Editorial

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

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

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

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

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

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

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

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

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

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

## AVAILABILITY OF DATA AND MATERIAL

Not applicable.

## AUTHOR CONTRIBUTIONS

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## CONFLICT OF INTEREST

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