate manifestations. In MMD patients with headache, TIAs, hemiparesis, dysarthria, numbness, and visual disturbances are commonly reported in association with headache episodes (Table 2).[28,29,31,33] This pattern of alternating or concurrent headache and focal neurological deficits is strongly suggestive of an underlying cerebrovascular disorder and should prompt consideration of MMD in the differential diagnosis, particularly in young patients without conventional vascular risk factors.

Provocation factors for headache in MMD offer insights into pathophysiological mechanisms. Physical exertion, stress, and straining effort are reported triggers in several cases.[5,30,31] Seol et al.[8] specifically demonstrated that hyperventilation triggered headache in four patients, three of whom also experienced TIAs, suggesting a shared hemodynamic mechanism involving vasoconstriction and reduced cerebral perfusion. Morning predominance of headache was reported in 31.8% of patients in the same study, potentially reflecting nocturnal hypercapnia or positional changes in cerebral perfusion.

The diagnostic challenge of headache in MMD lies in its phenotypic overlap with primary headache disorders. Several distinguishing features should raise suspicion for underlying MMD, including: (1) atypical age of onset (very young children or young adults without family history of migraine); (2) concurrent or alternating focal neurological deficits; (3) headache triggered by exertion or hyperventilation; (4) refractory headache unresponsive to conventional treatments; and (5) unusual aura phenomena, particularly prolonged or atypical aura symptoms. The presence of these features should prompt consideration of neurovascular imaging, even in patients with otherwise typical-appearing headache presentations (Figure 1).

PATHOPHYSIOLOGICAL MECHANISMS OF HEADACHES IN MOYAMOYA DISEASE

The underlying pathophysiological mechanisms of headaches in MMD remain poorly understood. These mechanisms are complex and involve both primary and secondary headaches. Several plausible mechanisms have been proposed.

First, nociceptors in cerebral arteries and the dura have been suggested as one of the culprits. MMD is a chronic, progressive steno-occlusive disease characterized by the development of compensatory collateral circulation, particularly involving vasodilation of cortical vessels and small

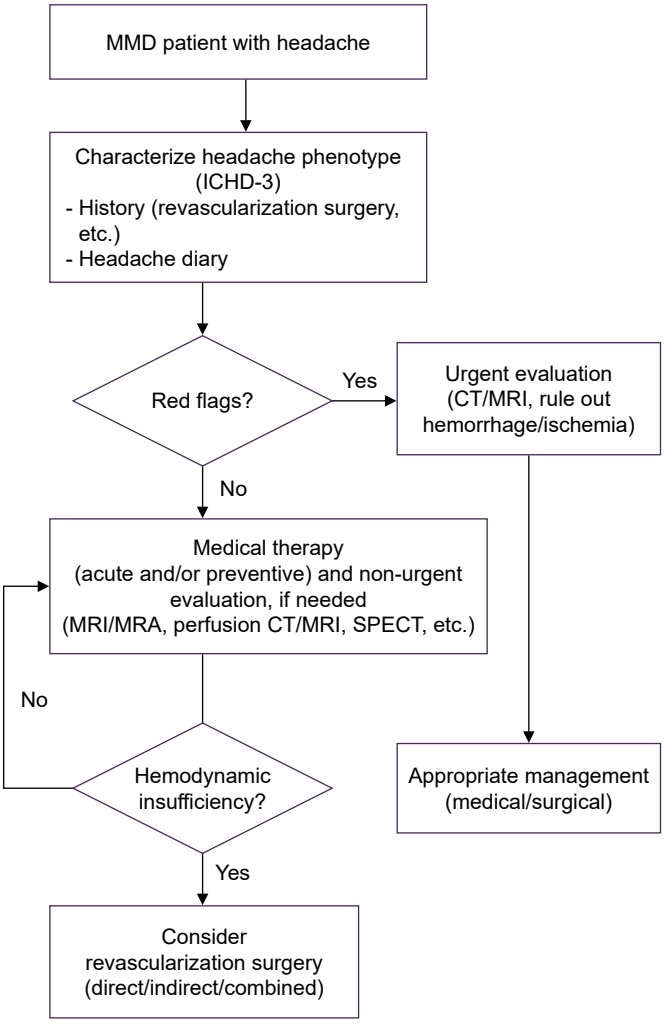

Figure 1. A practical approach to headache associated with Moyamoya disease (MMD). "Red flags" include the presence of sudden focal neurological deficits; the occurrence of thunderclap headache characterized by abrupt and severe pain; the presence of seizures or cognitive changes associated with headache; and new-onset or worsening headache.
ICHD-3, International Classification of Headache Disorders, 3rd edition; CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; SPECT, single-photon emission computed tomography.

perforators in the skull base. This vasodilation may stimulate dural nociceptors, especially through transdural or leptomeningeal collaterals, and perivascular nociceptors.[38] Additionally, cerebral aneurysms are observed in 3%–18% of MMD patients and may occur in major trunks of the circle of Willis or peripheral vessels, including the choroidal, lenticulostriate, meningeal, or moyamoya arteries.[39] Enlargement of these aneurysms may lead to activation of vascular nociceptors.

Second, neurogenic inflammation, a form of inflammation initiated by the activation of peripheral sensory nerve fibers (especially nociceptors), may contribute to headache in MMD.[40] Stimulation of dural nociceptors via dilated leptomeningeal collaterals could activate and sensitize the trigeminovascular system through the release of calcitonin gene-related peptide (CGRP), substance P, nitric oxide, and pituitary adenylate cyclase-activating polypeptide, resulting in neuroinflammatory responses such as mast cell degranulation, plasma protein extravasation, and vasodilation.[6,41-43] This mechanism shares features with the neuroinflammation underlying migraine pathophysiology.[5,17]

Third, chronic intracranial hypoperfusion and hypoxia may contribute to headaches, as cerebral hypoperfusion is known to lower the threshold for migraine and increase the risk of cortical spreading depression.[34,44] Migraine-like headaches are, in fact, the most commonly reported headache type in MMD. Cortical spreading depression triggered by chronic cerebral hypoperfusion may be associated with the high prevalence of migraine with aura in MMD.[17,45] Chronic ischemia leads to the overexpression of pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factor-α, as well as vascular endothelial growth factor, which can sensitize perivascular nerves.[6,46] Notably, revascularization aimed at improving ischemia and cerebrovascular reserve has been reported to reduce the intensity and frequency of preoperative headaches, regardless of the bypass type (direct or indirect) and age of onset.[10,13,21] However, most studies did not specify headache subtypes in detail. Conversely, headaches may also occur after revascularization surgery, often referred to as postoperative headaches. One study evaluating postoperative headaches following direct bypass surgery in adult MMD patients found that postoperative superficial temporal artery (STA) diameter and the rate of postoperative increase in STA diameter were significantly associated with postoperative headaches.[15] This suggests that STA dilation may be responsible, as the outer layer of the STA contains nociceptive nerve endings and sensory fibers derived from the trigeminal nerve.

Fourth, headaches—particularly in pediatric MMD patients—may result from platelet aggregation activity secondary to endothelial cell damage. In a study of 35 pediatric patients with ischemic-onset MMD, low-dose aspirin use was associated with an improvement in intractable headaches in 85% of patients within one month after revascularization surgery.[7]

Finally, it is important to consider that some patients may suffer from coincidental primary headaches such as migraine or tension-type headache, considering the high prevalence of primary headaches in the general population.

MANAGEMENT OF HEADACHES IN MOYAMOYA DISEASE

Migraine-like headaches, either alone or accompanied by tension-type headaches, are the most commonly reported headache types in MMD.[23] Treatment strategies for headaches in patients with MMD have not been standardized due to the lack of relevant studies. Although some approaches are derived from the management of migraine or tension-type headaches, they are mostly based on clinical experience and the underlying pathophysiological characteristics of MMD—chronic steno-occlusion with compensatory collateral formation, fragile vascular networks, and medication side effects.[47]

Medical management of headaches in MMD has not been systematically studied and the most appropriate and effective analgesics for MMD-related headaches remain unknown. From a safety standpoint, general pain relievers such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used, with vasoconstrictive drugs typically avoided. However, caution is needed when using NSAIDs due to their potential to increase bleeding risk.

Common migraine medications such as triptans (5-HT-1B/1D agonists) and dihydroergotamine should generally be avoided in MMD, particularly in cases with abundant leptomeningeal collaterals, due to their vasoconstrictive effects. Lasmiditan, a selective 5-HT1F receptor agonist

that inhibits neuropeptide release and pain transmission in the trigeminovascular system, may serve as a safer alternative for the abortive treatment of migraine-like headaches in MMD, as it does not induce vasoconstriction.[48,49] CGRP-targeted therapies, including monoclonal antibodies and CGRP antagonists, have recently emerged as a novel class of agents in migraine treatment. However, given that CGRP acts as a potent vasodilator,[50,51] these therapies may not be suitable for MMD patients, as they could inhibit essential compensatory vasodilation.

As mentioned earlier, low-dose aspirin may be more effective in pediatric MMD patients with intractable headaches than analgesics such as NSAIDs or acetaminophen.[7] In addition, a nationwide cohort study demonstrated that cilostazol use in patients with MMD was associated with improved survival compared with other antiplatelet agents, likely due to its combined antiplatelet, vasodilatory, and endothelial-protective effects.[52] Furthermore, a high-resolution MRI study showed that cilostazol was associated with favorable vessel wall changes and stabilization of disease progression in adult-onset MMD.[53] Although direct evidence on headache outcomes is lacking, these findings suggest that cilostazol may alleviate ischemia-related headaches by improving cerebral perfusion and modifying disease course, thus warranting further prospective studies. However, the efficacy of other antiplatelet agents or their combinations remains unclear due to a lack of relevant studies.

For migraine prevention, a range of pharmacological and non-pharmacological strategies can be considered in MMD, particularly when revascularization is not feasible or when headaches persist after surgery. Pharmacological preventives include antidepressants, anti-seizure medications, beta-blockers, calcium channel blockers, and botulinum toxin A.[54] In the context of MMD, however, beta-blockers and calcium channel blockers should be prescribed with caution because of their potential to worsen cerebral hypoperfusion. Among these, amitriptyline, topiramate, propranolol, and cyproheptadine are commonly used in pediatric migraine, whereas others, such as botulinum toxin A, are currently approved only for adult chronic migraine prophylaxis. Sodium valproate has also been reported in a pediatric MMD case to markedly reduce hemiplegic migraine–like attacks, highlighting its potential role as a preventive therapy, especially in patients with co-existing seizures.[55] Consistent with the Korean Headache Society guideline, valproate remains an established option for migraine prevention, although its safety profile requires careful consideration. Botulinum toxin A, while not specifically studied in MMD, is guideline-endorsed for chronic migraine prophylaxis in adults and may be considered in refractory MMD patients with chronic migraine–like headaches, given its lack of vasoconstrictive or hemodynamic effects. Non-pharmacological interventions- including regular sleep hygiene, dietary changes, adequate hydration, increasing physical activity, and behavior therapy-may be recommended as initial treatment and complement pharmacological therapies to both pediatric and adult MMD patients due to their high safety and tolerability.

Revascularization surgery, irrespective of the technique employed, has been reported to alleviate headaches in both pediatric and adult patients with MMD. Nevertheless, headaches may persist or newly emerge following surgery.[9,12] A recent study involving 119 Chinese MMD patients (80.6% underwent surgery; 19.4% received conservative treatment) assessed the impact of surgery on headache outcomes. While preoperative headaches improved in the surgical group, there was no significant difference between the surgical and conservative groups in terms of long-term effects on headache frequency and intensity over a 5-year follow-up.[23] These findings suggest that in MMD patients who undergo bypass surgery, the underlying mechanisms of postoperative headaches may be more complex and differ from the preoperative headache mechanisms discussed above. These include postoperative dynamic change of cerebral circulation, stimulation of dural trigeminal nociceptors and neurogenic inflammation following indirect or direct bypass, surgical trauma to intracranial structures caused by craniotomy, and aggravation of dilated collateral vessels in accordance with the disease progression.[6,8] Therefore, the primary goal of revascularization should remain the prevention of ischemic and hemorrhagic events rather than headache relief (Figure 1).

BROADER IMPLICATIONS, APPLICATIONS, AND CONCLUSIONS

Headache in MMD represents more than a comorbid symptom—it serves as a potential clinical indicator of hemodynamic compromise and cerebrovascular instability.

Recognizing the diverse and often migraine-like headache patterns associated with MMD may improve early detection, particularly in young or otherwise low-risk individuals. This review aims to provide a practical overview of headaches in MMD by synthesizing evidence on their epidemiology, clinical features, underlying mechanisms, and management strategies. Headache is one of the most frequent and disabling symptoms in MMD, particularly in pediatric patients, and can present with diverse phenotypes, including migraine-like, tension-type, and hemiplegic patterns. These overlapping features with primary headaches complicate diagnosis but may serve as an important clinical clue to underlying cerebrovascular disease.

Pathophysiological insights suggest contributions from chronic cerebral hypoperfusion, abnormal collateral circulation, and neurogenic inflammation, highlighting why MMD-related headaches are often severe and refractory to conventional therapies.

Treatment strategies remain empirical and individualized. While analgesics are used cautiously, vasoconstrictive agents such as triptans and ergotamines are generally avoided. Preventive therapies, including commonly used migraine medications, may be considered on a case-by-case basis, complemented by non-pharmacological approaches. Revascularization surgery can improve headaches in some patients, though long-term outcomes are inconsistent, and headache relief should not be the sole indication for surgery.

In conclusion, headaches in MMD are not only a source of disability but also a potential marker of disease activity. Greater awareness of their clinical spectrum and mechanisms can aid earlier recognition, guide more rational management, and improve quality of life for patients. Future studies should adopt prospective designs and standardized headache assessments to establish evidence-based guidelines for treatment.

AVAILABILITY OF DATA AND MATERIAL

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

AUTHOR CONTRIBUTIONS

Conceptualization: JCC; Writing–original draft: MYE, JMJ, JCC; Writing–review & editing: MYE, JMJ, JCC.

CONFLICT OF INTEREST

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

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Gepants for Migraine: An Update on Long-Term Outcomes and Safety Profiles

Soohyun Cho, Kimoon Chang

Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu, Republic of Korea

Abstract

Calcitonin gene-related peptide receptor antagonists, also referred to as gepants, represent a transformative advancement in migraine pharmacotherapy, providing both acute and preventive treatment options without the vasoconstrictive limitations of triptans. Since their initial approval in 2019, gepants have gained widespread clinical adoption, necessitating comprehensive evaluation of their long-term safety and efficacy. This review synthesizes current evidence on four calcitonin gene-related peptide receptor antagonists (rimegepant, atogepant, ubrogepant, and zavegepant) derived from pivotal trials, open-label extension studies, and real-world observational data. Rimegepant demonstrates sustained efficacy and minimal adverse events over 52 weeks, with no evidence of medication-overuse headaches or hepatotoxicity. Atogepant maintains progressive clinical benefits and favorable tolerability for up to 1 year, exhibiting low rates of treatment-emergent adverse events and discontinuation. Ubrogepant remains effective and well-tolerated during long-term intermittent use, with no clinically significant safety signals over extended exposure. Zavegepant, the first intranasal gepant, shows promising long-term tolerability, with the most frequently reported localized adverse event being transient dysgeusia. No consistent hepatic, cardiovascular, or serious systemic toxicity has emerged for any of the agents, and discontinuation rates due to adverse events remain consistently low. Current evidence supports gepants as safe and effective therapies for long-term migraine management, although ongoing surveillance and extended-duration studies remain essential to fully characterize their safety profile, particularly in high-risk populations and combination therapy scenarios. In conclusion, gepants offer a well-tolerated, non-vasoconstrictive alternative for migraine patients who require sustained treatment, representing a significant therapeutic advancement in migraine.

Keywords: Calcitonin gene-related peptide receptor antagonists, Longitudinal studies, Migraine disorders, Safety, Treatment outcome

INTRODUCTION

Migraine is a common, disabling neurologic disorder driven in part by activation of the trigeminovascular system and release of neuropeptides such as calcitonin gene-related peptide (CGRP).[1,2] CGRP is a critical mediator, which is released from trigeminal neurons during migraine attacks and potently dilates cranial blood vessels.[3] Elevated CGRP levels have been correlated with migraine pain, and infusion of CGRP can trigger migraine in susceptible individ-

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Correspondence: Soohyun Cho, M.D., Ph.D.
Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, 712 Dongil-ro, Uijeongbu 11749, Republic of Korea
Tel: +82-31-951-1000, Fax: +82-31-951-1093, E-mail: anttop@naver.com

uals.[4] These insights led to the development of CGRP-targeted therapies, notably the CGRP receptor antagonists (gepants).

Gepants are small-molecule compounds (molecular weight <1 kDa) that selectively antagonize CGRP receptors, thereby preventing CGRP from binding and triggering the pro-migraine signaling cascade.[5] These agents primarily inhibit CGRP signaling at peripheral sites outside the blood-brain barrier due to their minimal central nervous system penetration, effectively reducing neurogenic inflammation and pain transmission without inducing direct vasoconstriction.[5] This mechanism represents a critical therapeutic advantage over triptans: while triptans cause significant vasoconstriction of cranial and coronary vessels, gepants achieve antimigraine efficacy without compromising vascular function.[6] Although early first-generation gepants such as telcagepant demonstrated therapeutic promise, their development was discontinued due to hepatotoxicity concerns.[7] The subsequent development of second-generation gepants has successfully addressed these safety issues, establishing a new paradigm in migraine-specific pharmacotherapy.[7,8]

Four CGRP receptor antagonists have received regulatory approval since 2019, heralding a transformative era in migraine therapeutics. Ubrogepant and rimegepant were the pioneering oral gepants approved for acute migraine management, with ubrogepant gaining approval in late 2019 followed by rimegepant in 2020.[9-12] Both agents demonstrate rapid onset of pain relief while circumventing the cardiovascular contraindications that limit triptan use.[13] Atogepant represents a distinct therapeutic advance as the first oral gepant specifically developed for migraine prophylaxis. Initially approved in 2021 for preventive treatment of episodic migraine with once-daily dosing, its indication was subsequently expanded in 2023 to include chronic migraine prevention.[14,15] Zavegepant, classified as a third-generation gepant, introduced a novel delivery mechanism as the first intranasally administered CGRP antagonist, receiving approval in 2023 for acute migraine treatment.[16] The nasal spray formulation of zavegepant offers distinct clinical advantages through rapid mucosal absorption and provides a valuable therapeutic option for patients experiencing nausea or vomiting during migraine episodes, circumstances that often preclude effective oral medication administration.[16]

With the expanding clinical adoption of gepants, a growing number of patients are receiving long-term therapy, generating considerable interest and concern regarding the efficacy, safety, and potential adverse events associated with prolonged use. This review focuses specifically on the safety profiles of gepants and their long-term clinical outcomes in migraine management. Our objective is to provide clinicians with a comprehensive, up-to-date analysis of long-term safety data and therapeutic outcomes for gepants, thereby facilitating informed decision-making when considering these agents for migraine patients.

LONG-TERM OUTCOMES WITH GEPANTS

1. Rimegepant

Rimegepant demonstrated sustained efficacy over extended treatment periods when administered every other day for migraine prevention and/or as-needed for acute migraine management.[17] In a pivotal 52-week open-label study evaluating rimegepant for as-needed acute treatment, patients demonstrated a significant reduction in migraine frequency throughout the study period: monthly migraine days decreased from a baseline of 10.9 days to 8.9 days by week 52.[17] During the open-label study, long-term preventive and acute rimegepant treatment consistently reduced migraine frequency throughout the 52-week period, with patients experiencing a decrease from a baseline mean of 9.9 monthly migraine days to an average reduction of 6.2 days per month.[18] The proportion of patients achieving ≥50% reduction in mean moderate or severe monthly migraine days progressively increased from 63.6% during weeks 1–4 to 80.9% during weeks 49–52. Comparable improvements were observed for ≥75% reductions (increasing from 44.1% to 65.8%) and complete elimination of moderate to severe migraine days (increasing from 25.6% to 49.3%).[19] Throughout the 52-week treatment period, preventive and/or acute rimegepant therapy yielded significant improvements in quality of life, as evidenced by enhanced scores across improved EuroQol-5 Dimensions-3 Level utility values and multiple domains of the Migraine-Specific Quality of Life (MSQoL).[20] There was no evidence of medication-overuse headache development and migraine frequency remained stable or decreased despite some patients utilizing rimegepant on a near-dai-

ly basis.[21,22] In the long-term open-label extension study, rimegepant 75 mg taken as-needed up to once daily for acute migraine treatment showed that mean monthly tablet utilization remained stable or trended downward over 1 year of follow-up, decreasing from 7.9 tablets in weeks 4–8 to 7.3 tablets in weeks 48–52.[17] This contrasts markedly with the long-term use of triptans or analgesics in comparable populations, which frequently results in escalating headache frequency and medication-overuse headache development. The distinctive dual acute-preventive properties of rimegepant appear to be preserved with sustained use, representing a significant therapeutic advantage in migraine management. In contrast, Croop et al.[21] primarily focused on long-term safety assessments. The efficacy outcomes were restricted to patient-reported measures, including MSQoL, medication preference, patient satisfaction, and clinical global improvement relative to baseline, and did not provide detailed reporting on reductions in headache attack frequency.[21]

2. Atogepant

Atogepant is developed exclusively as a preventive treatment option for migraine.[23] The 52-week open-label trial of once-daily atogepant 60 mg demonstrated progressive and sustained efficacy in migraine prevention, with mean monthly migraine days reduction increasing from –3.8 during weeks 1–4 to –5.2 at weeks 49–52.[24] The proportion of participants achieving clinically meaningful response rates showed marked improvement over time: ≥50% monthly migraine days reduction increased from 60.4% early in treatment to 84.2% by study end, while ≥75% and 100% reduction rates similarly improved from 37.2% and 20.7% to 69.9% and 48.4%, respectively.[24] These findings demonstrate that atogepant provides not only immediate preventive benefits but also enhanced efficacy with continued long-term use, establishing its durability as a migraine-specific preventive therapy. Another positive outcome is sustained improvements in patient-reported outcomes, with MSQoL scores showing least-squares mean changes from baseline of 30.0 (95% confidence interval [95% CI], 28.2–31.9) at week 12, further improving to 34.7 (95% CI, 32.7–36.7) at week 52.[25] Significant improvements were also observed across other MSQoL domains, as well as in Activity Impairment, Productivity Impairment, and Headache Impact Test-6 total scores throughout the study period. These findings demonstrate that atogepant provides progressive and durable benefits in migraine-related quality of life and functional outcomes, with improvements maintained and enhanced over long-term treatment.[25] The sustained patient-reported outcome improvements complement the clinical efficacy data, supporting atogepant's role as an effective preventive therapy that meaningfully impacts patients' daily functioning and well-being.[24,25]

3. Ubrogepant

The 52-week extension study following the 12-week pivotal studies (ACHIEVE I and II trials)[26,27] demonstrated sustained therapeutic efficacy, with 2-hour pain freedom achieved in approximately 23% (50 mg) and 25% (100 mg) of treated attacks, while 2-hour pain relief was observed in 65%–68% of cases.[28,29] Efficacy was markedly superior when treating mild-intensity attacks during a 52-week treatment period. In a within-subject analysis, ubrogepant 50 mg and 100 mg demonstrated significantly higher 2-hour pain freedom rates when taken at the mild headache (50 mg: 51.2%, 100 mg: 54.3%) compared to the moderate/severe headache (50 mg: 24.6%, 100 mg: 27.2%).[30] These findings suggest that early treatment with ubrogepant leads to improved efficacy in acute migraine management.[30]

LONG-TERM SAFETY PROFILES WITH GEPANTS

An overview of long-term safety data from open-label studies of rimegepant, atogepant, ubrogepant, and zavegepant is summarized in Table 1.

1. Rimegepant

Long-term safety profile has been characterized through a large open-label extension study and supported by real-world registry data and subgroup analyses.[21,22,31,32] A 52-week, open-label study evaluated the long-term safety of rimegepant 75 mg as-needed therapy in 1,798 adults with migraine.[21] The results demonstrated good tolerability, with 13.8% of participants experiencing treatment-emergent adverse events (TEAEs) considered drug-related. The most frequently reported TEAEs were mild and included

Table 1. Long-term safety profiles of gepants based on open-label studies

Drug (dose)	Patients (n)	Exposure (wk)	Treatment-related TEAEs	Serious AEs	Discontinuation due to AEs
Rimegepant (75 mg PRN)	1,798	52	13.8% overall; most common: URI (8.8%), nasopharyngitis (6.8%), sinusitis (5.1%)	No treatment-related SAEs. In the CV risk subgroup (n=570): 14.2% TEAEs, similar AE spectrum	2.6%. Reasons not individually listed >1%. In subgroups: 2.5% (CV risk)
Atogepant (60 mg QD)	372	52	≥1 TEAE in 64.5% (vs. 78.6% in standard care). Most common: URI (7.7%), constipation (5.0%–6.0%), nausea (4.6%), UTI (5.2%)	3.8% (vs. 3.6% in control); mostly unrelated to treatment; no dose-dependent pattern; no liver toxicity	4.3%. Most common reasons: nausea (0.5%), dizziness (0.3%)
Ubrogepant (50/100 mg)	813 (404/409)	52	66% (50 mg), 73% (100 mg); most common: URI, nasopharyngitis, nausea; treatment-related: 10.4% (50 mg), 10.5% (100 mg)	SAEs occurred in 2%–3% of patients; none were considered treatment-related; no deaths reported	2.2% (50 mg), 2.7% (100 mg). Reasons not individually listed <1%
Zavegepant (10 mg nasal)	603	52	62.2% any TEAE; 10.5% treatment-related. Most common: dysgeusia (13.5%), nausea (3.4%), nasal discomfort (2.5%)	SAEs in 1.3% of patients, none were treatment-related. Liver enzyme elevation in 2.3% (no Hy's Law cases); no BP or CV signal	7.3% overall; dysgeusia most common reason (4.3%)

TEAE, treatment-emergent adverse event; AE, adverse event; PRN, as needed (pro re nata); QD, once daily; URI, upper respiratory infection; SAE, serious adverse event; CV, cardiovascular; UTI, urinary tract infection; BP, blood pressure.

upper respiratory tract infection (8.8%), nasopharyngitis (6.8%), and sinusitis (5.1%). Treatment discontinuation due to adverse events occurred in 2.7% of patients, and serious adverse events (SAEs) were reported in 2.6% of patients, with drug-related SAEs in 0.6%. Importantly, no cases of drug-induced liver injury were identified, confirming rimegepant's hepatic safety profile during long-term intermittent use. In addition to the primary open-label study,[21] two subgroup analyses have been reported.[31,32] True et al.[31] analyzed 570 patients stratified by cardiovascular risk factors, showing that the long-term safety and tolerability of rimegepant were consistent regardless of baseline cardiovascular risk, with treatment-related TEAEs occurring in 14.2% of patients and discontinuation due to adverse events in 2.5%. Similarly, Berman et al.[32] evaluated 695 patients stratified by concomitant preventive medication use. The rate of treatment-related TEAEs classified as related to rimegepant was comparable between the cohort using preventives (22.2%) and the cohort not using them (19.7%). The incidence of serious treatment-related AEs was also low in both groups, occurring in 1.6% and 0.4% of participants, respectively.[32] These subgroup findings support that the favorable safety profile of rimegepant is preserved across clinically relevant patient groups. Real-world validation comes from the GAINER study, a prospective, multicenter Italian study evaluating rimegepant for acute migraine treatment.[22] This study demonstrated adverse events reported in 15.5% of participants and no SAEs documented. Patient-reported tolerability was rated as good or excellent in 85.4% of patients, and no treatment discontinuations due to adverse events were reported.[22]

2. Atogepant

Safety of atogepant was established in 12-week phase 3 studies and further supported by open-label extension studies. There were open-label 52-week and 40-week long-term safety studies with an ongoing follow-up to 156 weeks (NCT04686136). Participants who completed one of pivotal studies were eligible to participate in the long-term safety studies.[24,33] In a 52-week randomized open-label trial of once-daily atogepant 60 mg (n=744), ≥1 TEAE was reported in 67.0% of participants, most commonly upper respiratory tract infection (10.3%), constipation (7.2%), nausea (6.3%), and urinary tract infection (5.2%). Serious TEAEs occurred in 4.4% and discontinuations due to adverse events in 5.7%.[24]

In a separate 40-week open-label extension of the AD-

VANCE trial (n=685), ≥1 TEAE occurred in 62.5% of participants.[33] The most common TEAEs were upper respiratory tract infection (5.5%), urinary tract infection (5.3%), nasopharyngitis (4.8%), sinusitis (3.6%), constipation (3.4%), and nausea (3.4%). Serious TEAEs occurred in 3.4% of patients, none considered treatment-related, and discontinuation due to adverse events occurred in 3.2%. In this Ashina et al.'s study,[24] efficacy outcomes were not collected, as this extension focused solely on safety.

From open-label extension studies, atogepant is well tolerated, with few patients requiring treatment cessation due to adverse events, and that most side effects are manageable within clinical practice. Atogepant 60 mg once daily has been reported to induce clinically meaningful weight loss in patients with migraine who are overweight or obese, as presented at the 2025 American Headache Society Annual Scientific Meeting and supported by data from the ongoing long-term extension study (NCT04686136). Approximately one-third of participants achieved a ≥5% reduction in body weight after 52 weeks, with a mean weight loss of 3.4 kg.

3. Ubrogepant

A 52-week phase 3 extension study provides robust evidence for ubrogepant's long-term safety profile in acute migraine treatment.[28] The study enrolled 813 participants (404 receiving 50 mg, 409 receiving 100 mg) who collectively treated 21,454 migraine attacks with 31,968 doses of ubrogepant.[28] Overall TEAEs were reported in 66% of patients receiving 50 mg and 73% receiving 100 mg. However, the majority of these events were mild to moderate in severity, with the most frequently reported being upper respiratory tract infection, nasopharyngitis, and nausea. Treatment-related TEAEs remained low across both dosing groups, occurring in 10.4% of patients receiving 50 mg and 10.5% receiving 100 mg. SAEs occurred in 2%–3% of patients, and treatment discontinuation due to adverse events was low (2.2% in the 50 mg group and 2.7% in the 100 mg group). No deaths occurred during the trial period. Real-world safety data from the VigiAccess and U.S. Food and Drug Administration's adverse event reporting system databases provide valuable post-marketing insights.[34] Through March 2024, 3,478 adverse event reports associated with ubrogepant were identified. The most frequently reported adverse events in post-marketing surveillance included nausea (4.7%), fatigue (1.8%), vomiting (1.6%), and headache (0.8%). Hepatobiliary adverse events were rare, with no strong positive safety signal detected. Cardiovascular events and severe hypersensitivity reactions were infrequent, corroborating the safety profile observed in controlled clinical trials.[34]

4. Zavegepant

Given the recent approval of zavegepant, real-world data are currently scarce, and long-term safety assessments rely largely on findings from one open-label study.[35] The long-term safety of zavegepant nasal spray 10 mg for the acute treatment of migraine was evaluated in a 52-week, open-label, phase 2/3 study involving 603 adult participants. Over the study period, 21,052 migraine attacks were treated with 48,504 doses of zavegepant.[35] TEAEs were reported in 76.1% of patients, most commonly dysgeusia (39.1%), nasal discomfort (10.3%), COVID-19 infection (7.5%), nausea (6.1%), nasal congestion (5.5%), throat irritation (5.5%), and back pain (5.3%). Discontinuation due to adverse events occurred in 6.8% of participants, most frequently from dysgeusia (1.5%). Severe adverse events were reported in 3.6% and SAEs in 1.2%, none considered treatment-related. Alanine transaminase or aspartate transaminase elevations >3× upper limit of normal were observed in 2.6% of patients, but no Hy's law cases occurred. Importantly, no cases of medication-overuse headache, cardiovascular events, or suicidality-related adverse events were identified, supporting the favorable long-term safety profile of zavegepant.[35]

SPECIAL ISSUES

1. Combination treatment with calcitonin gene-related peptide monoclonal antibodies

Recent evidence supports the feasibility and safety of combining gepants with CGRP monoclonal antibodies (mAbs). The COURAGE real-world observational study showed that ubrogepant, when used in patients already receiving an anti-CGRP mAb, provided meaningful pain relief and return to normal function, with high levels of patient satisfaction and treatment optimization, and without

new safety concerns.[36] In line with these findings, a retrospective analysis of 234 patients treated with rimegepant or ubrogepant in addition to CGRP mAbs reported that the combination was generally well tolerated, with only mild and transient adverse events that did not necessitate discontinuation.[37] These studies suggest that combination therapy targeting the CGRP pathway at different sites may be a safe and practical treatment strategy, although larger prospective randomized trials are still needed to confirm long-term safety and efficacy.

2. Efficacy in patients with prior failure of acute migraine therapies

Emerging data indicate that gepants remain effective for acute migraine relief in patients who have previously experienced insufficient response or tolerability with triptans. A pooled post hoc analysis of three phase 3 trials found that rimegepant 75 mg provided comparable rates of pain freedom and most bothersome symptom relief at 2 hours in participants with inadequate response to one or more triptans, current triptan users, and triptan-naive individuals ($p \leq 0.013$).[38] Moreover, long-term safety and preference for rimegepant were consistent across subgroups with a history of triptan discontinuation.[39] These findings underscore the clinical value of gepants as a well-tolerated and effective alternative for migraine patients with prior acute treatment failures. However, focused prospective studies in these refractory subpopulations remain warranted.

3. Effectiveness in traditionally suboptimal responders: medication-overuse headache and psychiatric comorbidity

Gepants appear to be particularly advantageous in traditionally challenging migraine subgroups, such as patients at risk of medication-overuse headache and those with psychiatric comorbidities. Crucially, long-term use of rimegepant (up to 52 weeks as needed [pro re nata]) has been associated with a sustained reduction in monthly migraine days without increases in monthly medication usage, suggesting a low risk of medication-overuse headache development.[17] Regarding psychiatric comorbidities, adults with migraine and histories of anxiety and/or depression tolerated rimegepant well, demonstrating favorable safety and tolerability profiles.[40] These findings support gepants as effective and well-tolerated options for migraine management in populations traditionally considered suboptimal responders, although further targeted prospective studies are warranted.

CURRENT EVIDENCE GAPS AND FUTURE DIRECTIONS

While gepants have established themselves as both effective and safe for long-term migraine management, several critical questions remain unresolved. First, comprehensive safety data extending beyond 1–2 years remain limited. The available safety evidence through 1 year of treatment is reassuring, demonstrating no significant organ toxicity or increased incidence of adverse events. However, migraine frequently represents a lifelong condition requiring decades of preventive intervention, and the consequences of sustained CGRP receptor blockade over such extended periods remain incompletely understood. Given CGRP's widespread expression across multiple organ systems including cardiovascular, gastrointestinal, and endocrine tissues prolonged receptor inhibition may reveal subtle physiological effects that are not apparent in shorter-term studies, necessitating continued long-term surveillance and research.[41] Future studies, including a 3-year atogepant safety trial (NCT04686136) will be essential for detecting any late-emerging adverse events.

Second, the cardiovascular safety profile of gepants in high-risk populations represents one of the most significant unresolved questions in migraine therapeutics. Most pivotal clinical trials systematically excluded patients with significant cardiovascular disease, creating a substantial evidence gap regarding gepant safety in individuals with active coronary artery disease, cerebrovascular conditions, or multiple vascular risk factors. This exclusion of high-risk cardiovascular patients from foundational studies means that formal safety evaluation in real-world populations with established vascular disease remains incomplete. Critical questions persist regarding long-term cardiovascular outcomes during gepant therapy, including potential effects on blood pressure regulation, risk of vascular events, and safety in patients with compromised cardiovascular reserve. Limited observational data suggest that gepants may be well-tolerated in patients with

cardiovascular risk factors.[31] Long-term registries tracking vascular outcomes, blood pressure changes, and cardiac events during gepant therapy are essential to address this knowledge gap. In addition, it should be noted that most available long-term safety data are derived from open-label extension studies and industry-sponsored clinical trials, which may introduce a higher risk of bias compared with randomized controlled trials.

CONCLUSION

Gepants represent a significant therapeutic advancement in migraine management, offering robust efficacy for both acute and preventive treatment with an excellent safety profile. Clinical trials and real-world evidence consistently demonstrate that rimegepant, ubrogepant, atogepant, and zavegepant are well-tolerated across diverse patient populations, avoiding the cardiovascular contraindications associated with traditional therapies. The available safety data support sustained therapeutic benefit with minimal long-term concerns, enabling patients to achieve improved quality of life even with extended use. As clinical experience continues to expand, ongoing pharmacovigilance remains essential to monitor for rare or delayed adverse events and ensure the continued safety of this promising therapeutic class.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

AUTHOR CONTRIBUTIONS

Conceptualization: SC; Data curation: SC; Investigation: SC, KC; Writing–original draft: SC, KC; Writing–review & editing: SC, KC.

CONFLICT OF INTEREST

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

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Headache and Pain Research

Headache as a Somatic Symptom in Pediatrics: Diagnosis and Integrated Management

Hye Eun Kwon

Department of Pediatrics, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, Incheon, Republic of Korea

Abstract

Somatization—the expression of psychological distress through physical symptoms—presents a frequent and complex challenge in pediatric practice. Headache and dizziness are among its most common manifestations. This review addresses the diagnostic challenge of determining whether these symptoms indicate a primary headache disorder or reflect somatic symptom presentations. The difficulty becomes particularly evident when conditions manifest in severe or persistent forms, such as chronic primary headache (CPH) and somatic symptom and related disorders (SSRD), where clinical overlap is considerable and coexistence may occur. We first explore the shared pathophysiological mechanisms, emphasizing central sensitization as a unifying process. We then propose a clinical framework for differential diagnosis that includes careful evaluation of predisposing risk factors and contrasts the defined diagnostic criteria of CPH with the maladaptive psychological responses frequently observed in SSRD. Management strategies diverge pharmacologically but converge on key non-pharmacological approaches. For primary headaches, pharmacotherapy is primarily used for prophylaxis, although its efficacy remains limited in pediatric trials. In contrast, for somatic presentations, medication typically serves as an adjunctive treatment targeting comorbidities, while psychotherapy (particularly cognitive behavioral therapy [CBT]) functions as the cornerstone of care. Non-pharmacological interventions such as CBT and biofeedback are essential for improving functioning across both conditions. Therefore, effective management relies on a framework of comprehensive psychoeducation, holistic assessment, and integrated interdisciplinary care.

Keywords: Dizziness, Headache, Somatoform disorders

INTRODUCTION

Somatization, defined as the expression of psychological distress through physical symptoms, is a frequent and complex challenge in pediatric clinical practice.[1] Instead of verbalizing emotions such as anxiety or stress, children and adolescents may present with significant somatic complaints. Importantly, these symptoms are not feigned; the suffering is genuine and can cause substantial functional impairment, including chronic school absenteeism.[2]

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Correspondence: Hye Eun Kwon, M.D.
Department of Pediatrics, International St. Mary's Hospital, Catholic Kwandong University College of Medicine, 25 Simgok-ro 100beon-gil, Seo-gu, Incheon 22711, Republic of Korea
Tel: +82-32-290-2716, Fax: +82-32-290-3879, E-mail: romani33@hanmail.net

The tendency toward somatic expression is often shaped by a confluence of factors, ranging from individual psychological vulnerabilities and prior life experiences to socio-environmental pressures like family stress, highly competitive environments, or cultural contexts that discourage emotional disclosure.[3]

These manifestations exist along a spectrum of severity. At one end are transient functional symptoms that resolve spontaneously with minimal disruption; at the other are persistent, disabling presentations that may fulfill the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria for somatic symptom and related disorders (SSRD).[4,5] This spectrum naturally provokes varying levels of parental concern and requires tailored clinical intervention. Headache and dizziness are among the most common medically unexplained symptoms in this population. Their considerable clinical overlap with primary headache disorders creates significant diagnostic challenges—particularly in children, whose headache characteristics are often less distinct than in adults.[6]

Prevalence data highlight the scale of these conditions: while chronic primary headache (CPH) affects approximately 1%–2% of adolescents,[7] broader functional somatic symptoms occur in up to one in four youths.[8] To clarify this clinical context and severity spectrum, Table 1 provides a comparative summary of the key characteristics and functional impact associated with both conditions in the pediatric population.

Because these symptoms frequently present first to non-psychiatric services, insufficient recognition at the initial encounter may result in extensive diagnostic testing and medication-centered management strategies that are often ineffective.[9] Understanding the interplay between primary headache disorders and somatic symptom presentations is therefore essential for all clinicians caring for pediatric patients.

Therefore, a critical need exists for the integration of the primary headache and SSRD frameworks, which specifically emphasizes shared central sensitization (CS) as a unifying mechanism. This transdiagnostic perspective facilitates clearer clinical differentiation and underscores the necessity of integrated care models.

Moreover, these cases frequently strain the physician–family relationship, underscoring the need for clear communication and integrated care. Against this background, the present review aims to assist clinicians by examining shared pathophysiological mechanisms, identifying risk factors for somatization in youth, differentiating between CPH and somatic symptom presentations, and outlining management strategies, highlighting differences in pharmacological approaches and similarities in non-pharmacological ones.

A SHARED PATHOPHYSIOLOGY: THE SENSITIZED BRAIN

Building on the clinical overlap described in the introduction, a substantial pathophysiological convergence exists between the chronification of primary headaches and SSRD. CS has emerged as the key unifying mechanism linking these conditions.[10,11] CS reflects a state of amplified neural signaling within the central nervous system, producing heightened pain sensitivity and characteristic features such as allodynia and hyperalgesia.[10] Notably, migraine—a prototypical primary headache disorder—shares this sensitization pathway with functional somatic syndromes and psychiatric comorbidities, underscoring its transdiagnostic importance.[11]

Table 1. Comparative summary of chronic primary headache and broader functional somatic symptoms in pediatric patients

Feature	Chronic primary headache	Broader functional somatic symptoms
Prevalence	Approximately 1%–2% of adolescents	Up to one in four youths
Onset age	Can occur across all age groups	Can occur across all age groups
Prototypical conditions	Chronic migraine; chronic tension-type headache; new daily persistent headache	A clinical spectrum, ranging from transient functional symptoms with minimal disruption to persistent, disabling presentations that qualify as somatic symptom and related disorders
Functional impact	Restriction of daily activities	Varies widely by specific diagnosis, ranging from mild to severe
Initial clinical contact	Pediatric neurology settings	Often presents first to non-psychiatric services (e.g., general pediatric clinics or pediatric neurology settings)

Children and adolescents may be particularly susceptible to maladaptive sensitization due to their neuroplasticity and ongoing brain maturation.[12] Pediatric neuroimaging studies reveal altered connectivity within pain-related networks and disrupted resting-state activity, suggesting that the developing brain is vulnerable to long-term functional reorganization.[12]

Biopsychosocial factors further shape this sensitized state. Childhood maltreatment and early life stress have been shown to program lasting dysregulation of the hypothalamic–pituitary–adrenal axis and to trigger low-grade systemic inflammation, thereby increasing vulnerability to chronic pain conditions.[13,14] In adolescence, the surge of gonadal hormones contributes additional instability by reorganizing neural circuits that govern both emotion regulation and nociception.[15]

At the systems level, convergent processing of emotional and sensory signals in the anterior cingulate cortex and insula provides a structural substrate for cross-sensitization.[12] During neurodevelopment, these circuits remain plastic, and persistent activation by psychological distress can more readily "spill over" into adjacent pain-processing networks, reinforcing a cycle of symptom chronification.[16]

For instance, when prolonged psychological distress is processed in key emotional areas like the insula, the resulting chronic activation allows the emotional signal to "spill over" into adjacent pain-processing networks. This crossover leads to the misinterpretation of harmless inputs—such as minor muscle tension or light touch—causing them to be experienced as severe pain signals and ultimately manifesting as increased headache frequency or severity.

Taken together, these findings suggest that pediatric pain syndromes are rooted in CS within the developing nervous system, rather than being purely psychogenic.

RISK FACTORS FOR SOMATIZATION IN YOUTH

The emergence of somatic symptoms in children and adolescents reflects the interplay of biopsychosocial risk factors. At the individual level, vulnerability may arise from psychological predispositions such as high anxiety sensitivity, neuroticism, and perfectionism, some of which have a genetic basis.[17,18] Comorbid psychiatric conditions—especially anxiety and depressive disorders—are also strong predictors, as is alexithymia, the difficulty in identifying and describing emotions.[19]

These risks can be amplified by previous adverse experiences, including serious medical illness, trauma, or neglect, which heighten sensitivity to bodily sensations.[20]

Socio-environmental stressors further shape these predispositions. Within the family, parental modeling of illness behavior, high level of family stress, and overprotective parenting exert strong influence.[21] In schools, academic and social pressures may add to the burden, while cultural norms that discourage emotional expression can further reinforce somatic tendencies.[22]

Once established, symptoms persist through reinforcing mechanisms, as the sick role is maintained by secondary gains like increased attention or relief from stressors.[20]

CLINICAL DIFFERENTIATION OF PRIMARY HEADACHE DISORDERS AND HEADACHE AS A SOMATIC SYMPTOM

Differentiating between primary headache disorders and headache presenting as a somatic symptom is a significant clinical challenge, given their considerable phenomenological and pathophysiological overlap.

The diagnosis of CPH—including chronic migraine, chronic tension-type headache, new daily persistent headache (NDPH), and medication overuse headache (MOH)—is established according to the objective criteria outlined in the International Classification of Headache Disorders, 3rd edition (ICHD-3).[23] For instance, chronic migraine is defined by headache on ≥15 days per month, with migrainous features on at least 8 of those days. Clinically, patients with SSRD may present with headache patterns that closely mimic these primary disorders. In particular, the abrupt and unremitting pain of NDPH or the analgesic-driven progression into MOH may resemble the headache presentations seen in SSRD.[24]

When diagnosing headache as a manifestation of SSRD, the diagnosis is not based on specific headache features—which are often vague, atypical, and notably not outlined in the DSM-5 criteria—but instead relies on the patient's excessive and maladaptive psychological responses as defined by those criteria.[5,25] Clinically, SSRD expresses itself in ways that significantly amplify the headache experience, such as pain amplification, chronic, high-level health

anxiety centered on the head (e.g., fear of tumor despite clear scans), or functional neurological presentations like unexplained neurological deficits (e.g., transient blindness or severe imbalance during a headache). Diagnostic clues include disproportionate thoughts, emotions, and behaviors related to the headache, such as pain catastrophizing and significant functional impairment. Patients with SSRD typically emphasize these maladaptive responses—particularly the disabling impact of symptoms and associated emotional distress.[26]

Notably, not all patients express distress overtly; many exhibit alexithymia, a difficulty in recognizing and articulating emotions, which may result in emotional numbing or poor awareness of discomfort.[19] Such presentations require careful clinical attention, as they can obscure the psychological drivers of symptoms. Additional indicators include the presence of multiple medically unexplained symptoms beyond headache and a tendency toward "symptom shifting."[26] The essential differences in the diagnostic focus between CPH and SSRD are summarized in Table 2.

Diagnostic clarity becomes especially challenging when CPH and SSRD coexist. This comorbidity may create a vicious cycle of mutual reinforcement, whereby psychological distress lowers the pain threshold while chronic pain exacerbates psychological symptoms.[27] This complexity is further compounded by differences in diagnostic frameworks (DSM-5 for SSRD versus ICHD-3 for "headache attributed to a psychiatric disorder"), underscoring the importance of interdisciplinary awareness. Because patients typically present with headache as the primary complaint, the underlying psychiatric contribution may easily be overlooked unless specifically considered.[28]

PHARMACOLOGICAL DIVERGENCE AND NON-PHARMACOLOGICAL CONVERGENCE

Although pharmacological approaches differ between primary headache disorders and somatic symptom presentations, there is clear convergence in the value of non-pharmacological interventions. Across both conditions, cognitive behavioral therapy (CBT) has consistently demonstrated efficacy in reducing symptom burden, functional impairment, and healthcare utilization by reframing maladaptive thoughts and enhancing coping strategies.[29,30] Biofeedback, by providing real-time awareness of physiological processes, has likewise been reported to promote self-regulation and reduce symptom frequency and intensity.[31,32]

The primary distinction lies in pharmacological strategy. Treatment of primary headache disorders typically emphasizes prophylaxis with agents such as anticonvulsants (e.g., topiramate) or beta-blockers (e.g., propranolol) to decrease headache frequency and severity.[33] However, in pediatric and adolescent populations, evidence indicates that the efficacy of pharmacological prophylaxis is limited. The Childhood and Adolescent Migraine Prevention trial demonstrated that neither topiramate nor amitriptyline was superior to placebo in reducing headache frequency,

Table 2. Key differences between chronic primary headache and somatic symptom and related disorders

Feature	Chronic primary headache	Somatic symptom and related disorders
Diagnostic criteria	Classification of headache types using ICHD-3 criteria	To classify the psychological and behavioral impact of the symptoms on the patient's life according to DSM-5
Subtypes	Chronic migraine; chronic tension-type headache; new daily persistent headache	Somatic symptom disorder; illness anxiety disorder; conversion disorder; factitious disorder
Core diagnostic focus	Specific symptom features (frequency, duration, quality, associated symptoms)	Excessive, maladaptive psychological response to physical symptoms and associated distress/dysfunction
Symptom requirements	Headache occurring on ≥15 days/mo for >3 months (for chronic forms), fulfilling criteria for migraine or tension-type headache phenotype	One or more somatic symptoms that are distressing or result in significant disruption of daily life (e.g., headache, abdominal pain, fatigue)
Psychological component	Not required for diagnosis (may be an associated comorbidity)	Required for diagnosis
Clinical goal	Reduction in headache frequency and intensity, and functional recovery	Reduction in health-related anxiety and excessive behaviors, improvement in patient coping skills, and concurrent mental health treatment

ICHD-3, International Classification of Headache Disorders, 3rd edition; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.

underscoring the limitations of medication-based strategies in this age group.[34] This limitation highlights that a poor response to medication should prompt clinicians to look beyond purely pharmacological strategies, considering both the possibility of headache as a somatic expression and the integration of non-pharmacological therapies.

By contrast, the cornerstone of treatment for somatic symptom presentations is psychotherapy—most notably CBT—which prioritizes functional improvement rather than complete symptom elimination. Pharmacotherapy, most often with selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, is typically adjunctive and directed toward comorbid anxiety or depressive disorders.[35]

Effective management strategies are best supported by the following principles:[1,36]

- Providing comprehensive psychoeducation: Clear communication that enhances patient and family understanding of the diagnosis is fundamental for improving adherence and achieving long-term outcomes.
- Conducting holistic assessment: Clinicians must extend evaluation beyond the presenting complaint to identify comorbid medical or psychiatric conditions that may require additional support.
- Fostering interdisciplinary collaboration: Optimal care depends on coordinated input from neurologists, psychiatrists, psychologists, and allied health professionals. Importantly, a patient's differing responses to various interventions may itself provide valuable diagnostic insight.

CONCLUSION

Headache and dizziness in children often blur the distinction between primary headache disorders and somatic symptom presentations. CS offers a shared neurobiological framework, yet primary headaches are defined by ICHD-3 criteria, whereas somatic symptom disorders are characterized by maladaptive psychological responses, frequently complicated by alexithymia and psychiatric comorbidities.

Management diverges in pharmacological strategies but converges in non-pharmacological approaches. Pediatric trials demonstrating the limited efficacy of preventive medications underscore the importance of psychotherapy and integrated, function-oriented care.

Effective management may therefore require early recognition of somatic presentations, avoidance of unnecessary investigations, and interdisciplinary collaboration. Future research should focus on refining diagnostic clarity and treatment efficacy by prioritizing several key areas. Specifically, research efforts should be directed toward the validation of pediatric-specific diagnostic tools that consider both ICHD-3 and DSM-5 criteria, conducting longitudinal studies to map the trajectory and prognosis of somatic symptom presentations, and performing rigorous evaluation of integrated programs to establish best practices for holistic care and optimized outcomes for affected youth.

AVAILABILITY OF DATA AND MATERIAL

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

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

Hye Eun Kwon is the 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.

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Headache and Pain Research

Interictal Burden of Migraine: A Narrative Review

Soo-Kyoung Kim[1,2], **Todd J. Schwedt**[3]

[1]Department of Neurology, Gyeongsang National University Hospital, Gyeongsang National University College of Medicine, Jinju, Republic of Korea
[2]Institute of Medical Science, Gyeongsang National University College of Medicine, Jinju, Republic of Korea
[3]Headache Division, Department of Neurology, Mayo Clinic, Phoenix, AZ, USA

Abstract

Migraine is a chronic neurological disorder associated with substantial disability and societal costs. Traditionally, research and clinical care have focused on the ictal phase, characterized by headache and accompanying symptoms. However, growing evidence suggests that a considerable portion of migraine-related disability occurs between attacks, known as the interictal burden (IIB). IIB encompasses a wide spectrum of cognitive, emotional, sensory, and functional impairments that persist during headache-free periods, including fatigue, allodynia, photophobia, cognitive dysfunction, anticipatory anxiety, and social withdrawal. These symptoms can markedly reduce quality of life, work productivity, and family functioning, even in individuals with infrequent attacks. In a descriptive survey of 506 migraine respondents, 67% experienced severe IIB. The effects of IIB extend beyond patients themselves, contributing to presenteeism in the workplace and imposing emotional and logistical strain within families. Several instruments, including the Migraine Interictal Burden Scale (MIBS-4), Migraine-Specific Quality of Life Questionnaire (MSQ v2.1), Headache Impact Test (HIT-6), and Migraine Disability Assessment (MIDAS), have been employed to assess different dimensions of IIB. Nonetheless, no single comprehensive and standardized tool fully captures the multidimensional nature of IIB. Recognizing and addressing IIB is essential for delivering holistic, patient-centered migraine care. Future research should focus on developing validated assessment instruments and incorporating IIB measures into clinical trials and routine practice to better understand and alleviate the hidden burden of migraine.

Keywords: Activities of daily living, Burden of illness, Disability evaluation, Migraine disorders, Quality of life

INTRODUCTION

Migraine is a disabling chronic neurological disease characterized by episodic attacks consisting of headache and non-pain symptoms such as nausea, sensory hypersensitivities, mood changes, and cognitive dysfunction.[1,2] Previous studies have demonstrated that migraine imposes a substantial burden on patients, families, the workplace, and society.[3,4] At the population level, "migraine-attributed burden" is defined as the sum of the negative impact of migraine on individuals with migraine plus the impact on people without migraine.[5] Migraine most commonly occurs between the second and sixth decades of life, which are crucial years for education, career development, and

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Correspondence: Todd J. Schwedt, M.D.
Headache Division, Department of Neurology, Mayo Clinic, 5777 East Mayo Blvd, Phoenix, AZ 85054, USA
Tel: +1-480-301-8000, Fax: +1-480-342-6546, E-mail: Schwedt.Todd@mayo.edu

productivity.[6,7] Understanding the magnitude of and contributors to both ictal and interictal migraine burden is essential for accurately assessing the true impact of migraine and developing targeted interventions to reduce it.[8,9] While its burden has traditionally been quantified based on ictal features such as attack frequency, severity, and duration, a growing body of research emphasizes that migraine is not confined to the ictal phase. Interictal burden (IIB) refers to the constellation of symptoms and restrictions experienced between attacks, including sensory hypersensitivity, cognitive impairment, anticipatory anxiety, and impaired social and occupational functioning.[10] For this review, the interictal period is defined as a headache-free interval of at least 24 hours since the last migraine ictus, excluding prodromal and postdromal phases. Prior studies have adopted varying definitions. For example, Lampl et al.[11] described IIB as the "loss of health or wellbeing attributable to a headache disorder reportedly experienced while headache-free, affecting all areas of life on any day." Peng and May,[12] from a clinical perspective, characterized the interictal phase as the interval between two attacks during which patients are "usually relatively symptom free". Such heterogeneity in definitions may influence estimates of IIB, particularly in chronic migraine (CM) where headache-free days are scarce.

The objective of this narrative review is to provide an overview of IIB in migraine, focusing on its epidemiology, domains of impact, assessment tools, clinical implications, and future directions.

METHODS

This article was prepared as a narrative review to provide an overview of current knowledge on IIB in migraine. The review was structured and reported according to the SANRA (Scale for the Assessment of Narrative Review Articles) guidelines to ensure clarity, transparency, and scientific rigor.

We performed a literature search using MEDLINE (via PubMed) and Embase databases. The search covered the period from January 1, 2000 to September 1, 2025, with no geographic restrictions. The search strategy combined controlled vocabulary (MeSH/Emtree terms) and free-text keywords related to migraine and IIB. The core search string included terms such as: "migraine" OR "headache disorders" AND ("interictal burden" OR "interictal symptoms" OR "migraine burden" OR "anxiety" OR "cognitive impairment" OR "presenteeism" OR "quality of life").

Relevant literature was identified through the review of key published studies and large epidemiological projects as well as other peer-reviewed research articles and systematic reviews. Articles were selected for their relevance to the main themes of this review: (1) epidemiology of IIB, (2) domains of impact (cognitive, psychological, sensory, social, and functional), (3) assessment tools used to measure IIB, and (4) clinical and societal implications.

Inclusion criteria were peer-reviewed English-language publications that reported data on people with migraine, including both episodic and CM, and addressed at least one of the themes above. Exclusion criteria included abstracts without full text, case reports with fewer than 10 participants, and studies unrelated to migraine or IIB.

As this was a narrative review, a formal risk-of-bias tool was not applied. However, study design and methodological quality were considered when interpreting findings, and greater weight was given to systematic reviews and large observational studies.

1. Epidemiology of interictal burden

Epidemiological surveys demonstrate that IIB is common and clinically meaningful. The OVERCOME (Japan) study reported that approximately 41.5% of respondents with migraine had moderate-to-severe IIB, and a comparable proportion (53.8%) was seen in OVERCOME (US).[13] Similarly, European data from the Eurolight study revealed that 26.0% of individuals with migraine reported IIB, including 10.6% with interictal anxiety and 14.8% with avoidance behaviors.[11] CM is consistently associated with higher interictal impairment than episodic migraine.

2. Domains of interictal burden

IIB can be categorized into several key domains, each contributing to a patient's overall disability and reduced quality of life (QoL) (Table 1).

1) Cognitive and behavioral dysfunction

Many patients report cognitive impairments during the interictal phase, often described as "brain fog." These difficulties may include reduced selective attention and defi-

Table 1. Domains of interictal burden

Domain	Description	Symptoms
Cognitive dysfunction	Cognitive inefficiency persisting between attacks	"Brain fog," poor concentration, reduced attention, impaired memory, executive dysfunction
Psychological distress	Anticipatory anxiety and emotional comorbidities	Anxiety, depression, avoidance behaviors, fear of next attack
Sensory symptoms	Persistent sensory hypersensitivity outside ictal periods	Allodynia, photophobia, phonophobia, osmophobia, vestibular disturbance
Social stigma & isolation	Impact of misunderstanding migraine as "just a headache"	Concealment, social withdrawal, delayed diagnosis, underreporting
Work productivity loss	Limitations in occupational performance between attacks	Presenteeism, reduced efficiency, economic cost
Family burden	Effect on family functioning and relationships	Reduced participation in family activities, parental strain, adolescent stress

cits in executive function, impacting the ability to concentrate, remember, and perform complex tasks.[14] One study found evidence of mild executive dysfunction in patients with migraine without aura during the interictal period.[15] Patients with CM demonstrate poorer frontal lobe–related cognitive performance, especially in executive function, compared with episodic migraine and healthy controls. Deficits in executive tasks such as the Trail Making Test and Wisconsin Card Sorting Test have been documented in CM, and higher migraine severity has been associated with reduced attention and slower processing speed.[15-18]

2) Psychological distress

The constant threat of an impending attack often leads to anticipatory anxiety, which may result in avoidance behaviors that limit daily activities and affect the ability to make plans or commitments. Anxiety and depression may be associated with more severe migraine disease. In the Nord-Trøndelag Health Study (HUNT) cohort study, anxiety was associated with a two-fold increased risk and depression with a 2.6-fold increased risk of developing medication overuse headache (MOH).[19] Depression is associated with a higher risk of transformation from episodic to CM, the risk of which is greatest among those with more severe depression.[20]

3) Social stigma and isolation

Migraine is frequently misunderstood as a simple headache, leading to social stigma. Patients may hide their condition from colleagues, friends, and family, resulting in social isolation and feelings of being misunderstood.[21] Stigma also contributes to underreporting and delays in diagnosis, while reinforcing avoidance behaviors. In the OVERCOME (US) cohort, 45.1% of migraine patients reported ever hesitating to seek care, with hiding migraine and perceived stigma being among the strongest associated factors.[22] Higher stigma scores were strongly associated with greater disability, poorer QoL, and reduced care seeking.[23] Over time, these dynamics can affect career advancement, education, and family planning.[24] Additionally, stigma may discourage patients from seeking treatment, exacerbating the emotional burden and resulting in unnecessary suffering from untreated migraine.[24,25] To better quantify stigma, the migraine-related stigma (MiRS) questionnaire was recently developed and validated using OVERCOME data, providing a standardized tool for measuring perceived stigma and its clinical impact.[26]

4) Persistent non-pain symptoms

Many symptoms associated with the ictal phase—such as allodynia, photophobia, phonophobia, osmophobia, vestibular disturbances and motion sickness—can persist into the interictal phase at lower intensity. In the OVERCOME (US) cohort, 31.7% of participants reported frequent interictal symptoms such as sensitivity to light or sound, cognitive difficulties, and fatigue, even on non-headache days.[8,23] Neuroimaging studies, including functional magnetic resonance imaging and structural analyses, demonstrate persistent cortical hyperexcitability and alterations in regional brain structure in pain-processing regions and regions responsible for processing other sensory stimuli, supporting a neurobiological basis for these ongoing symptoms.[9,27,28]

5) Work and productivity loss

Workplace productivity is profoundly affected by migraine, especially through presenteeism—working while symptomatic but at reduced capacity. One study estimated that 89% of total productivity loss due to migraine was attributable to presenteeism rather than absenteeism.[29] In the Japanese OVERCOME cohort, presenteeism accounted for a substantial portion of work time impairment—up to 49.9% of work hours—while absenteeism rates remained low (3.8%–6.2%). This suggests that presenteeism-related costs far exceed those from absence in this population. Although direct data linking interictal fatigue or reduced vitality to presenteeism costs in Japanese cohorts are lacking, the high proportion of productivity impairment attributable to presenteeism supports the possibility that interictal symptoms contribute meaningfully to economic burden.[30,31] Furthermore, higher Migraine Interictal Burden Scale (MIBS-4) scores have been shown to correlate with greater activity impairment and lower workplace productivity.[8,32]

6) Family and social burden

Longitudinal data from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study highlight the widespread impact of migraine on family functioning. Nearly half of respondents with migraine reported reduced participation in family activities, with the highest burden observed among those with CM. They felt their partner did not understand the severity of their condition, and a substantial proportion believed they would be better parents without migraine.[33] Furthermore, adolescents living with a parent with CM experienced greater anxiety, missed activities, and assumed more household responsibilities than those with a parent who had episodic migraine.[34] In a study of headache specialty clinic patients with migraine in the United States, 19.9% of women avoided pregnancy due to their migraine, mostly because of concerns about negative impacts of migraine on their pregnancy and child.[35] These findings demonstrate that migraine is not only a personal condition but also a family disease, with implications for emotional health and household dynamics.

3. Assessment tools for interictal burden

Recognition of IIB as a major contributor to migraine-related disability has led to the development and adaptation of various assessment tools. Although a fully comprehensive, validated instrument for IIB remains unavailable, both migraine-specific and general instruments are used (Table 2).

1) Migraine-specific instruments

Most migraine-specific instruments were originally developed to assess global headache-related disability, with particular emphasis on ictal burden. While not specifically designed to evaluate interictal effects, certain items—such as those addressing fatigue, concentration difficulties, or reduced vitality—may inadvertently capture functional limitations that persist during headache-free intervals. Accordingly, these measures should be interpreted as providing only partial and indirect insights into IIB rather than as dedicated assessments. This limitation highlights the need for rigorously validated instruments explicitly designed to quantify IIB, such as the MIBS-4.

(1) Migraine Interictal Burden Scale

The MIBS-4 is currently the only instrument explicitly designed to assess IIB. It comprises four items assessing emotional distress, difficulty in making plans or commit-

Table 2. Migraine-specific instruments for measuring IIB

	Purpose	Domains	Limitations
MIBS-4	Specific IIB	Emotional distress, planning difficulty, social disruption, work/school impairment	Brief, easy to use, but limited scope
MSQ v2.1	Migraine-specific QoL	Role Function–Restrictive, Preventive, and Emotional	Sensitive to functional changes, but partial interictal coverage
HIT-6	Headache impact and disability	Pain, fatigue, cognitive impairment, role limitation	Not interictal-specific, indirect measure
MIDAS	Headache-related productivity loss	Absenteeism, reduced productivity, overall disability	Mixed ictal/interictal contributions

IIB, interictal burden; MIBS-4, Migraine Interictal Burden Scale; MSQ, Migraine-Specific Quality of Life Questionnaire; QoL, quality of life; HIT-6, Headache Impact Test; MIDAS, Migraine Disability Assessment.

ments, social or leisure disruption, and impairment in work or school life. Each item is rated on a 0–3 scale (total score 0–12), with higher scores indicating greater burden. Scores are categorized as none (0), mild (1–2), moderate (3–4), or severe (≥5). Validation data from real-world studies such as OVERCOME (Japan, US) show correlation with health-related QoL, productivity loss, and daily functioning.[9] In the OVERCOME (Japan) study, higher MIBS-4 scores were associated with greater activity impairment, productivity loss, absenteeism, and presenteeism within Headache Impact Test (HIT-6) strata.[8]

(2) Migraine-Specific Quality of Life Questionnaire

The Migraine-Specific Quality of Life Questionnaire (MSQ v2.1) is a widely used instrument for assessing the impact of migraine on health-related QoL. It consists of three domains: Role Function–Restrictive, Role Function–Preventive, and Emotional Function. While originally developed to measure ictal-related quality-of-life impairment, items within the Role Function–Restrictive domain are sensitive to interictal functional limitations, such as reduced energy, motivation, and social participation on non-headache days.[36] In a validation study of the Greek version of MSQ v2.1, significant moderate correlations were observed between MSQ scores and the Migraine Disability Assessment (MIDAS), with correlation coefficients ranging from ρ=–0.562 to –0.519 ($p<0.001$).[37] These findings support that the Role Function–Restrictive domain reflects functional limitations in daily life and is relevant for assessing the broader impact of migraine beyond headache episodes.[36]

(3) Headache Impact Test

HIT-6 measures headache-related disability, including difficulty concentrating, fatigue, and role limitations. Although not designed specifically for IIB, psychometric studies suggest that some items indirectly reflect interictal cognitive and functional impairment.[38,39]

(4) Migraine Disability Assessment

MIDAS assesses productivity loss over the past three months due to migraine. Although it aggregates both ictal and interictal days, it can indirectly reflect persistent functional limitations in individuals with frequent attacks, providing a partial estimate of IIB.[40,41]

2) Generic and complementary instruments

In addition to migraine-specific tools, several broadly applicable instruments can be utilized to capture specific domains of IIB that are otherwise underrepresented (Table 3).

(1) Cognitive Failures Questionnaire

The Cognitive Failures Questionnaire (CFQ) is a self-reported survey that assesses daily memory, attention, and execution failures. In migraine patients, CFQ scores have been shown to correlate significantly with subjective cognitive impairment during attacks, supporting its utility as a complementary tool for evaluating cognitive dysfunction.[42]

(2) Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) assesses anxiety (HADS-A) and depression (HADS-D), which are key components of anticipatory anxiety and emotional distress between migraine attacks. In a cross-sectional study, individuals with migraine scoring ≥11 on HADS-A had over twice the odds of interictal anxiety compared to those with lower scores. Elevated HADS-A and HADS-D scores are also common in patients with MOH and significantly decrease following detoxification treatment, highlighting their clinical relevance. Furthermore, higher monthly headache days are associated with a dose-dependent increase in psychological distress, with ≥3 days linked to anxiety and ≥19 days to depression and severe disability.[43-45]

Table 3. Generic and complementary instruments

	Purpose	Domains	Application in migraine research
CFQ	Cognitive performance in daily activities	Memory, attention, executive failures	Elevated in both ictal and interictal periods
HADS	Emotional well-being	Anxiety (HADS-A), depression (HADS-D)	Identifies anticipatory anxiety, emotional distress
WPAI	Work productivity and activity impairment	Presenteeism, absenteeism, total activity loss	Estimates economic and occupational impact
WHODAS 2.0, SF-36, EQ-5D	General health-related quality of life	Physical, psychological, and social functioning	Assesses vitality, role function, social participation

CFQ, Cognitive Failures Questionnaire; HADS, Hospital Anxiety and Depression Scale; WPAI, Work Productivity and Activity Impairment questionnaire; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0; SF-36, 36-item short-form; EQ-5D, EuroQol-5 Dimensions.

(3) Work Productivity and Activity Impairment questionnaire

The Work Productivity and Activity Impairment questionnaire (WPAI) measures absenteeism, presenteeism, and overall activity impairment.[46] In Japan, presenteeism has been shown to consume 29.8%–49.9% of work time in migraine patients, far exceeding absenteeism rates (3.8%–6.2%).[31] WPAI scores have also been found to increase with headache frequency, with presenteeism rising from 41.7% in patients with 0–3 monthly headache days to 67.5% in those with ≥15 days.[47]

(4) World Health Organization Disability Assessment Schedule 2.0 and 36-item short-form/EuroQol-5 Dimensions

Generic health-related QoL instruments such as World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), 36-item short-form (SF-36), and EuroQol-5 Dimensions (EQ-5D) have been used in headache and pain research to capture interictal functional impairments, particularly in domains of vitality, social participation, and role limitations.[48-50] A large European study demonstrated that higher frequency of headache days (≥4 monthly headache days) is associated with significantly lower health-related QoL (SF-6D, EQ-5D, and SF-36 summary scores) and increased work/activity impairment.[51] Clinical data using 5-level EQ-5D (EQ-5D-5L) confirm that patients with CM report lower health utility scores compared to those with episodic migraine, even outside of headache episodes.[39] Population-based data from England using SF-36 show broad impairment across vitality, role limitation, and social functioning domains among those with migraine, particularly in those with moderate to severe disability.[52]

DISCUSSION

The construct of IIB in migraine demonstrates that the impact from migraine extends beyond the ictal phase, encompassing persistent cognitive, emotional, sensory, and functional impairments even during headache-free periods. Epidemiological studies have shown that IIB is highly prevalent across all migraine subtypes, even including individuals with low-frequency episodic migraine. This highlights the limitation of traditional metrics, such as monthly headache days, which primarily focus on ictal symptoms and do not fully capture the full burden of migraine. Even when headache frequency is relatively low, the psychological burden of anticipating the next attack, along with ongoing symptoms such as fatigue, allodynia, photophobia, and cognitive dysfunction, can significantly reduce health-related QoL. These findings highlight the need to redefine migraine as a persistent neurological disorder rather than an episodic condition. They also emphasize the importance of integrating IIB into clinical assessment and treatment strategies.

IIB has widespread functional and societal implications. Beyond the direct suffering experienced by those with migraine, migraine significantly impacts the workplace, family life, and social interactions. Reduced workplace productivity is a major concern, with presenteeism consistently identified as the primary driver of economic loss. IIB not only affects individuals, but also imposes a substantial economic burden on employers and society.

The impact of migraine on families is also profound. The CaMEO study demonstrates that migraine interferes with family activities and relational dynamics, with the highest burden observed among those with CM. These findings emphasize that migraine is a family disease, influencing relationships, emotional well-being, and the daily functioning of household members.

Assessing IIB remains challenging due to methodological limitations. The MIBS-4 is the only tool specifically designed to measure IIB. Other instruments such as MSQ v2.1, HIT-6, and MIDAS were originally developed for ictal assessment but can provide partial insights into interictal effects. In addition, generic tools like the CFQ, HADS, WPAI, WHODAS 2.0, SF-36, and EQ-5D can complement migraine-specific measures by evaluating cognitive, psychological, and social dimensions. However, there is no single comprehensive tool that addresses all aspects of IIB, and many instruments lack cross-cultural validation, particularly for patients with CM. Furthermore, IIB is rarely included as a primary outcome measure in clinical trials, limiting our understanding of its responsiveness to treatment. Nonetheless, recent evidence indicates that IIB can be improved by preventive therapies. In a prospective cohort of 150 CM patients, onabotulinumtoxinA treatment reduced MIBS-4 scores by approximately 29% at 3 months and 42% at 12 months, reflecting sustained improvements in daily functioning.[53] Similarly, clinical data with CGRP monoclonal antibodies, such as galcanezumab, demonstrate reductions in interictal symptoms including allo-

dynia and fatigue.[54] These findings highlight the potential of recent preventive treatments to alleviate both ictal and IIB, underscoring the need to systematically include IIB endpoints in future trials and clinical practice to provide a more comprehensive and patient-centered assessment of therapeutic benefit.

To address these gaps, several key steps are needed. First, a standardized definition of the interictal period should be established, particularly for CM, where headache-free days are less common. Second, new multidimensional instruments must be developed to comprehensively assess the cognitive, emotional, sensory, and social aspects of IIB and validated across diverse cultures and age groups. Third, both clinical trials and real-world registries should incorporate IIB measures to better evaluate its prognostic value and the effectiveness of preventive and behavioral interventions on reducing IIB. Finally, future research should investigate how cultural and sociodemographic factors influence the perception and reporting of IIB, thereby enhancing the global relevance and applicability of migraine management strategies.

In conclusion, IIB is a substantial yet underrecognized component of migraine-related burden. Even in the absence of headache, individuals with migraine may experience persistent symptoms that significantly impact QoL, work productivity, and family relationships. The development of comprehensive, validated assessment tools and the integration of IIB into longitudinal studies and clinical trials are essential steps toward addressing this hidden burden.

AVAILABILITY OF DATA AND MATERIAL

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

AUTHOR CONTRIBUTIONS

Conceptualization: SKK, TJS; Data curation: SKK; Formal analysis: SKK; Investigation: SKK; Methodology: SKK; Supervision: TJS; Writing–original draft: SKK; Writing–review & editing: SKK, TJS.

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.

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The Hidden Risks of Medication Underuse in Migraine Progression

Heui-Soo Moon, Pil-Wook Chung

Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea

Abstract

Migraine is a progressive neurological disorder in which inadequate treatment can lead to chronification. For decades, clinical attention has centered on medication overuse headache (MOH) as the primary iatrogenic risk factor for this progression. However, medication underuse (MU) has emerged as a critical yet less established framework for understanding gaps in migraine care. This review reframes MU, which includes ineffective therapies, delayed administration, and non-adherence due to intolerability, as an active contributor to disease progression. Untreated or undertreated migraine attacks promote the development of central sensitization, a state of neuronal hyperexcitability that increases attack frequency, severity, and treatment resistance. This paper posits that MU and MOH are not opposing concepts but interconnected manifestations of suboptimal disease management. Specifically, disease progression driven by MU can directly precipitate the escalating medication use that characterizes MOH, resulting in a more refractory clinical state. Therefore, preventing chronification requires a paradigm shift from merely avoiding overuse to achieving optimal use. This entails adherence to evidence-based guidelines for both acute and preventive therapy—implementing stratified acute care within the neurobiological window to prevent central sensitization and initiating timely preventive treatment in eligible patients to reduce the overall attack burden. The integration of novel targeted therapies provides new opportunities to overcome the limitations of traditional agents. Ultimately, reducing the risks associated with MU through proactive, evidence-based management and strong patient–clinician communication is essential to alter the natural history of migraine and prevent the long-term disability associated with its progression.

Keywords: Central nervous system sensitization, Medication overuse, Medication underuse, Migraine disorder

INTRODUCTION

Migraine is a highly prevalent neurological disorder, affecting approximately 12%–15% of the global adult population and representing the leading cause of disability in individuals under 50 years of age.[1] The condition imposes a significant burden, leading to impaired quality of life, reduced productivity, and substantial socioeconomic costs from both direct healthcare expenditures and indirect losses.[2] Migraine is not a static condition but a progressive disorder, with an estimated 2.5% of individuals with episodic migraine transitioning to chronic migraine (CM) an-

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Correspondence: Pil-Wook Chung, M.D.
Department of Neurology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Republic of Korea
Tel: +82-2-2001-2050, Fax: +82-2-2001-2049, E-mail: chungpw@hanmail.net

nually.[3] This progression highlights the need for effective management strategies to mitigate its extensive personal and societal impact.

Current standard treatments include acute therapies for rapid symptom relief and preventive regimens to reduce attack frequency and severity. The prompt and appropriate application of these medications is fundamental to achieving favorable outcomes and preventing chronification.[4] However, a pivotal and often underrecognized issue in clinical practice is medication underuse (MU), defined as the suboptimal application of indicated treatments, including underutilization, poor adherence, delayed administration, or premature discontinuation.[5] Such underuse can aggravate migraine progression by permitting the neuroplastic changes, such as central sensitization, that amplify attack frequency, intensity, and treatment resistance.[6]

The hidden risks of MU include an increased likelihood of chronification, exacerbation of comorbid conditions, and greater healthcare demands, which are often overshadowed by the clinical emphasis on medication overuse headache (MOH). This review investigates the complex relationship between MU and migraine progression, highlighting its foundational risks and advocating for proactive clinical interventions. Subsequent sections will outline the mechanisms of underuse, its clinical impact, and evidence-based guidelines for optimized care, with the goal of mitigating these underappreciated risks.

PATHOPHYSIOLOGY OF MIGRAINE CHRONIFICATION

1. Central sensitization as a core mechanism

Central sensitization is a key neurophysiological phenomenon underlying migraine chronification.[7] It refers to a state of hyperexcitability in central pain-transmitting neurons, particularly in the trigeminocervical complex and thalamus, induced by persistent and intense nociceptive input.[8] In this state, the activation threshold of neurons is lowered, leading to responses to stimuli that are normally not painful and to spontaneous neuronal firing.

Clinically, central sensitization manifests as allodynia, where innocuous stimuli, such as combing hair or light touch, are perceived as painful.[9] When migraine attacks are recurrent and inadequately treated, the intense afferent signals from the peripheral trigeminal system induce neuroplastic changes that alter synaptic strength in central neurons.[10] This activity-dependent process establishes a persistent state of hypersensitivity in the pain system, creating a vicious cycle of increased attack frequency, greater intensity, and diminished treatment response. Thus, CM should be understood not merely as frequent headaches but as a disease state characterized by chronic sensitization of the central nervous system.

2. The role of neuropeptides and neuroinflammation

Neuropeptides, particularly calcitonin gene-related peptide (CGRP), and subsequent neurogenic inflammation play a pivotal role in migraine attacks and chronification.[11] During a migraine attack, CGRP is released in large quantities from activated trigeminal nerve endings.[12] The released CGRP acts on dural blood vessels, causing vasodilation, and stimulates mast cells to release inflammatory mediators such as histamine and serotonin.[13]

This cascade triggers a localized, sterile inflammatory response in the dura mater, which in turn stimulates trigeminal nerve endings, creating a positive feedback loop that amplifies pain signals.[14] Each inadequately treated migraine attack represents a significant inflammatory event that provides a powerful afferent stimulus, promoting and maintaining central sensitization. The cumulative effect of these repeated, uncontrolled inflammatory processes can induce long-term changes in central pain circuits, thereby facilitating the transition to CM.[15] This highlights that the goal of migraine therapy should extend beyond simple pain relief to the rapid and effective termination of the underlying neuroinflammatory process.

THE ROLE OF MEDICATION OVERUSE IN MIGRAINE PROGRESSION

For decades, MOH has been the most prominent iatrogenic factor in the study and clinical management of migraine chronification.[16] Considered the “best-documented iatrogenic factor in migraine chronification,” MOH is a secondary headache disorder caused by the excessive use of acute headache medications.[17] The International Classification of Headache Disorders (ICHD)-3 defines MOH as the worsening of a pre-existing headache or the development

of a new type of headache in the context of regular overuse of specific medications for more than 3 months.[18] The core pathophysiology of MOH is a vicious cycle. To manage escalating headaches, patients increase their intake of acute medication. The medication overuse itself then disrupts the brain's endogenous pain modulation systems, lowering the headache threshold and increasing headache frequency (Figure 1).[19] This leads patients to consume even more medication to treat the worsening pain. This cycle is thought to involve complex biological mechanisms, including neurotransmitter receptor downregulation, dysfunction of endogenous pain control systems, and exacerbation of central sensitization.[20] Furthermore, behavioral and psychological factors, such as anticipatory anxiety and pain-related fear, can reinforce medication dependency and perpetuate the cycle.[21]

The identification of MOH and research into its mechanisms have led to significant advances in migraine care. Warning patients about its risks is an essential component of patient safety. As a result, MOH has become a central topic in clinical guidelines, patient education, and academic research for decades.[22] Clinicians worldwide now consider it standard practice to instruct patients to track their acute medication use and adhere to established limits. These efforts have undoubtedly prevented many patients from developing MOH. However, this intense focus on MOH has created a consequential oversight in clinical paradigms. Clinical discourse regarding medication use has concentrated almost exclusively on the dangers of using "too much," while the potential risks of using "too little" have been relatively neglected. The powerful message that frequent use of acute medication is dangerous has framed the conversation around restriction and regulation. Consequently, there has been a lack of systematic investigation into the negative impact of failing to use appropriate medication when needed—a phenomenon termed MU on migraine progression.[5] This has created a paradoxical situation where the system designed to prevent one iatrogenic problem (MOH) may inadvertently contribute to another: disease progression due to MU.

A PARADIGM SHIFT: INVESTIGATING MEDICATION UNDERUSE AS A CATALYST FOR PROGRESSION

1. Defining and quantifying medication underuse

MU is a multidimensional concept that encompasses several distinct patterns of suboptimal treatment. These include the ineffective utilization of appropriate therapies, where a medication is not well-matched to attack severity, leading to prolonged headache exposure and heightened risk of central sensitization.[5,23] It also involves underutilization among eligible patients, where a significant propor-

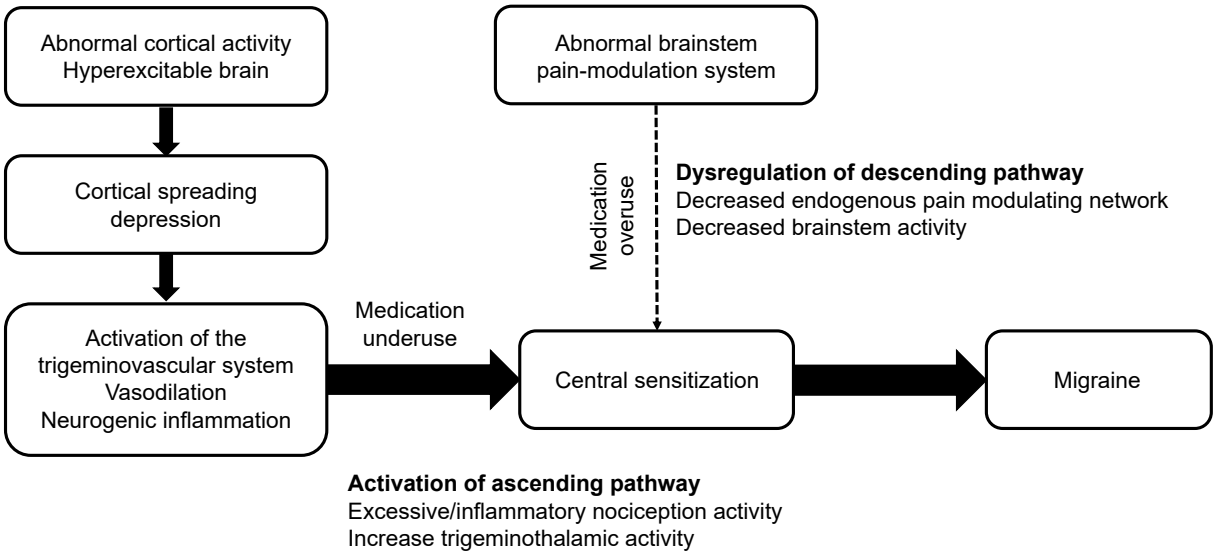

Figure 1. Interplay of medication underuse and overuse in migraine progression.

tion of individuals who warrant acute or preventive therapy do not receive it, contributing to disease progression.[24,25] Another critical aspect is the inappropriate timing of administration, particularly delaying acute medication until an attack is severe, which significantly reduces efficacy by failing to halt the propagation of central sensitization.[5,26] Finally, patient dissatisfaction, stemming from insufficient efficacy or intolerable side effects, often leads to non-adherence or premature discontinuation of therapy, which are major factors in poor adherence for both acute and preventive medications.[25,27] Objectively measuring these dimensions presents methodological challenges, requiring a comprehensive approach that utilizes patient diaries, prescription data, and validated questionnaires to quantify the patterns and extent of underuse.[28]

2. Key manifestations of acute medication underuse

The underuse of acute medication is a critical iatrogenic factor in migraine progression, manifesting primarily through inadequate treatment efficacy, suboptimal prescribing and delayed administration, and poor tolerability leading to non-adherence.[5] Suboptimal efficacy is a principal contributor to chronification. The American Migraine Prevalence and Prevention (AMPP) Study found a direct, graded association between poor treatment response and the risk of new-onset CM, with individuals reporting "very poor" efficacy having 2.55 times the odds of progressing compared to those with "maximal" efficacy.[23] This is mirrored in South Korean claims data, where extremely high discontinuation rates for acute therapies—with only 25.2% of new triptan users persisting after three months—suggest a significant issue with perceived efficacy or tolerability.[29]

The timing of medication intake also profoundly influences therapeutic success. Contemporary paradigms favor immediate treatment at headache inception to prevent the establishment of central sensitization.[5] The TEMPO study demonstrated that early triptan administration (<1 hour post-onset) yielded significantly higher rates of 2-hour pain freedom compared to late administration (≥1 hour).[30] Furthermore, suboptimal prescribing contributes to underuse. In South Korea, for instance, newly diagnosed migraine patients are most frequently prescribed non-steroidal anti-inflammatory drugs (NSAIDs) (69.9%) or acetaminophen (50.0%), rather than migraine-specific triptans, which may be inadequate for moderate-to-severe attacks.[29] Lastly, poor tolerability is a major barrier to effective treatment. Data from the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study revealed that 35.5% of individuals who had ever used acute prescription medications had discontinued them, with tolerability (24.9%) and efficacy concerns (28.2%) being key reasons.[31] The challenge of non-adherence is starkly illustrated in South Korea, where 65.7% of newly diagnosed patients discontinue their initial acute treatment within 3 months, highlighting a critical gap in maintaining effective therapy.[29]

3. Key manifestations of preventive medication underuse

Underuse of preventive medication represents a significant gap in migraine care, leaving many patients vulnerable to disease progression. This issue is influenced by low initiation rates among eligible patients, poor adherence, and high discontinuation rates for those who start therapy, and challenges with tolerability. A substantial proportion of individuals who meet established criteria for preventive therapy do not receive it. In the United States, it is estimated that while approximately 38% of people with migraine qualify for prophylaxis, only 12%–13% actually use it.[32,33] This treatment gap is a global issue, with European data showing that only 26% of eligible patients use traditional preventive agents, and a South Korean analysis finding that only 7.3% of newly diagnosed patients were prescribed preventive treatment.[29,34]

Even when preventive therapy is initiated, adherence and persistence are notably poor, particularly with traditional oral agents. Real-world data report adherence rates as low as 17%–20% at 12 months, with persistence even lower in CM populations.[35,36] Data from South Korea mirror these findings, showing persistence rates for some preventive treatments dropping to just 6%–7% after 12 months.[29] A primary factor in this low adherence is the adverse effect profile of many traditional preventive medications. Meta-analyses show that approximately 23% of patients withdraw from clinical trials due to side effects, and in real-world settings, tolerability concerns contribute to discontinuation in up to 30% of cases.[37,38] This dissatisfaction is a key factor leading to treatment abandonment, which perpetuates a cycle of underuse and leaves patients

exposed to the risks of migraine progression.[39]

4. Etiology of underuse

MU is a complex behavior resulting from the interplay of psychological, educational, and socioeconomic factors. These can be broadly categorized into patient-centered barriers and system- or clinician-related barriers. Patient-centered barriers include fear of side effects, which many find more distressing than the headache itself, and concerns about addiction or tolerance, which may be an unintended consequence of warnings about MOH.[21,40] Distrust in efficacy from past negative experiences can also lower expectations for new treatments, while social stigma may cause patients to avoid taking medication in public.[27,41]

System- and clinician-related barriers are also significant. Limited access to care, due to geographic distance or long wait times, can prevent timely management.[24] The high cost of newer, more effective treatments is another substantial barrier that can cause patients to ration or forgo medication.[42] Finally, insufficient clinician education can lead to a failure to adequately address patient fears and misconceptions or to provide clear instructions, resulting in a passive or hesitant approach to treatment on the part of the patient.[43]

5. A hypothesized mechanism for underuse-mediated progression

The central hypothesis of this review is that underuse of acute migraine medication is causally linked to the progression to CM. The proposed biological mechanism involves a cascade beginning with the repetition of uncontrolled neuroinflammation. When a migraine attack is untreated or undertreated, the release of CGRP and subsequent neurogenic inflammation persist at maximum intensity and for a prolonged duration (Figure 1).[11] This potent and sustained inflammatory state strongly stimulates trigeminal nerve endings, sending a massive barrage of nociceptive signals to the central nervous system.[8] The repeated transmission of these intense pain signals acts as a powerful stimulus that strengthens synaptic connections and lowers activation thresholds in the trigeminocervical complex and thalamus, effectively inducing and consolidating a state of central sensitization.[9] At the clinical level, these neurobiological changes manifest as an increased frequency and severity of headache attacks, diminished responsiveness to future treatments, and ultimately, the transformation to CM.[5] In summary, MU accelerates chronification by sustaining ascending nociception and eroding descending inhibition, underscoring the need for timely pharmacotherapy to preserve neural homeostasis.

MU and overuse are not mutually exclusive phenomena; rather, they can interact dynamically within a patient's disease course. A patient might initially adopt an underuse strategy due to fears of MOH and side effects. This underuse could promote disease progression and deepen central sensitization, making headaches more frequent and severe. Faced with intractable pain, the patient may then overcome their initial fears and begin using medication frequently out of desperation, transitioning into a state of overuse. This suggests that underuse is not merely the opposite of overuse, but can be a direct precursor, facilitating the disease progression that culminates in the frequent medication use characteristic of MOH. To emphasize the relationship between MU and MOH, Table 1 summarizes their key features including definitions, behaviors, pathophysiological mechanisms, clinical consequences, and management strategies, emphasizing their interconnected roles in disease progression.

CLINICAL IMPLICATIONS AND A NEW FRAMEWORK FOR MIGRAINE MANAGEMENT

1. Re-evaluating the therapeutic window

The primary goal of acute migraine treatment is rapid pain cessation, ideally within 2 hours, to halt the underlying neuroinflammatory cascade and prevent attack recurrence.[44] Effective and timely treatment is critical because a migraine attack is a progressive neurological event. The development of cutaneous allodynia—pain from normally non-painful stimuli—serves as a clinical marker for the establishment of central sensitization.[8] This process follows a distinct timeline: within 1 hour of headache onset, allodynia may appear on the same side as the pain; by 2 hours, it can spread to the opposite side of the head and even the limbs, indicating that sensitization has progressed from second- to third-order neurons in the thalamus.[8] This neu-

Table 1. Comparative analysis of medication overuse and underuse in migraine progression

Features	Medication underuse	Medication overuse
Definition	The suboptimal application of indicated treatments, including underutilization, delayed administration, or premature discontinuation	The frequent use of acute headache medications exceeding ICHD-3 criteria for more than 3 months
Primary behavior	Avoidance, delayed intake, and non-adherence, often due to fear of side effects or concerns about developing MOH	Frequent, excessive consumption of acute medication in a vicious cycle to manage escalating headache pain
Pathophysiology	Repetitive and intense neuroinflammation from untreated attacks, induction and reinforcement of central sensitization via uncontrolled nociceptive input	Dysfunction of endogenous pain modulation systems, neurotransmitter receptor downregulation, and exacerbation of central sensitization
Clinical consequences	Progression of episodic to chronic migraine by increasing headache frequency, severity, and treatment resistance	The development of a new type of headache or worsening of a pre-existing one, leading to a more refractory state
Management strategy	Patient education to correct misconceptions, identification and resolution of treatment barriers, emphasis on early treatment, shared decision-making, a stratified care approach for acute treatment, and timely initiation of preventive therapy	Discontinuation of the overused medication (with inpatient care if needed), often with bridge therapy, and implementation of an effective preventive treatment plan

ICHD, International Classification of Headache Disorders; MOH, medication overuse headache.

robiological cascade creates a critical therapeutic window. Preclinical and clinical studies demonstrate that early intervention can block central sensitization, whereas delayed treatment is significantly less effective. For example, the response rate to sumatriptan is 93% in non-allodynic patients but only 15% in those who have already developed allodynia.[8] Therefore, optimal use of acute medication is not merely for symptomatic relief but is a crucial strategy to prevent the neuroplastic changes that facilitate treatment resistance and disease progression.

2. Acute treatment guidelines to prevent underuse

To prevent the underuse that facilitates chronification, clinical guidelines advocate for a stratified care approach, which tailors therapy to attack severity rather than employing a step care model.[45] This strategy is more effective and cost-efficient in reducing disability. For mild attacks, NSAIDs are recommended as initial therapy. For moderate to severe attacks, migraine-specific agents, triptans are first-line. Triptans should be administered at an adequate dose early in the attack, ideally within 60 minutes of onset, to optimize efficacy and prevent central sensitization.[5] If the initial response is inadequate, options include combining a triptan with an NSAID or switching to an alternative triptan, as individual responses can vary. For patients in whom triptans are ineffective, poorly tolerated, or contraindicated due to cardiovascular risk, newer classes of medication, such as gepants (ubrogepant, rimegepant) or lasmiditan are recommended.[45,46] These agents provide effective alternatives without the vasoconstrictive properties of triptans. Patient education is crucial to prevent MOH, limiting simple analgesics, NSAIDs, or lasmiditan to fewer than 10 days per month, and combined analgesics or triptans to 8 days per month. Gepants may be preferable in individuals at higher risk for MOH, as there is currently no evidence linking gepants to MOH.[46]

3. Preventive treatment guidelines to prevent underuse

Preventive therapy is a cornerstone of migraine management, aimed at reducing attack frequency, severity, and duration, which in turn decreases reliance on acute medications and lowers the risk of both underuse and overuse.[47] Prophylaxis is indicated for patients with 4 or more monthly headache days, significant disability despite acute treatment, or contraindications to acute therapies. To combat underuse, guidelines recommend selecting first-line agents with high-level evidence, such as beta-blockers, certain anticonvulsants, and CGRP-targeted therapies.[48,49] Treatment should be initiated at a low dose and titrated slowly to improve tolerability and prevent premature discontinuation. A crucial element to prevent underuse is

allowing an adequate trial period before judging efficacy: at least 2 to 3 months for oral agents at a target dose, and 3 to 6 months for injectable therapies. If a treatment is ineffective or poorly tolerated, switching to an agent from a different class is recommended over abandonment of preventive strategy.

4. The role of novel targeted therapies in addressing underuse

The advent of CGRP-targeted therapies, including monoclonal antibodies (mAbs) and gepants, has significantly advanced migraine prevention by offering superior efficacy and tolerability compared to many traditional oral agents.[45] Their targeted mechanism results in higher response rates and fewer systemic side effects, which can improve adherence and persistence. Consequently, recent guidelines endorse anti-CGRP mAbs as a potential first-line option, removing the requirement to fail multiple older medications first.[45] However, significant barriers contribute to their underuse. High costs and restrictive reimbursement policies often limit access to patients with refractory migraine who have failed several other treatments.[34] For example, in South Korea, reimbursement for CGRP mAbs is restricted to patients with CM who have failed at least three oral preventives.[29] This is problematic, as a higher number of prior treatment failures is a negative predictor of response to anti-CGRP therapy.[50] Emerging evidence on response predictors such as lower baseline headache frequency and good response to triptans suggests that earlier initiation of these targeted therapies may optimize outcomes and prevent the progression of disease burden.

CONCLUSION

Migraine is a progressive neurological disorder, but its progression is often preventable. This review repositions MU not as a passive failure of treatment but as an active, iatrogenic risk factor for migraine chronification. The long-held clinical focus on MOH has, while important, overshadowed the reality that underuse and overuse are two facets of the same core problem: suboptimal disease management. Ineffective or delayed acute treatment allows for the establishment of central sensitization, which increases headache frequency and reduces therapeutic response.[5] This, in turn, can lead patients toward more frequent medication intake, creating a direct pathway from underuse to overuse and a more refractory disease state.[23]

Halting this progression requires a paradigm shift toward optimal use, guided by evidence-based principles. This includes the timely and effective application of acute therapies within the critical neurobiological window to prevent central sensitization, and the early consideration of preventive therapy for eligible patients to reduce the overall attack burden. A crucial component of this strategy is the ongoing assessment of treatment efficacy and tolerability, fostering a collaborative relationship between clinician and patient to identify and overcome barriers to adherence. Educating both healthcare providers and patients on the profound risks of underuse is paramount. By treating each migraine attack effectively and implementing preventive strategies proactively, it is possible to alter the natural history of the disease, prevent the cycle of underuse and overuse, and mitigate the long-term disability associated with CM.

AVAILABILITY OF DATA AND MATERIAL

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

AUTHOR CONTRIBUTIONS

Conceptualization: HSM, PWC; Writing–original draft: HSM; Writing–review & editing: HSM, PWC.

CONFLICT OF INTEREST

Heui Soo Moon received honoraria as a moderator/speaker/advisor from Abbvie Korea, Teva-Handok, Lundbeck Korea, Pfizer Korea, Oganon Korea, Dong-A Pharm, YuYu Pharm, SK Pharm, and Ildong Pharm. She was a site investigator for a multicenter trial sponsored by Biohaven Pharmaceuticals, Allergan Korea, and Ildong Pharmaceutical Company. She has received lecture honoraria from Eli Lilly and Company, Handok-Teva, and Ildong Pharmaceutical Company over the past 24 months. The other author has no other conflicts of interest to declare.

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Trigeminal Autonomic Cephalalgias Following Unilateral Dorsolateral Medullary Infarction: A Case Series and Literature Review

Jae-Myung Kim, Hak-Loh Lee, You-Ri Kang, Joon-Tae Kim, Seung-Han Lee

Department of Neurology, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Republic of Korea

Abstract

Purpose: Secondary trigeminal autonomic cephalalgias (TACs) are typically associated with posterior fossa abnormalities, such as tumors and vascular malformations. However, TACs following brainstem infarctions are rarely reported. This study aimed to characterize the clinical and anatomical features of TACs after unilateral dorsolateral medullary infarction.

Methods: We analyzed four patients with dorsolateral medullary infarction who developed secondary TACs, diagnosed using the International Classification of Headache Disorders, third edition criteria. All patients underwent detailed neurological examinations and neuroimaging, including diffusion-weighted magnetic resonance imaging and magnetic resonance angiography. Additionally, five published cases were identified through a literature review and analyzed in conjunction with our cohort.

Results: All patients exhibited stabbing or electric shock-like pain in the ipsilateral periorbital, hemifacial, and temporal regions. Headaches developed weeks to months post-stroke with brief attacks (1–2 minutes) occurring 1–5 times daily. Lacrimation and conjunctival injection were common. Three patients were diagnosed with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), while a fourth had short-lasting unilateral neuralgiform with cranial autonomic symptoms (SUNA). Each patient, as well as four of the five from the literature, exhibited ipsilateral facial sensory loss, suggesting involvement of the trigeminal spinal tract and nucleus. Delayed headache onset was more frequent in persistent cases.

Conclusion: Headache characteristics were more consistent with SUNCT/SUNA than with typical cluster headaches. Careful neurological examination is essential to detect focal signs and guide neuroimaging for identifying secondary causes. Clinicians should consider secondary TACs in patients with new-onset SUNCT/SUNA and focal brainstem signs.

Keywords: Brain stem infarctions, Headache, Lateral medullary syndrome, Trigeminal autonomic cephalalgias

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Correspondence: Seung-Han Lee, M.D., Ph.D.
Department of Neurology, Chonnam National University Hospital, 42 Jebong-ro, Dong-gu, Gwangju 61469, Republic of Korea
Tel: +82-62-220-6274, Fax: +82-62-228-3461, E-mail: nrshlee@chonnam.ac.kr

INTRODUCTION

Trigeminal autonomic cephalalgias (TACs) are a group of primary headache syndromes characterized by severe, short-lasting, unilateral headaches accompanied by paroxysmal cranial autonomic symptoms.[1] Although several cases of secondary TACs have been reported, a definitive causal relationship between the underlying pathophysiology and the associated structural lesion in most cases remains uncertain.[2,3] Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform with cranial autonomic symptoms (SUNA) are categorized under TACs and are typically considered primary headache disorders.[4] Although rare, secondary causes, including structural lesions such as neoplasms, vascular malformations, demyelinating plaques, and infarctions, have been documented, particularly in patients with atypical features or poor treatment response.[4,5] A comprehensive review by Cao et al.[5] reported that approximately 15%–20% of SUNCT/SUNA cases may also present a secondary etiology, most commonly involving lesions in the pons, medulla, or cavernous sinus. According to Kang and Cho,[4] structural abnormalities have been observed in some patients with SUNCT or SUNA, especially in those presenting with neurological signs or unusual headache characteristics. These findings underscore the importance of neuroimaging and detailed neurological examinations in patients with SUNCT/SUNA to identify potential secondary causes that may significantly influence diagnosis, management, and prognosis.

However, reports of secondary TACs remain limited, and additional case-based observations are needed to provide a more comprehensive understanding of the underlying mechanisms and clinical course.[4,6-9] Thus, this study represents a case series of patients with secondary TACs following unilateral dorsolateral medullary infarction, aimed at clarifying the clinical characteristics and anatomical substrates of this patient subset.

MATERIALS AND METHODS

1. Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Chonnam National University Hospital (IRB No. CNUH-2025-258), and all patients provided written informed consent for publication.

2. Participants and procedures

The study subjects were consecutively enrolled from patients who visited Chonnam National University Hospital between January 2015 and April 2025. The inclusion criteria in this study were as follows: 1) a unilateral high signal intensity lesion involving the dorsolateral medulla suggestive of cerebral infarction on brain magnetic resonance imaging (MRI) including diffusion-weighted imaging (DWI); 2) a headache that developed after the index infarction, fulfilling the diagnostic criteria of TACs according to the International Classification of Headache Disorders, third edition (ICHD-3). Patients with a prior history of chronic headache, underlying structural brain lesions unrelated to infarction, or incomplete imaging data were excluded.

All patients underwent emergency brain MRI on admission as part of the institutional acute stroke protocol. The MRI protocol consisted of DWI (slice thickness, 4 mm), fluid-attenuated inversion recovery, gradient echo imaging, and time-of-flight magnetic resonance angiography (MRA) sequentially.

Additionally, all patients received detailed neurological examinations at the time of the initial event. Baseline demographics and headache characteristics, including timing of onset, frequency, duration, location, quality, and associated cranial autonomic features, were systematically evaluated through clinical interviews and chart reviews. SUNCT or SUNA diagnoses were performed in accordance with the ICHD-3 criteria (Table 1).

3. Data collection

To identify previously reported cases of secondary SUNCT/SUNA associated with dorsolateral medullary infarction, we searched the PubMed and MEDLINE databases up to April 2025 using the terms “SUNCT,” “SUNA,” “secondary,” and “medullary infarction.” Inclusion was limited to peer-reviewed case reports or case series with radiologically confirmed medullary infarcts and headache features consistent with TACs.

Table 1. Diagnostic criteria of SUNCT/SUNA according to the ICHD-3

SNUHA
A. At least 20 attacks fulfilling criteria B–D
B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting 1–600 seconds and occurring as single stabs, series of stabs, or in a saw-tooth pattern
C. At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain:
1. conjunctival injection and/or lacrimation
2. nasal congestion and/or rhinorrhoea
3. eyelid oedema
4. forehead and facial sweating
5. forehead and facial flushing
6. sensation of fullness in the ear
7. miosis and/or ptosis
D. Occurring with a frequency of at least once daily
E. Not better accounted for by another ICHD-3 diagnosis.
SUNCT
A. Attacks fulfilling criteria for SNUHA, and criterion B below
B. Both of the following are ipsilateral to the pain:
1. conjunctival injection
2. lacrimation (tearing)
SUNA
A. Attacks fulfilling criteria for SNUHA, and criterion B below
B. Only one or neither of conjunctival injection or lacrimation (tearing).

SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA, short-lasting unilateral neuralgiform with cranial autonomic symptoms; ICHD-3, International Classification of Headache Disorders, third edition; SNUHA, short-lasting unilateral neuralgiform headache attacks.

RESULTS

Among the 231 patients diagnosed with dorsolateral medullary infarction during the study period, 204 completed at least 6 months of follow-up after the index stroke and were eligible for analysis. Of these, four patients (three males; mean age, 58.3±8.4 years; 4/204 [1.96%]) developed headache syndromes consistent with TACs and were included in this study. Baseline demographics, characteristics of the index stroke, MRI-identified lesions, and headache characteristics are summarized in Table 2 and Figure 1. All patients exhibited either stabbing (50%) or electric shock-like pain in the ipsilateral periorbital, hemifacial, and temporal regions. Headaches developed 2.5 to 4 months after the initial infarction (mean, 3 months) with brief attacks lasting 1–2 minutes, occurring 1–5 times daily. Lacrimation (100%) and conjunctival injection (75%) were common cranial autonomic symptoms, all of which were observed on the ipsilateral side. According to the diagnostic criteria of ICHD-3, three patients (75%) were compatible with a SUNCT diagnosis, while one experienced SUNA, rather than a typical trigeminal neuralgia (TN) or cluster headache. The headaches persisted for several years in three patients (75%) despite empirical treatment with medications including gabapentin, amitriptyline, or lithium.

Notably, all patients showed at least one focal neurological sign during the acute stroke phase, which preceded the onset of the headache. These included sensory loss on the ipsilateral hemiface (100%), sensory loss on the contralateral hemibody, ipsilateral limb ataxia and/or truncal ataxia, and spontaneous horizontal and torsional nystagmus beating toward the contralesional side. Based on the neuroimaging results of the patients, a clinico-anatomical correlation analysis invariably revealed the involvement of the trigeminal spinal tract and nucleus, as well as the adjacent spinothalamic tract, inferior cerebellar peduncle, and vestibular nucleus.

Stroke mechanism analysis using the Trial of Org 10172 in Acute Stroke Treatment classification revealed small vessel occlusion in two patients, large artery atherosclerosis in one patient, and stroke of other determined etiology (i.e., vertebral artery [VA] dissection) in one patient. MRA findings varied: one patient had VA stenosis, one had VA hypoplasia, one had VA dissection, while another showed no vascular abnormality (Table 2).

From a literature review, we identified five additional published cases of secondary SUNCT/SUNA associated with dorsolateral medullary infarction (Table 2).[6,7,10-12] Compared to our case series, the onset of headache in these cases varied, ranging from the day of stroke to 6 months later (mean, 1.43 months), indicating considerable heterogeneity.[6,7,10-12] In three cases, the frequency of pain exceeded 10 episodes per day.[7,11,12] Otherwise, the duration, character, and location of pain were similar to those observed in our cases. Four of the five cases provided detailed neurological findings, and each of these four exhibited ipsilateral facial sensory disturbance (4/4, 100%).[6,10-12] Among the three patients with available angiographic data, VA stenosis, dissection, and occlusion were each observed in one patient.[6,7,11]

Table 2. Clinical characteristics of TACs secondary to dorsolateral medullary infarction: present cases and literature review

Case	Age (yr)	Sex	Index stroke						Headache characteristics							Diagnosis of headache (ICHD-3)
			Risk factor	TOAST	Angiography	MRI lesion	Associated neurological signs	Onset after stroke	Side	Location	Duration	Nature	Frequency (times)	Outcome	Autonomic symptoms	
Present cases																
Patient 1	70	Male	HTN, DL	SVO	Normal	Rt. LMI	SL (i-F and c-B), AT (i-L and T), hoarseness	3 mo	i	Periorbital, hemifacial, and temporal	1–2 min	Stabbing	3–4/day	Persistent	LC, CI, rhinorrhea	SUNCT
Patient 2	57	Male		SVO	VA hypoplasia	Lt. LMI	SL (i-F and c-B), DysP, AT (i-L), vertigo, NY	2.5 mo	i	Periorbital, hemifacial, and temporal	1–2 min	Stabbing	1–5/day	Resolved after several years	LC, CI	SUNCT
Patient 3	56	Male	Lipid	LAA	VA severe stenosis	Lt. LMI	SL (i-F and c-B), AT (T), HS, vertigo, NY	4 mo	i	Periorbital, hemifacial, and temporal	<1 min	Electric shock-like	1–5/day	Persistent	LC, CI, nasal congestion	SUNCT
Patient 4	50	Female	HTN, HCC, RA	SOD	VA dissection	Rt. LMI	SL (i-F and c-B), AT (i-L and T), HS, vertigo, NY	2.5 mo	i	Periorbital, hemifacial, and temporal	<1 min	Electric shock-like	1–5/day	Persistent	LC	SUNA
Published cases																
Rodrigues et al. (2007)[12]	54	Male	HTN	N/A	N/A	Rt. LMI	SL (i-F and c-B), AT (i-T), DysA	6 mo	i	Orbital	20 sec	N/A	>10/hr	Persistent	LC, CI	SUNCT
Jin et al. (2016)[6]	64	Male	HTN, DM	LAA	VA occlusion	Lt. LMI	SL (i-F), HS, AT (i-T), vertigo	13 day	i	Periorbital	3–10 sec	Stabbing	1–4/day	Resolved after 19 days	LC, CI, rhinorrhea	SUNCT
Lambru et al. (2017)[7]	58	Male	HTN	SOD	VA dissection	Rt. LMI (hemorrhagic)	N/A	21 day	i	Periorbital–temporal radiating to cheek/jaw	5–20 sec	Stabbing, sharp	12–15 (up to 50–60)/day	Persistent	LC, CI, ptosis, eyelid edema, rhinorrhea	SUNCT and TN
Lei et al. (2020)[11]	44	Male	None	LAA	VA stenosis	Rt. LMI	SL (i-F and c-B), DysP, DysA, hiccup, hoarseness, HS, AT (i-L and T), hemiparesis (i), NY, vertigo, gag reflex ↓	0 day*	i	Hemifacial, temporal, occipital	10–180 sec	Tearing	>10/day	Resolved after 1 month	LC, CI, nasal congestion	SUNCT
Gadah et al. (2025)[10]	~40	Male	None	N/A	N/A	Rt. LMI	SL (i-F; V1 and V2), hand numbness (i)	4 day	i	Hemifacial	1 min	Burning	>4/day	Improved after 1 month, but persisted until 1 year	LC, CI, nasal discharge, facial grimacing with facial edema	SUNCT
Total (n=9)		Male (n=8)					SL (i-F)=8 of 9	0 day*–6 mo	i (100%)					Persistent=5, resolved=4		SUNCT=8, SUNA=1

TAC, trigeminal autonomic cephalalgia; TOAST, Trial of Org 10172 in Acute Stroke Treatment; MRI, magnetic resonance imaging; ICHD-3, International Classification of Headache Disorders, third edition; HTN, hypertension; DL, dyslipidemia; SVO, small vessel occlusion; Rt., right; LMI, lateral medullary infarction; SL, sensory loss; i, ipsilateral; F, face; c, contralateral; B, body; AT, ataxia; L, limb; T, trunk; LC, lacrimation; CI, conjunctival injection; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; VA, vertebral artery; Lt., left; DysP, dysphagia; NY, nystagmus; LAA, large artery atherosclerosis; HS, Horner's syndrome; HCC, hepatocellular carcinoma; RA, rheumatoid arthritis; SOD, stroke of other determined etiology; SUNA, short-lasting unilateral neuralgiform with cranial autonomic symptoms; N/A, not available; DysA, dysarthria; DM, diabetes mellitus; TN, trigeminal neuralgia.
*Same day as stroke onset.

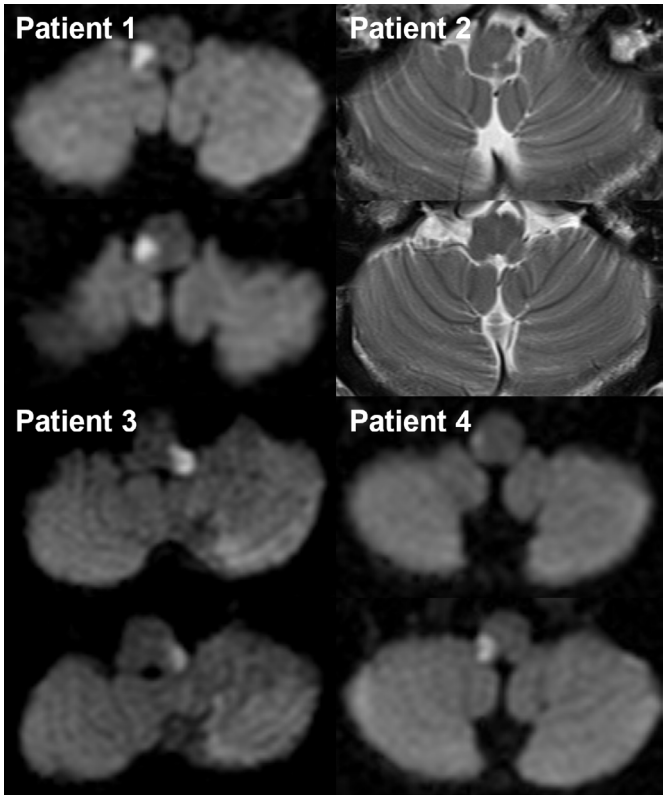

Figure 1. Neuroimaging of the four patients who presented with dorsolateral medullary infarction. Diffusion-weighted (patients 1, 3, and 4) or T2-weighted (patient 2) brain magnetic resonance imaging shows high signal intensity lesions involving the unilateral dorsolateral medulla. An additional lesion in the ipsilateral cerebellar hemisphere is also observed in patient 3.

We analyzed the time of headache onset after the index stroke and the persistence of the headache in our four cases and five previously reported cases (Table 3). Among these nine patients, five experienced persistent symptoms, and four showed resolution. In the persistent group, headache onset occurred at a mean of 3.24 months (range, 0.7–6 months) after the stroke. In contrast, the resolved group showed a mean onset time of 0.76 months (range, 0–2.5 months).

DISCUSSION

Secondary TACs are relatively uncommon and are related to a wide range of structural brain lesions, including neoplasms, vascular malformations, demyelinating diseases, arterial dissections, and infarctions.[3,6,7,9,11,13,14] Among these, dorsolateral medullary infarction—also known as Wallenberg syndrome—is a rare but increasingly recognized etiology of secondary TACs, particularly those resembling SUNCT and SUNA phenotypes.[6,7,10-13]

In our case series, all four patients developed headache syndromes, consistent with secondary TACs, 2.5 to 4 months after unilateral dorsolateral medullary infarction. The pain was characterized by brief, stabbing or electric shock-like episodes in the ipsilateral periorbital and hemifacial regions, accompanied by prominent cranial autonomic symptoms such as lacrimation and conjunctival injection. The clinical features in three patients met the ICHD-3 diagnostic criteria for SUNCT, while one patient met the criteria for SUNA. This predominance of SUNCT/SUNA, rather than cluster headache, is consistent with prior reports of brainstem-related secondary TACs.[3,6,7,9,11,13] Conversely, differentiating between TN-like features and SUNCT/SUNA is often clinically challenging because of overlapping clinical features, as illustrated by a case in our literature review by Lambru et al.,[7] which demonstrated coexisting SUNCT- and TN-like features due to dorsolateral medullary hemorrhagic infarction.[4,15,16] In Lambru et al.,[7] the patient with dorsolateral medullary infarction expected two distinct types of attacks: one with short-lasting stabbing pain (5–20 seconds) accompanied by cranial autonomic symptoms such as lacrimation and conjunctival injection, fulfilling the diagnostic criteria of SUNCT; another type, similarly localized, but triggered by innocuous stimuli (e.g., touch, wind), lacking autonomic signs, and featuring a dull post-attack ache, consistent with TN. The coexistence of these patterns led the authors to diagnose concurrent SUNCT and TN, rather than a single disorder.[7] Traditionally, TN is characterized by the involvement of second or third divisions in the trigeminal nerve, a refractory period following exposure to triggers, and the absence of cranial autonomic symptoms.[4,7,15,16] In contrast, SUNCT/SUNA typically involves the first division of the trigeminal nerve, presents with longer-lasting attacks (up to 600 seconds), lacks a refractory period, and prominently features autonomic symptoms.[4,7,15,16] However, several cases of TN may occasionally present with mild cranial autonomic features, meaning the presence or absence of a refractory period can be difficult to assess, especially in patients with complex stroke-related presentations.[7,15,16] In our current series, all patients reported cranial autonomic symptoms,

Table 3. Comparison of clinical features between persistent and resolved secondary TACs following dorsolateral medullary infarction

Group	Case (Ref.)	Headache onset after stroke	Headache duration	Diagnosis	Tx. regimen (max. daily dose)	Duration (mo)	Associated neurological signs
Persistent (n=5)	Patient 1 (this study)	3 mo	Persistent	SUNCT	VER 80 mg/GBP 800 mg/LIT 600 mg/ VPA 250 mg	42/96/66/72	SL (i-F and c-B), AT (i-L and T), hoarseness
	Patient 3 (this study)	4 mo	Persistent	SUNCT	VER 180 mg/AMI 5 mg/GBP 300 mg	87/90/75	SL (i-F and c-B), AT (T), HS, vertigo, NY
	Patient 4 (this study)	2.5 mo	Persistent	SUNA	PGB 150 mg/GBP 800 mg	74/118	SL (i-F and c-B), AT (i-L and T), HS, vertigo, NY
	Rodrigues et al. (2007)[12]	6 mo	Persistent	SUNCT	VER*/CBZ*/LTG*	N/A	SL (i-F and c-B), AT (i-T), DysA
	Lambru et al. (2017)[7]	21 day	Persistent	SUNCT/TN	CBZ 800 mg/OXC 1,350 mg/GBP 900 mg/AMI 40 mg/LTG 50 mg/DLX 30 mg	N/A	N/A
Mean	-	3.24 mo	-	-			-
Resolved (n=4)	Patient 2 (this study)	2.5 mo	Resolved	SUNCT	GBP 400 mg	60	SL (i-F and c-B), DysP, AT (i-L), vertigo, NY
	Jin et al. (2016)[6]	13 day	Resolved	SUNCT	No Tx.	N/A	SL (i-F), HS, AT (i-T), vertigo
	Lei et al. (2020)[11]	0 day	Resolved	SUNCT	N/A	N/A	SL (i-F and c-B), DysP, DysA, hiccup, hoarseness, HS, AT (i-L and T), hemiparesis (i), NY, vertigo, gag reflex ↓
	Gadah et al. (2025)[10]	4 day	Resolved	SUNCT	LTG*	12	SL (i-F; V1 and V2), hand numbness (i)
Mean	-	0.76 mo	-	-			-

TAC, trigeminal autonomic cephalalgia; Ref., reference; Tx., treatment; max., maximum; SUNCT, short-lasting unilateral neuralgiform headache with conjunctival injection and tearing; VER, verapamil; GBP, gabapentin; LIT, lithium; VPA, valproic acid; SL, sensory loss; i, ipsilateral; F, face; c, contralateral; B, body; AT, ataxia; L, limb; T, trunk; AMI, amitriptyline; HS, Horner's syndrome; NY, nystagmus; SUNA, short-lasting unilateral neuralgiform with cranial autonomic symptoms; PGB, pregabalin; CBZ, carbamazepine; LTG, lamotrigine; N/A, not available; DysA, dysarthria; OXC, oxcarbazepine; DLX, duloxetine; TN, trigeminal neuralgia; DysP, dysphagia.
*Exact medication doses were not reported in the original case reports.

and none had a definite refractory period. Moreover, none of the attacks were clearly stimulus-provoked in a way consistent with TN. Based on these clinical characteristics, these patients were diagnosed with SUNCT/SUNA rather than TN.

While some post-stroke pain syndromes may emerge in the acute phase, others, including central post-stroke pain, can have a delayed onset.[17] Similarly, secondary SUNCT/SUNA in our series tended to develop in the subacute or even chronic phase following the index infarction. Notably, our findings suggest that the timing of headache onset may have prognostic implications. Among the nine patients analyzed (our four cases and five from the literature), those with persistent headache symptoms had a later onset (mean, 3.24 months) compared to those whose symptoms eventually resolved (mean, 0.76 months). This observation raises the possibility that delayed onset is associated with a greater risk of chronification, potentially reflecting distinct pathophysiological mechanisms, such as central sensitization or maladaptive reorganization, within trigeminal–autonomic pathways.[18,19] These findings underlie the importance of temporal profiling in secondary TACs and emphasize the need for prospective studies with larger cohorts to clarify the temporal relationship between infarction and headache onset in secondary TACs.

Although the clinical presentation of a cluster headache and SUNCT/SUNA can be quite similar, the headache duration, clustering pattern, and treatment responses (e.g., oxygen therapy or indomethacin) can be used to differentiate these conditions.[2,4,20] While the precise mechanisms remain unclear, the characteristic clustering of pain in cluster headache suggests that, in addition to involvement

of the trigeminal spinal tract and nucleus at the medullary level, dysfunctions of the hypothalamus and the broader trigeminal–autonomic network may also play a significant role.[21-23] Consequently, we speculate that the more complex pathophysiology of cluster headache may explain the lower observed incidence of this condition compared to SUNCT/SUNA in cases of isolated dorsolateral medullary infarctions. Nonetheless, further research is warranted to prove our hypothesis.

A cerebral infarction involving the dorsolateral medulla, commonly referred to as Wallenberg syndrome, presents with a constellation of neurological signs, including ipsilateral facial sensory disturbances, contralateral hemibody sensory loss, ataxia, vertigo, and Horner's syndrome, depending on the specific anatomical structures involved.[24] In our series, all four patients exhibited ipsilateral facial sensory deficits (Table 2). Among the five previously published cases of TACs associated with dorsolateral medullary infarction, four provided detailed neurological findings, and all of these described ipsilateral facial sensory loss (Table 2). This consistent pattern across both our cases and the literature strongly implicates the spinal trigeminal tract and nucleus as the key anatomical structures involved in the development of secondary TACs. Although the precise pathomechanisms underlying secondary TACs in dorsolateral medullary infarction remain to be elucidated, it is thought that disruption of the spinal trigeminal tract and nucleus within the dorsolateral medulla may lead to disinhibition or aberrant activation of the trigeminal–autonomic reflex arc.[6,18] This may represent the underlying issue attached to the SUNCT or SUNA phenotypes observed in these patients. Given the convergence of nociceptive and autonomic pathways in this region, the spinal trigeminal complex appears to serve as a critical neuroanatomical substrate for secondary TACs following medullary infarction.[6,7,13]

Importantly, all of our patients exhibited additional focal neurological signs, including crossed sensory loss, nystagmus, ataxia, and Horner's syndrome, at the time of the index stroke. These neurological features preceded or accompanied the onset of a headache, providing critical diagnostic clues to a secondary etiology. This stands in contrast to other common secondary TACs such as those caused by pituitary tumors or vascular malformations, where diagnosis is frequently delayed for several months to years, mostly due to isolated headache symptoms without overt focal neurological signs.[2,25]

This study has several limitations. First, this study was not a prospectively designed trial with a predefined, systematic treatment approach for secondary TACs, particularly SUNCT and SUNA. Instead, treatment strategies were heterogeneous across cases, largely reflecting stroke-centered management approaches. Furthermore, patients were initially classified under the broader category of TACs rather than being specifically diagnosed with SUNCT or SUNA. Although the current literature suggests using lamotrigine as a first-line preventive treatment for SUNCT/SUNA,[4] none of our four patients received this therapy. Notably, in a previously reported case,[10] lamotrigine was associated with substantial symptom resolution. This observation suggests that earlier recognition and targeted preventive therapy may influence long-term outcomes in similar cases.

In conclusion, dorsolateral medullary infarction can be a causative lesion for secondary TACs. Based on our results, most patients exhibited a SUNCT or SUNA phenotype and consistently presented with ipsilateral hemifacial sensory loss. Moreover, the delayed onset of headache was often associated with a reduced response to treatment and persistent headache. Thus, future studies should further investigate the pathophysiological mechanisms and prognostic implications of delayed-onset secondary TACs in brainstem infarctions.

AVAILABILITY OF DATA AND MATERIAL

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

AUTHOR CONTRIBUTIONS

Conceptualization: JMK, SHL; Data curation: JMK, HLL, YRK, JTK; Formal analysis: SHL; Investigation: JMK, HLL, YRK, JTK; Validation: SHL; Writing–original draft: JMK, SHL; Writing–review & editing: JMK, HLL, YRK, JTK, SHL.

CONFLICT OF INTEREST

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

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Headache and Pain Research

Isolated Dental and Lower-Facial Pain Mimicking Trigeminal Neuropathy: An Indirect Carotid-Cavernous Fistula

Byoungchul Choi, Chulho Kim, Sung-Hwan Kim, Jong-Hee Sohn

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

Abstract

Carotid-cavernous fistula (CCF) is a pathological arteriovenous communication in which carotid arterial flow is diverted into the cavernous sinus. Clinical manifestations typically include ocular signs, cranial neuropathies, and headache. Neurologic deficits most commonly reflect involvement of cranial nerves III, IV, V1/V2, and VI within or along the cavernous sinus; in contrast, isolated trigeminal presentations are rare, and V3 involvement is particularly uncommon. A 69-year-old woman presented with isolated V2/V3-territory pain, perceived as molar, gingival, and lower facial discomfort. Her symptoms were initially misattributed to trigeminal neuropathy or dental pathology. Subsequently, she developed horizontal diplopia, and bedside testing localized a right abducens palsy. Brain magnetic resonance imaging revealed findings suspicious for a CCF, which was angiographically confirmed as an indirect CCF. Following embolization, the patient's pain markedly improved, implicating the CCF as the source of the V2/V3 symptoms. This case highlights that an atypical, trigeminal-predominant onset—even with pain limited to the V2/V3 distribution—may indicate an indirect CCF. When atypical trigeminal neuropathy is suspected and dental or other peripheral causes are excluded, clinicians should consider the possibility of a CCF.

Keywords: Abducens nerve diseases, Carotid-cavernous sinus fistula, Trigeminal nerve diseases

INTRODUCTION

A carotid-cavernous fistula (CCF) is defined as an abnormal shunt between the carotid arterial circulation and the venous system of the cavernous sinus.[1] CCFs can be classified into two main types: direct and indirect (or dural).[2] The direct type refers to a high-flow fistulous communication where the cavernous portion of the internal carotid artery (ICA) ruptures directly into the cavernous sinus. In contrast, the indirect type is characterized by low-flow fistulas supplied by dural branches of the ICA and/or external carotid artery (ECA) that drain into the cavernous sinus via the meningeal network.[3] Characteristic manifestations can be organized as follows: ocular symptoms/signs—conjunctival hyperemia, orbital congestion with proptosis or chemosis, increased intraocular pressure, orbital bruit, pulsatile exophthalmos, orbital pain, and blurry vision; neurologic symptoms—diplopia from cranial nerve

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Correspondence: Jong-Hee Sohn, Ph.D.
Department of Neurology, Chuncheon Sacred Heart Hospital, 77 Sakju-ro, Chuncheon 24253, Republic of Korea
Tel: +82-33-252-9970, Fax: +82-33-241-8063, E-mail: deepfoci@hallym.or.kr

(CN) III/IV/VI palsies; and headache.[3] Anteriorly draining fistulas are more likely to produce ocular symptoms. By contrast, posteriorly draining fistulas may present with neurologic manifestations such as diplopia from ocular motor nerve palsy, confusion-particularly when cortical venous reflux is present.[1] Involvement of the trigeminal nerve in patients with CCF is uncommon, and published data are limited compared with ocular motor findings.[3,4] V3 involvement has been reported only sporadically,[4,5] and an initial presentation confined to V3 or V2/V3 has been only rarely described. Here, we report a case of CCF that initially presented with V2/V3 involvement and was mistaken for a dental disorder or trigeminal neuropathy. To our knowledge, this report describes an exceptionally rare indirect CCF presenting solely with isolated V2/V3-territory pain at onset, underscoring a diagnostic pitfall in which the lesion can mimic primary trigeminal or dental disease.

CASE REPORT

A 69-year-old woman with a medical history of bipolar disorder, not on any medications, presented with a 1-month history of severe right molar, adjacent gingival pain, and lower facial pain, accompanied by progressively worsening bifrontal headache. The headache was described as a crushing pain, rated 7–8/10 on the numeric rating scale (NRS), associated with nausea and vomiting. Each episode persisted for several hours and, without analgesics, could last throughout the day, with progressive day-to-day worsening over the preceding month. The pain was bifrontal, not clearly positional, and not worsened by Valsalva maneuvers or routine activity. No consistent aggravating or relieving factors were identified, and short-acting analgesics such as acetaminophen/isopropylantipyrine/caffeine combination provided only partial, transient relief. There was no history of photophobia, phonophobia, similar prior headaches, or identifiable triggers such as stress, upper respiratory tract infection, or head trauma. Cranial autonomic features were absent, and neither scalp tenderness nor jaw claudication was reported. The V2/V3-territory pain was predominantly constant and pressure-like, with brief, electric shock-like paroxysms lasting only seconds; during these paroxysms, peaking at 7–8/10 on the NRS. Classical trigeminal neuralgia triggers—chewing, talking, light facial contact, or cold exposure—were not identified.

The patient initially visited a dentist, where dental evaluation, including radiographic studies, revealed no abnormalities. As symptoms persisted and worsened, she presented to the emergency department. On initial assessment, there were no ocular signs (no proptosis or chemosis, no conjunctival arterialization, no orbital bruit), extraocular movements were full without diplopia, and the rest of the neurologic examination was unremarkable. Initial brain computed tomography (CT) and screening labs were normal. Given the normal dental evaluation, unremarkable screening labs and brain CT, and a presentation dominated by facial/V2–V3 pain without objective neuro-ophthalmic findings, the emergency department established a working diagnosis of trigeminal neuropathy and prioritized symptomatic care with short-interval follow-up; advanced neurovascular imaging was deferred until localizing red flags emerged. A brief therapeutic trial of carbamazepine 200 mg twice daily was initiated, which provided only transient, partial relief, with subsequent pain recurrence.

One week before admission, she developed new-onset binocular diplopia. On red-glass testing (red lens over the right eye), the patient exhibited horizontal, uncrossed diplopia with the red image to the right of the white image, worsening on right gaze and at distance, consistent with right abducens (CN VI) palsy. Additionally, the patient continued to experience persistent V2–V3 area pain and aggravated bifrontal headache.

Baseline hematology and chemistry—including complete blood count, electrolytes, renal/hepatic indices—and coagulation tests (prothrombin time/international normalized ratio, activated partial thromboplastin time) were within reference limits. Erythrocyte sedimentation rate and C-reactive protein were normal. A focused screen for secondary trigeminal neuropathy (thyroid-stimulating hormone, vitamin B12, HbA1c) was negative. There were no clinical signs of infection. Brain magnetic resonance imaging (MRI) demonstrated high flow related signal in the right cavernous sinus and asymmetric dilation of the superior ophthalmic veins (right>left), raising suspicion for a CCF (Figure 1). Definitive diagnosis was established on digital subtraction angiography (DSA), which identified a right CCF. DSA demonstrated an indirect CCF supplied by the right meningohypophyseal trunk of the ICA and by right ECA branches, including the internal maxillary

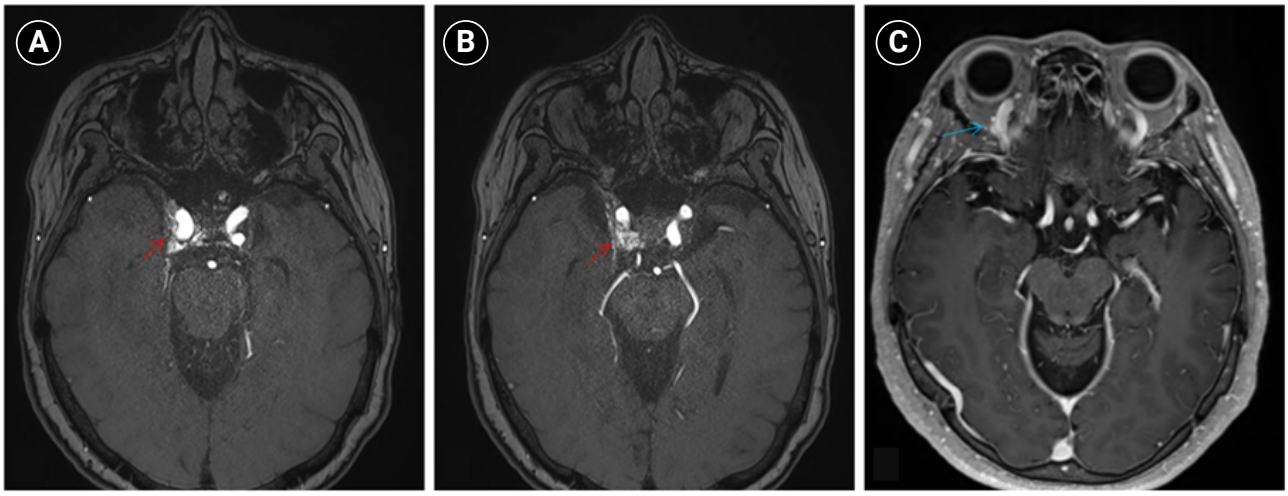

Figure 1. Brain magnetic resonance imaging (MRI) findings. (A, B) Non-contrast time-of-flight magnetic resonance angiography shows a high flow-related signal (red arrows) within the right cavernous sinus. (C) Contrast-enhanced T1-weighted MRI demonstrates asymmetric dilation of the superior ophthalmic veins (blue arrow), more prominent on the right.

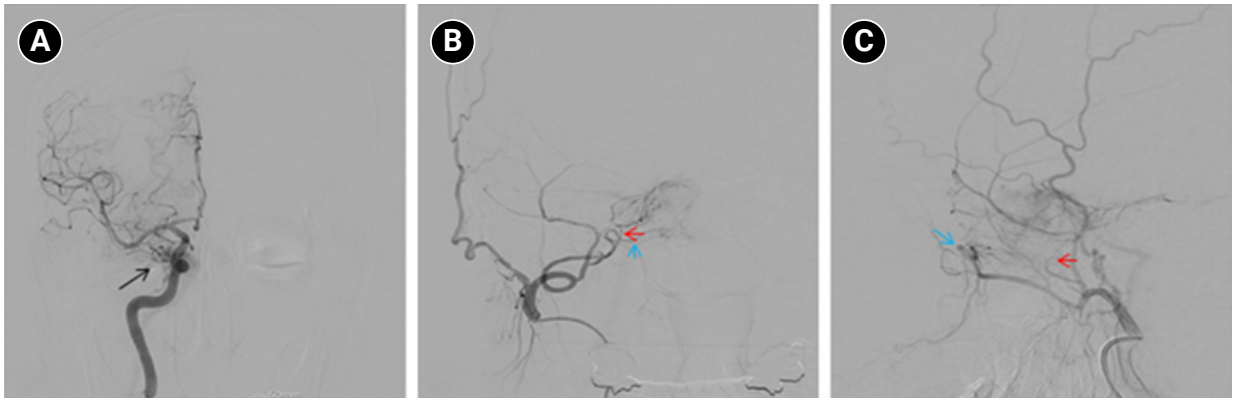

Figure 2. Digital subtraction angiography findings in the patient. (A) Right internal carotid artery (ICA) angiogram shows an indirect carotid-cavernous fistula supplied by the meningohypophyseal trunk of the cavernous ICA (black arrow). (B, C) Right external carotid artery angiogram demonstrates additional arterial supply from external carotid branches, including the internal maxillary artery (blue arrows) and the cavernous branch of the middle meningeal artery (red arrows).

artery and the cavernous branch of the middle meningeal artery, consistent with Barrow type D (Figure 2).[6] Barrow type D denotes an indirect, low-flow fistula with dual ICA/ECA dural supply; unlike direct type, indirect types present more insidiously, and symptom patterns are largely determined by venous drainage, with posterior drainage often manifesting as CN VI palsy and headache (Table 1).[1,3,6,7] The fistula was treated with transvenous Onyx embolization. On post-procedure day 1, non-contrast time-of-flight magnetic resonance angiography (TOF-MRA) demonstrated a marked reduction of flow related hyperintensity within the right cavernous sinus, and the right superior ophthalmic vein caliber decreased from 6.63 to 4.61 mm (Figure 3A, B). Follow-up DSA (at 3 weeks) likewise showed substantial attenuation of fistulous opacification (Figure 3C), supporting a significant interval decrease in arteriovenous shunting. At 1–2 weeks, the patient reported an ~80%–90% reduction in dental/lower-facial pain and bifrontal headache from NRS 7–8 to 1–2. By 1 month, red-glass testing demonstrated resolution of primary-position diplopia. Formal prism measurements were unavailable; bedside ocular-motor grading was recorded using a standard duction underaction scale

Table 1. Barrow classification of carotid-cavernous fistula[1,3,6,7]

Barrow type	Definition (angio-architecture)	Typical flow/Etiology	Clinical course/Severity
A (direct)	Direct fistulous connection between cavernous ICA and cavernous sinus	High-flow; usually traumatic ICA tear	Acute/abrupt onset; more severe overall
B (indirect)	Dural meningeal branches of the ICA → cavernous sinus	Low-flow; spontaneous	Insidious/gradual course; less severe overall
C (indirect)	Dural meningeal branches of the ECA → cavernous sinus	Low-flow; spontaneous	Insidious/gradual course; less severe overall
D (indirect)	Dural meningeal branches of both ICA and ECA → cavernous sinus	Low-flow; spontaneous	Insidious/gradual course; less severe overall

Clinical manifestations are primarily determined by flow and venous outflow pattern: anterior drainage typically produces ocular/orbital congestion, whereas posterior drainage is more often associated with neurologic complications and headache. High flow fistula tends to present more acutely with more pronounced orbital signs than low flow fistula.[3]
ICA, internal carotid artery; ECA, external carotid artery.

(–4 to 0). Right abduction improved from –1 to 0, and primary-position diplopia was absent at distance and near, consistent with recovery from abducens palsy.

DISCUSSION

Trigeminal involvement in CCF is generally uncommon, with most patients presenting primarily with ocular signs and CN III/IV/VI palsies. When trigeminal involvement dose occur, it most often localizes to the V1 or V2 divisions and is accompanied by ocular congestion or ocular motor cranial neuropathies—features more characteristic of cavernous-sinus pathology such as CCF, or other secondary entities (e.g., secondary trigeminal autonomic cephalalgias), than of isolated primary trigeminal disease.[4,5,8,9] A rare instance of V3 involvement has been reported, but it is usually accompanied by additional cranial neuropathies.[5] An initial presentation confined to the V2/V3 divisions with subsequent misdiagnosis has been only rarely described in the published literature. Although the symptomatic distribution overlapped with ours (V2/V3-territory pain), Rizzo et al.[4] reported an indirect, predominantly external-carotid CCF with V2/V3 pain plus hypoesthesia and vascular clues (pulsatile tinnitus/cranial bruit)—features that already pointed to a secondary vascular cause. By contrast, our patient initially had V2/V3-only pain without ocular congestion, bruit, or other cranial neuropathies, which led to initial misattribution to dental disease/trigeminal neuropathy. In Rizzo's era, diagnosis relied on selective angiography (no MRI and no standardized follow-up imaging) and treatment was surgical ligation; in our case, TOF-MRA demonstrated characteristic findings; DSA confirmed an indirect CCF. Transvenous Onyx embolization yielded temporally concordant imaging and clinical improvement. In Jensen et al.[5]'s Case 1, the patient likewise reported V2/V3-territory symptoms, but—unlike our case—there were early ocular congestive signs (lid swelling, conjunctival chemosis) and abnormal ocular ductions of the left eye documented at presentation. These accompanying neuro-ophthalmic findings would more readily cue clinicians to a cavernous-sinus process, whereas our patient's initial V2/V3-only pain without ocular signs contributed to early misattribution to dental disease/trigeminal neuropathy.

According to prior literature, posteriorly directed, high-pressure venous drainage in indirect CCFs can precipitate venous congestion around Meckel's cave, providing a substrate for V2/V3 territory pain; this builds on earlier evidence implicating vascular compromise at the trigeminal (Gasserian) ganglion level.[4,5] In our case, the post-procedure reduction in TOF-MRA flow related signal, along with decreased superior ophthalmic vein engorgement, indicates reduced cavernous venous pressure, plausibly relieving congestion around Meckel's cave and thereby improving V2/V3 pain. The bifrontal, pressure-like headache with nausea/vomiting can be explained by posteriorly directed venous outflow from the fistula, which produces venous hypertension in the cavernous sinus and posterior dural venous pathways.[1,3,7] Resultant venous engorgement distends pain-sensitive dura and activates trigeminal meningeal afferents, yielding a secondary dural headache rather than a primary migraine phenotype; the bifrontal topography is compatible with referral from the anterior cranial fossa/cavernous region dura via the ophthalmic and maxillary divisions.[1,7] In line with this mecha-

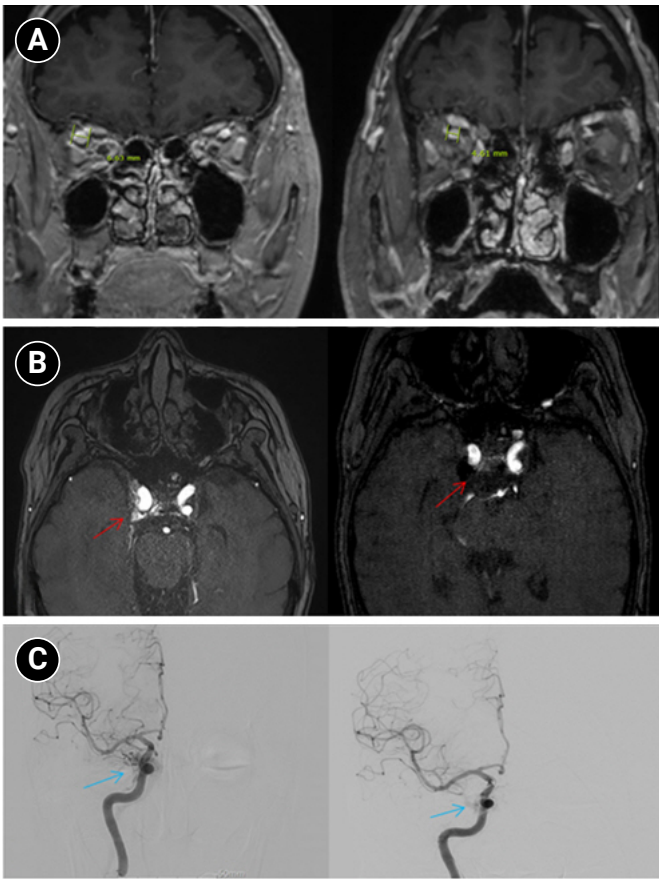

Figure 3. Imaging changes before and after embolization. (A) Brain magnetic resonance imaging (coronal section through the orbits) shows a decrease in the diameter of the right superior ophthalmic vein from 6.63 mm pre-embolization to 4.61 mm post-embolization, indicating reduced venous congestion. (B) Axial time-of-flight magnetic resonance angiography demonstrates that flow-related hyperintensity within the right cavernous sinus is markedly reduced after embolization (red arrows), consistent with decreased shunt flow. (C) Digital subtraction angiography images before embolization show abnormal early pericavernous venous filling along the right cavernous sinus region (blue arrows), compatible with carotid-cavernous shunting. On follow-up, this abnormal filling is no longer visualized, consistent with interval reduction in shunt flow.

nism, headache occurs more often in indirect CCF than in direct CCF, reflecting posterior venous drainage and dural venous hypertension. Correspondingly, headache improvement tracked with the post-embolization decrease in shunt on TOF-MRA, supporting a venous-driven mechanism linked to posterior drainage. Likewise, abducens palsy—given the nerve's central course through the cavernous sinus and vulnerability near Dorello's canal—would be expected to improve as cavernous venous hypertension resolves, consistent with the observed normalization of right abduction on bedside duction grading.

In indirect CCFs as in our patient, endovascular therapy was selected as first-line; if endovascular access is not achievable or durable occlusion cannot be obtained, surgical management may be required.[2,3] Given the indirect (Barrow D) angio-architecture, a transvenous approach—typically via the inferior petrosal sinus or, if inaccessible, the superior ophthalmic vein—was preferred, as transarterial embolization of dural feeders in indirect CCFs is associated with a higher embolic stroke risk.[6,7] Transvenous embolization is commonly favored for indirect CCFs given the relatively straightforward venous anatomy, and high angiographic occlusion rates have been reported. Overall, endovascular treatment across techniques and access routes yields clinical improvement in approximately 60%–95% of cases.[10] Post-embolization TOF-MRA demonstrated a marked reduction of flow related signal in the right cavernous sinus with decreased superior ophthalmic vein engorgement, consistent with interval shunt reduction and accompanied by ~80%–90% relief of dental/facial pain and improvement in diplopia. As shunt flow decreased, the V2/V3 territory pain improved in parallel, supporting the fistula as the proximate source of the pain.

In patients who present with severe pain localized to a molar and the adjacent gingiva, initial evaluation should prioritize exclusion of dental pathology and primary trigeminal neuralgia. However, when dental assessment is unrevealing and the pain exhibits atypical features—poor localization within the V2/V3 territory, non-paroxysmal quality, improvement only with short-acting analgesics, and a relapsing course—clinicians should maintain vigilance for evolving neuro-ophthalmic signs (e.g., new horizontal diplopia suggestive of abducens nerve palsy). Our case underscores that, under these circumstances, an atypical CCF presentation should be considered in the differential, and early neurovascular imaging (MRA/computed tomography angiography with confirmatory DSA when indicated) may prevent delayed diagnosis and treatment.

AVAILABILITY OF DATA AND MATERIAL

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

AUTHOR CONTRIBUTIONS

Conceptualization: BC, SHK; Data curation: BC; Investigation: BC, CK, SHK; Methodology: BC, CK, SHK, JHS; Supervision: JHS; Validation: BC; Visualization: BC; Writing–original draft: BC; Writing–review & editing: CK, SHK, JHS.

CONFLICT OF INTEREST

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

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Correction

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Headache and Pain Research

Erratum to "Premonitory Symptoms in Migraine: Implications for Disease Burden and Cognitive Impairment, with Some Promising Answers"

Utku Topbaş[1], Bahar Taşdelen[2], Nevra Öksüz Gürlen[1], Aynur Özge[1]

[1]Department of Neurology, Mersin University School of Medicine, Mersin, Turkey
[2]Department of Biostatistics, Mersin University School of Medicine, Mersin, Turkey

This is a correction to an already published paper (Headache Pain Res 2025;26(2):130-141; https://doi.org/10.62087/hpr.2024.0031). We found errors in the IQR values in Tables 1 and 3. Appropriately adjusted are as below.

Table 1. Comparison of demographic features between the PS+ and PS– groups

Parameter	PS+ (n=139)	PS– (n=47)	p-value†
Mean age (yr)	35.1±10.4	36.9±11.3	0.397
Female sex	117 (84.2)	42 (89.4)	0.477
Chronic migraine	28 (20.1)	10 (21.3)	0.837
Migraine with aura	51 (36.7)	8 (17.0)	0.017*
MMD (IQR)	5 (3–10)	6 (3–10)	0.889
VAS (IQR)	8 (7–9)	8 (7–10)	0.498
Oral preventatives: small molecule	73 (52.5)	16 (34.0)	0.042*
Onabotulinumtoxin-A	18 (12.9)	1 (2.1)	0.048*
GON blockage	27 (19.4)	11 (23.4)	0.677

Values are presented as mean±standard deviation, number (%), or median (IQR).
PS+, premonitory symptom positive; PS–, premonitory symptom negative; MMD, monthly migraine days; IQR, interquartile range; VAS, visual analogue score; GON, greater occipital nerve.
*Asterisk indicates a statistically significant (p<0.05). †For parameters given as either mean±standard deviation or median (IQR), the Mann-Whitney U-test was used to obtain p-values. For parameters given as frequency, the chi-square test was used to obtain p-values.

Table 3. Comparison of the PS+ and PS– groups in terms of migraine trigger factors

	PS+ (n=139)	PS– (n=47)	p-value†
MIDAS (IQR)	26 (14–40)	16 (10–33.5)	0.05
Mig-SCOG (IQR)	10 (7–14)	7 (4–10)	<0.001*
EUROHIS-8 (IQR)	3.12 (2.75–3.62)	3.62 (3.12–4.00)	<0.001*

Values are presented as or median (IQR).
PS+, premonitory symptom positive; PS–, premonitory symptom negative; MIDAS, Migraine Disability Assessment Scale; IQR, interquartile range; Mig-SCOG, Migraine Attack Related Subjective Cognitive Scale; EUROHIS-8, European Health Impact Scale.
*Asterisk indicates a statistically significant (p<0.05). †For parameters with IQR values, the significance between groups was tested with the Mann-Whitney U-test.

This error does not change the text and the conclusions of our paper. We apologize for the unintentional mistake and appreciate the opportunity to correct and clarify the issue.

CONFLICT OF INTEREST

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

Correspondence: Aynur Özge, M.D.
Department of Neurology, Mersin University School of Medicine, Çiftlikköy Mah., MEÜ Çiftlikköy Kampüsü, 33110 Yenişehir/Mersin, Turkey
Tel: +90-324-2410000 (1902), Fax: +90-3242410000-1907, E-mail: aozge@mersin.edu.tr

Instructions for authors

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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

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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).

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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.

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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

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  - Biological names of organisms: *Saccharomyces cerevisiae, E. coli*
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  - Latin words: in vivo, in vitro, in situ
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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).
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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.
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- 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.

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- 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.
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- 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

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- 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.
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- The statistical significance of observed differences in the data should be indicated by the appropriate statistical analysis.

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- Multiple figures mentioned in the text should be described as follows, e.g., Figures 1, 3.
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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.

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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

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- 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.
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Headache and Pain Research

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

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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

수벡스정
(Sumatriptan/Naproxen sodium)

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), 뇌출증, 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

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

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References. 1. AQUIPTA® Product information (2023.11.15)

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* FDA 승인시점 기준

Reference 1. Do TP, et al. Acta Neurol Scand. 2018;137:442-451. **2.** Silberstein SD, et al. J Neurol Neurosurg Psychiatry. 2015;86(9):996-1001.
3. Aurora SK, et al. Headache. 2011;51(9):1358-1373. **4.** 보톡스® 제품설명서(개정년월일 2024.02.08)

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[제조원] Allergan Pharmaceuticals Ireland **[수입·판매원]** 한국애브비㈜, 서울특별시 강남구 영동대로 421 삼탄빌딩 6층, 전화: (02)-3429-9300 www.abbvie.co.kr

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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) 편마비, 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 치료용량 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, 어지럼, 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.

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

NARAMIG (naratriptan)