REVIEW

Microembolism and Other Links Between Migraine and Stroke

Clinical and Pathophysiologic Update

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Abstract

Migraine and stroke are highly prevalent diseases with a high effect on quality of life, with multiple epidemiologic, pathophysiologic, clinical, and prognostic areas of overlap. Migraine is a risk factor for stroke. This risk is explained by common risk factors, migraine-specific mechanisms, and non–migraine-specific mechanisms that have a relevant role in patients with migraine with aura (e.g., atrial fibrillation and paradoxical embolism through a patent foramen ovale). Another important link between migraine aura and ischemic stroke is cardiac embolism. Cardioembolism is the most frequent cause of ischemic stroke, and increasing evidence suggests that microembolism, predominantly but not exclusively originating in the heart, is a contributing mechanism to the development of migraine aura. In this review, we discuss epidemiologic aspects of the association between migraine and ischemic stroke, the clinical presentation of ischemic strokes in patients with migraine, and the differentiation between migrainous and nonmigrainous infarctions. After that, we review migraine-specific and non–migraine-specific stroke mechanisms. We then review updated preclinical and clinical data on microembolism as a cause of migraine aura. In the last section, we summarize knowledge gaps and important areas to explore in future research. The review includes a clinical vignette with a discussion of the most relevant topics addressed.

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Glossary

5HT = serotonin; **CADASIL** = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; **CBF** = cerebral blood flow; **FHM** = familial hemiplegic migraine; **fMRI-BOLD** = functional MRI–bold oxygen level dependent; ***ICHD-3*** = *International Classification of Headache Disorders, Third Edition*; **MA** = migraine with aura; **MELAS** = mitochondrial encephalopathy with lactic acidosis and stroke-like episode; **MO** = migraine without aura; **OR** = odds ratio; **PFO** = patent foramen ovale; **SD** = spreading depression.

Migraine and stroke are highly prevalent diseases with a strong effect on individuals and health systems. One billion people live with migraine, with a global age-standardized prevalence of 14.4% (18.9% of women and 9.8% of men).[1] Migraine prevalence peaks in early adulthood and declines with aging.[1] Migraine with aura (MA) is a unique subtype of migraine occurring in an estimated 20%–30% of the migraine population. Migraine is also ranked among the most disabling disorders worldwide, representing a major cause of disability.[1] Several studies have proven that migraine and stroke are associated. Migraine, especially MA, is an established risk factor for ischemic stroke and constitutes one of the most frequent differential diagnoses in specialized stroke clinics. The exact mechanisms underlying the association between migraine and ischemic stroke are unclear. Still, there seems to be a higher susceptibility to ischemic injury in the brain of subjects with MA. The present review updates current evidence on the clinical characteristics of ischemic stroke in patients with migraine, the pathophysiologic association between migraine and ischemic stroke, and the role of embolic mechanisms as a potential cause of MA. The literature search strategy is described in the supplementary file.

Clinical Vignette

A 47-year-old right-handed woman with a known history of MA was washing her hands when she suddenly felt that something was off. She looked down and saw the hand under the tap but did not immediately register that it was hers. She wondered if her husband had reached around from behind to rinse his hand. Only when she realized that it was her hand, she called her husband, who was 6 feet behind her at the time. To her surprise, her speech was slurred. She tried to consult a first-aid book, but she could not understand what she was reading. Most of these symptoms lasted for 2 minutes, but she had difficulty forming sentences for around 30 minutes. By the time she fully recovered, she had developed her usual crescent-shaped migraine aura on her left visual field, followed by a typical migraine headache.

The patient had a longstanding history of MA, dating back to her childhood, always presenting with scintillating scotoma and sometimes with right arm numbness. Her MA had increased in frequency in the past year by her husband's account, with 2 predictably attacks per month related to her menstrual cycles. She had previously been on oral contraceptives, but they had been discontinued long before the presenting symptoms. The patient was a long-life nonsmoker, she rarely drank alcohol, and she was physically active, without any known vascular risk factors.

She was evaluated in the emergency department with a normal electrocardiogram and CT of the brain and angiography of the intracranial and extracranial arteries. Her LDL cholesterol was 4.05 μmol/L. The rest of her blood work, including examinations for thrombophilia and arteritis, did not show any abnormal results. She was started on aspirin 81 mg and referred to the Urgent Stroke Prevention Clinic, where her neurologic examination was unremarkable. An MRI of the brain ordered because of the atypical clinical presentation showed a small focus of diffusion restriction in the right frontal lobe, likely representing an acute infarct (Figure 1). No other acute intracranial abnormality was noted; there were no stenosis or occlusion of intracranial and extracranial blood vessels. Based on these findings, she was brought back to the clinic to complete her stroke workup, and she was started on atorvastatin 20 mg/d. A 14-day Holter monitor did not show atrial fibrillation. An echocardiogram was normal except for a right to left shunt noted after the injection of agitated saline contrast, both at rest and after the release of a Valsalva maneuver. A transesophageal echocardiogram confirmed the presence of a patent foramen ovale (PFO) with a mobile interatrial septum (high-risk PFO). Her bloodwork was negative for thrombophilia and autoimmune diseases.

The patient was referred to the Structural Heart Clinic, and she underwent an uneventful PFO closure. She remained free from stroke and MA recurrences but continued to experience migraine without aura (MO) attacks for the following 2 years. A 14-day Holter done postclosure did not show atrial fibrillation. The interpretation of the case in the context of current evidence is presented in the supplementary file.

Links Between Migraine and Stroke

Association Between Migraine and Ischemic Stroke

Presently, there are many studies that demonstrate an association between MA and ischemic stroke in the young. In 1 meta-analysis including 2,221,888 participants from 11 prospective cohort studies, the observed pooled relative risk of ischemic stroke in the MA population was 2.1 (95% CI 1.3–3.4) compared with the control population without migraine.[2] There was no association with ischemic stroke in the

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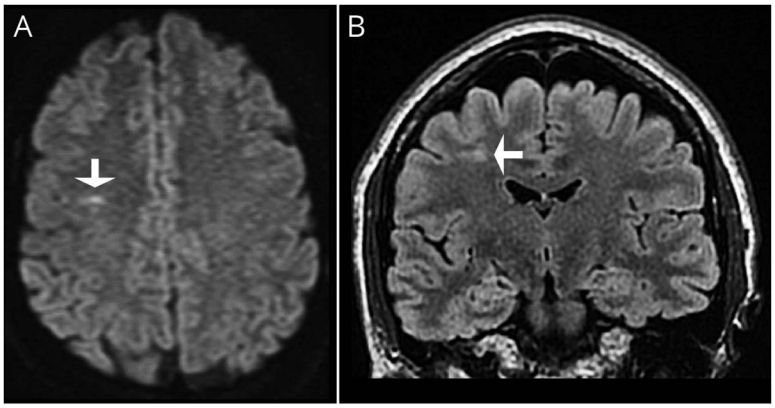
Figure 1 MRI (Clinical Vignette)



(A) Diffusion-weighted imaging sequence showing restricted diffusion in the right subcortical frontal lobe. (B) Corresponding hyperintense lesion on fluid-attenuated inversion recovery sequence.

MO population (risk ratio 1.0, 95% CI 0.7–1.5).[2] Given the overall low incidence of ischemic stroke in the young population, the 2-fold increased risk leads to few additional events in the overall population but considering that stroke can be debilitating and even fatal this additional increase is relevant.

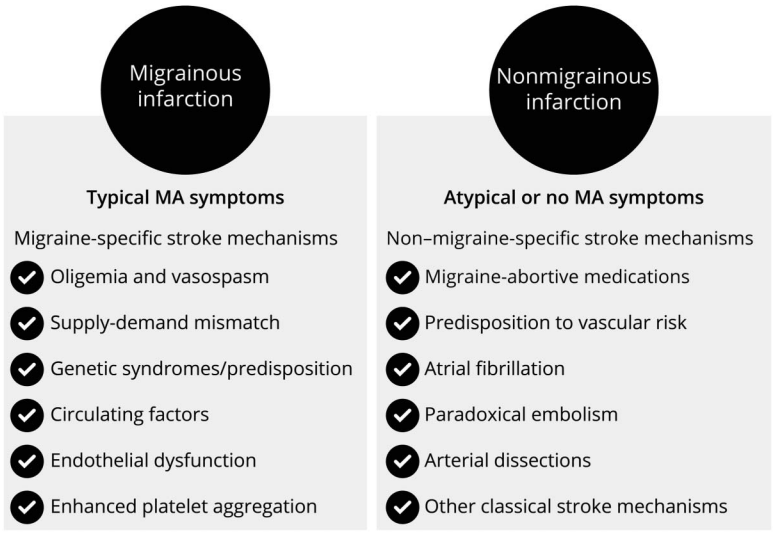
Clinical Presentation of Ischemic Strokes in Patients With Migraine

Diagnosing an acute ischemic stroke or TIA in patients with MA is sometimes challenging. Stroke patients with a history of migraines tend to underestimate stroke symptoms due to their similarity with prior MA attacks.[3] TIAs manifest themselves with focal neurologic symptoms and complete resolution that may go unnoticed as they may be attributed to an MA. The diagnosis of acute cerebrovascular events in patients with MA is even more complex because ischemic strokes can present with headaches, even with migraine-like features, resulting in missed or delayed diagnoses.[4,5] In addition, patients with migraine bear a higher risk of experiencing arterial dissections, which can also present with migraine-like headaches in the context of an acute stroke.[6] There are no definite clinical features or plasma biomarkers to reliably differentiate acute ischemic strokes presenting with migraine-like headaches from MA with focal neurologic symptoms. Research on biomarkers for differentiating MA from acute cerebrovascular events is highly needed.

Migrainous and Nonmigrainous Infarctions

Ischemic strokes in patients with migraine can be classified into migrainous and nonmigrainous infarctions (Figure 2). A migrainous infarction is defined by the *International Classification of Headache Disorders, Third edition* (*ICHD-3*) as "one or more migraine aura symptoms occurring in association with an ischemic brain lesion in the appropriate territory demonstrated by

Figure 2 Potential Mechanisms of Migrainous and Nonmigrainous Infarctions in Patients With Migraine



MA = migraine with aura.

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Table 1 *ICHD-3* Diagnostic Criteria for Migrainous Infarction

Criteria	Description
A	A migraine attack fulfilling criteria B and C
B	Occurring in a patient with migraine with aura, typical of previous attacks except that 1 or more aura symptoms persist for >60 min
C	Neuroimaging demonstrates an ischemic infarction in a brain region explaining the focal neurologic symptoms
D	Symptoms are not better accounted for by another *ICHD-3* diagnosis

Abbreviation: *ICHD-3* = *International Classification of Headache Disorders, Third Edition*.
Adapted from the *ICHD* criteria.

neuroimaging, with onset during the course of a typical migraine with aura attack."[4] The specific criteria for migrainous infarction are presented in Table 1. A specific subset of patients with stroke with a history of migraine may present with an MA and additional neurologic deficits that are not part of the patient's typical MA. As per the *ICHD-3* criteria, the latter type of strokes are migraine-related ischemic strokes but not strictly migrainous infarctions because of the presence of atypical symptoms. Indeed, the presence of atypical neurologic symptoms associated with an MA attack constitutes a red flag and should prompt urgent advanced neuroimaging, including MRI of the brain (see Clinical Vignette). Nonmigrainous infarctions in patients with a history of migraines can also present without MA symptoms and during or outside the course of a migraine or migraine-like attack. To what extent there are shared mechanisms between nonmigrainous and migrainous infarction in individuals with migraine is still unknown.

Studies comparing migrainous and nonmigrainous strokes in patients with migraine are lacking. The most frequently involved vascular territory in migrainous infarctions is the posterior circulation. Visual disturbances, including scintillating scotomas, visual field defects, oscillopsia, photopsia, and fortification spectra, are a frequent component of the clinical presentation.[3] Migrainous strokes are usually mild, with a median NIH Stroke Scale ranging from 2 to 5,[3] and the long-term risk of stroke recurrence is low.[7] Of interest, the burden of MA attacks seems to decrease after patients experience a migrainous ischemic stroke.[3,7]

Stroke Mechanisms in Patients With Migraine

Migraine-Specific Stroke Mechanisms

The pathophysiologic mechanisms explaining the association between MA and ischemic stroke remain abstruse. This uncertainty is primarily attributable to heterogeneous but not necessarily exclusive etiopathologic mechanisms.[8] Several mechanisms have been proposed for explaining ischemic infarction in migraine (Figure 2). However, the actual prevalence of these mechanisms and the relative proportion of migrainous infarctions vs nonmigrainous strokes in patients with migraine that do not fulfill the criteria for migrainous infarctions are difficult to estimate. A thorough etiologic stroke workup to address concurring mechanisms is mandatory. Even when a potential etiologic cause is found, there is the possibility that the interaction of this cause with the specific migraine vascular vulnerability may have favored the event. Regardless, identifying concurrent or alternative and treatable mechanisms (e.g., thrombophilia, paradoxical embolism, and arterial dissections) is crucial for establishing a tailored secondary stroke prevention strategy.

Oligemia and Vasospasm

Cortical spreading depression (SD) is an intense neuronal and glial depolarization that spreads slowly across the cortical surface at a rate of 2–5 mm/min and is the most likely electrophysiologic substrate for the visual, sensory, language, and motor disturbances of migraine auras.[9,10] Experimental research demonstrated that a brief 1–5-second tetanizing current stimulation of rabbit cortex produced diminutions in the spontaneous cortical electrical activity. The depression in cortical activity was accompanied by a wave of marked vasodilatation and increased blood flow that also traveled over the cortex and is followed by lasting oligemia.[10] In subjects experiencing MA attacks, perturbations in blood oxygen level–dependent (fMRI-BOLD) signals can be detected starting in the foveal representation and spreading slowly to parafoveal and then more peripheral areas. This spread of the fMRI-BOLD signal mirrored the timing of SD spread recorded in animals and confirmed that an SD-like phenomenon is the most likely neurophysiologic explanation for migraine aura.[11]

One proposed mechanism of ischemic strokes in patients with migraine is a prolonged or severe reduction in cerebral blood flow (CBF). It is estimated from positron emission tomography–Xenon 133 studies that during MA, SD-induced oligemia accounts for a 12%–17% reduction in CBF.[12,13] Such a reduction should not be sufficient to produce cerebral infarction unless there is a metabolic or genetic predisposition of the tissue itself towards injury (see the section on Increased Susceptibility to Metabolic Supply-Demand Mismatch).[8,14] Therefore, a mechanism involving the oligemia of SD alone is likely insufficient to explain most strokes in individuals with migraine. Furthermore, although SD likely spreads across the cortical surface without deference to any particular vascular territory, most cases of ischemic stroke in subjects with

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migraine are delimited by a distinct vascular distribution with few exceptions.[15] In a study of 17 patients with acute migrainous infarction, no single lesion spanned multiple territories.[3] Over 70% of the lesions involved a single vessel in the posterior circulation, consistent with other studies.[16] In a minority of these patients (n = 4), there was a reduction in flow-related signal in the vessel corresponding to the infarcted territory. Multivessel vasospasm was not found in this population. These data suggest that still unclear mechanisms other than severe oligemia or vasospasm may play a role in migrainous infarction.

Increased Susceptibility to Metabolic Supply-Demand Mismatch

Data from preclinical studies support the hypothesis that infarction in the setting of migraine results from increased tissue sensitivity to metabolic supply-demand mismatch.[14] Transgenic animals expressing a monogenic migraine variant (familial hemiplegic migraine [FHM] type 1) developed larger infarcts on middle cerebral artery occlusion, suggesting increased vulnerability to ischemic triggers. The phenotype was unrelated to vascular mechanisms because the absolute reduction in CBF (i.e., the perfusion defect) did not differ between the genotypes. Instead, brains in migraine transgenic mice required higher levels of residual CBF to remain viable compared with wild-type controls (42% vs 35%, respectively).[14] Higher SD susceptibility in patients with migraine might explain the increase in tissue sensitivity to metabolic supply-demand mismatch. Indeed, vulnerability to ischemic injury is abrogated by migraine preventive medications that elevate the SD threshold such as topiramate or lamotrigine.[17] Of interest, in clinical studies, Patients with MA present with completed infarcts (e.g., little or no mismatch), suggesting greater or earlier recruitment of vulnerable tissue into the infarct.[18] These human data support preclinical observations suggesting that the migraine state may modulate the vulnerability of brain tissue to ischemic infarction.

Genetic Syndromes and Predispositions

There are monogenic disorders characterized by migraine attacks and stroke whose pathologic mechanisms involve metabolic, tissue, and vascular factors. FHM types 1–3 are autosomal dominant monogenic forms of migraine with severe aura attacks with accompanying hemiplegia. FHM type 1 mouse models that express mutations in the pore-forming subunit of the voltage-gated calcium channel, $Ca_v2.1$, have increased cortical excitability, lowered thresholds for SD induction, larger infarct volumes following arterial occlusion, and a greater number of peri-infarct SDs.[14] In regional CBF studies of patients with hemiplegic migraine, reductions in CBF and spreading oligemia resulted in more severe and widespread hypoperfusion than that typically seen in patients with migraine aura.[19] Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a small vessel arteriopathy caused by a mutation in the *Notch3* gene leading to degeneration of smooth muscle cells. A few *Notch3* mutant mouse models have developed larger experimentally induced infarcts,[20] and the $TgNotch3^{R90C}$ CADASIL mutant mice have lower thresholds for SD.[21] Other migraine variants showing *Col4A1* and *TREX1* mutations are also associated with small vessel disease and vasculopathy.[8] Mitochondrial mutations in mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELASs) have also been associated with MA attacks. The stroke-like events in MELAS are also likely related to tissue metabolic supply-demand mismatch.[22]

It is unclear whether there are genetic contributions to nonmonogenic forms of MA. A meta-analysis of genome-wide data examining 23,585 migraine cases and 95,425 controls against 12,389 ischemic stroke cases and 62,004 controls found shared variants at different loci that may affect the risk of developing migraine and the risk of ischemic stroke. However, a more substantial genetic overlap in the MO subgroup suggests that shared genetic traits do not likely explain the relationship between MA and ischemic stroke.[23]

Endothelial Dysfunction and Platelet Aggregation

Several studies have examined biomarkers associated with increased thrombosis risk, including increases in C reactive protein levels and circulating cytokines in patients with migraine, with varied findings.[24] Of interest, patients with MA may have increased levels of circulating endothelial microparticles compared with controls, suggesting endothelial dysfunction as a potential contributing stroke mechanism in this population.[25] Enhanced platelet aggregation has been described in patients with migraine relative to nonmigraine individuals,[26] specifically during migraine attacks.[27]

Vascular Reactivity

Several studies have assessed cerebrovascular reactivity in patients with migraine with various methods and conflicting results. Current evidence suggests an impaired function of large arteries in patients with migraine compared with those without migraine, possibly indicating that vascular reactivity is impaired both in cerebral and systemic arteries in patients with migraine. In addition, a meta-analysis showed that patients with migraine have more severe cerebral arterial stiffness and worse vasodilatation compared with subjects without migraine. Impaired arterial reactivity and function might partly explain the association between migraine and vascular disease. However, it is unclear whether the association between migraine and impaired vascular function is due to a common pathologic process or to confounders. A commonly accepted pathophysiologic explanation for that association is also lacking.

Non–Migraine-Specific Stroke Mechanisms

Migraine-Abortive Medications

It has been postulated that exposure to acute medications used to treat migraine attacks could predispose to stroke. Triptans and dihydroergotamine, for example, have vasoconstrictive properties. Triptans are serotonin $(5HT)_{1B}$, $5HT_{1D}$, and, to a lesser extent, $5HT_{1F}$ receptor agonists. Although $5HT_{1B}$ receptors are

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located on vascular smooth muscle, triptans at typical doses given for migraine-abortive relief likely have a weak vasoconstrictive effect on human vessels compared with ergotamine and dihydroergotamine.[28] This is consistent with several studies demonstrating that although ergotamine and dihydroergotamine may be associated with an increased risk of vascular events, triptan use is not associated with an increased risk of vascular events.[29] The advent of newer medications targeting calcitonin gene-related peptide and its receptor has added to the antimigraine armamentarium. Recent preclinical studies raise concern that there may be an association between exposure to small-molecule blockers against calcitonin gene-related peptide receptors and worsened stroke outcomes after a coincident ischemic event.[30] However, this does not historically explain the associations between MA and ischemic stroke as these drugs are only recently Food and Drug Administration approved, nor would it explain the migraine subtype specificity of this association. Medication exposure, therefore, contributes minimally to the association between migraine and stroke.

Comorbid Vascular Risk Factors

Several studies have examined the effect of traditional vascular risk factors, including hypertension, hyperlipidemia, diabetes mellitus, and smoking, on the risk of ischemic stroke in patients with migraine.[31] Patients with diabetes seem to have a lower prevalence of migraine.[31] Framingham risk scores are higher in both MO (odds ratio [OR] 1.17, 95% CI 1.04–1.32) and MA populations (OR 1.54, 95% CI 1.21–1.95) relative to controls.[32] The main conventional vascular risk factors that appear to drive an increase in the Framingham risk score are dyslipidemia and cigarette smoking.[31] Most of the studies showing that migraine increases the risk of ischemic stroke, proved in the multivariable model that the increased risk is independent of conventional vascular risk factors. However, the higher vascular risk reported in both the MA and MO population than in controls does not fully explain the subtype-specific association with ischemic stroke.

Hormonal Contraceptives

The interplay between migraine and hormonal contraceptives is relevant for the risk of stroke in young women, as both frequently coexist during childbearing age. The use of combined hormonal contraceptives carries a small but well-established risk factor for ischemic stroke.[33] Even low-estrogen contraceptives bear increased ischemic stroke risk,[34] particularly in patients with MA.[35] Therefore, combined hormonal contraceptives are not recommended in women with MA.[36] Women with MO may use combined hormonal contraceptives in the absence of additional vascular risk factors, especially smoking, which is known to enhance their risk of ischemic stroke.[37]

Atrial Fibrillation

In the Atherosclerosis Risk in Communities study, MA was associated with cardioembolic mechanisms in patients with stroke[38,39] and incident atrial fibrillation in a population free from stroke.[40,41] Similar results were observed in a cohort study based on the Danish Medical Registry.[42] A more recent study found a strong association between MA and atrial fibrillation in a cohort of young (18–54 years of age) patients with stroke.[43] However, no relationship between MA or MO and atrial fibrillation was found in a large cohort from the Brescia Stroke Registry, including 1,738 patients with a mean age of 70 years.[44] Although the exact mechanism linking migraine and AF is unknown, potential causes include autonomic dysfunction–induced arrhythmia or AF-related microembolism.[45]

Paradoxical Embolism

PFO has also been proposed as a cardioembolic source in patients with MA. PFOs are more prevalent in the MA (50%–60%) population relative to MO and individuals without migraines (25%).[46] In a series from the University of California Comprehensive Stroke Center, 93% of the patients with cryptogenic stroke and MA had a PFO.[47] The reported prevalence of PFO was as high as 86% among patients with multifocal migrainous infarctions.[3] These data raise the possibility that a considerable subset of strokes occurring in the MA population is attributable to paradoxical embolism. Taken as a whole, PFO and atrial fibrillation seem to be the most commonly observed sources of embolism in the MA population, and cryptogenic- or cardioembolic-appearing strokes are the most common stroke subtypes.[39,41,44] Notably, the association between MA and cryptogenic stroke is independent from vascular risk factors and even from the presence of PFO.[48]

Arterial Dissection

A history of migraine doubles the risk of incident arterial dissections relative to no migraines.[49] In the Cervical Artery Dissection and Ischemic Stroke Patients collaboration, a history of MO was associated with an increased risk of carotid dissection–related ischemic stroke, with a stronger association found among men.[50] A large prospective cohort study confirmed a stronger association between MO and arterial dissections.[6] Furthermore, a genome-wide genetic correlation was observed between carotid artery dissection and migraine, particularly MO, suggesting that arterial dissections may explain a proportion of ischemic strokes in patients with migraine.[51] Two aspects of the association between migraine and arterial dissection should be noted. First, the association is typical of MO, representing an exception to the increased risk of ischemic stroke commonly attributed to MA. Second, the direction of the association is not established, and the possible causal links deserve further investigation.

Microembolism as a Cause of SD

Cortical hyperexcitability has been postulated as the likely mechanism predisposing to SD. In addition, recent preclinical data raise the possibility of contributing pathways to SD generation. Namely, there is preclinical evidence that microembolism triggers SD and may lead to ischemia.[52]

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Evidence From Animal Studies

Preclinical models have shown that SD may result in cerebral ischemia and that they share common mechanisms. Triggers for SD can either act directly by activating sodium and calcium channels or indirectly by inhibiting neuronal sodium-potassium ATPase (e.g., ischemia).[53] In animal models, endothelin-1–induced vasospasm leading to SD is associated with selective neuronal damage on histologic examination.[54] Other preclinical studies demonstrated that microembolism can cause SD. Air microemboli (<10 μm in diameter), polystyrene microspheres (10 μm), and cholesterol particles (<70 μm) were injected into the carotid arteries of 28 rats. Microembolism triggered SD in 16 (57%) of the animals. In some animals, ischemic changes were detected in cortical neurons without overt brain infarction.[52] Smaller emboli induced rapid and transient SD episodes associated with substantially decreased CBF. Larger emboli triggered delayed and long-lasting SD episodes, translating into small but prolonged reductions in CBF.[52] The largest emboli were also more likely to cause microinfarcts; however, none of those infarcts was detectable at brain imaging. The discrepancy between positive histology (microinfarcts) and negative brain imaging in the animal model might be attributed to the small size of the lesions caused by microembolism.[52] Most emboli may be too small and undergo rapid spontaneous lysis, thus inducing depolarization events without generating significant clinical ischemia. In contrast, larger emboli may require more time to undergo lysis and therefore cause overt infarctions. This view is substantiated by experimental evidence from a murine model in which unstable clots undergoing spontaneous lysis only caused SD events, whereas more stable clots were more likely to induce brain infarctions.[55] Larger emboli, coupled with SD triggered by the emboli themselves and causing overt ischemic events, may constitute the biological explanation for the association between migraine and ischemic stroke in patients prone to brain microembolism as those with atrial fibrillation and PFO but also those with arterial dissection where brain microembolism has an arterial origin.[47,48]

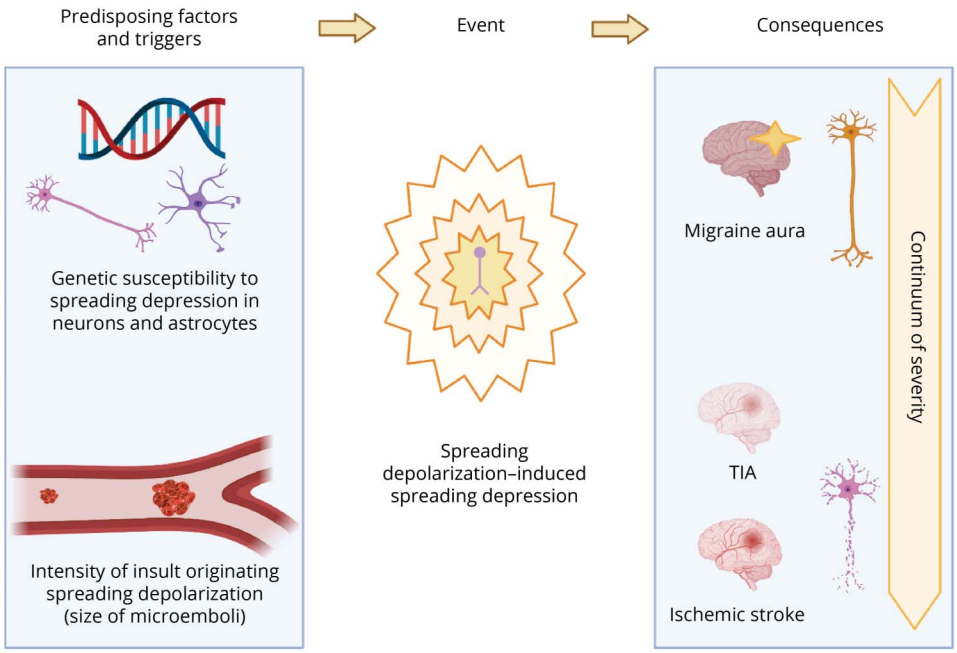
In summary, animal evidence suggests a continuum in the spectrum of SD-related hypoperfusion, ranging from asymptomatic phenomena to migraine auras, asymptomatic brain lesions, and brain ischemia (Figure 3).[56] The occurrence and degree of SD-induced neuronal death depend on the vulnerability of neurons and the entity of SD triggers.

Evidence From Human Studies

PFO

Evidence from human studies supports the findings of preclinical models. Transcranial Doppler ultrasound with air contrast is commonly used to demonstrate right-to-left shunt. In patients with migraine, air microembolism through PFO during transcranial Doppler sonography has been shown to elicit SD. In a consecutive case series, air microembolism during transcranial Doppler triggered typical MA in 7.5% of patients already known to have migraines.[57] Notably, episodes only occurred in patients with large PFOs.[57] On a mechanistic point of view, air microembolism on transcranial Doppler ultrasound could be considered as a weak trigger for SD, thus leading to clinical attacks only in a minority of cases, as previously suggested.[52] A larger right-to-left shunt might

Figure 3 Interplay Between Susceptibility to Cortical Spreading Depolarization and the Effect of Microembolization



Neuronal excitability, possibly led by genetic factors, together with the size of microemboli and duration of cardioembolism, may lead to different consequences of spreading depolarization–related spreading depression of neuronal activity. Those consequences span from migraine auras, in which altered neuronal activity and hypoperfusion are not linked to cell death, to ischemic infarction in which cell death occurs. Created with BioRender.com.

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lead to larger microembolism and therefore higher likelihood of having migraine after a transcranial Doppler study with the injection of air microbubbles. Another study showed that patients with MA presenting with higher cortical dysfunction during the aura (e.g., memory or language impairment) had more severe microembolism than those without.[58] Consistently with animal evidence, diffusion-weighted brain MRI did not show acute brain ischemic changes during the aura.[59] Indirect evidence also suggests that MA could be associated with a particular susceptibility to alterations in the electrical activity of the brain cortex after microembolism. An electroencephalography study showed that, among subjects with PFO, air microembolism led to changes in EEG signals only in those with MA, whereas those without migraine did not show any significant abnormalities.[60]

Results from observational studies in patients with cryptogenic stroke have revealed a significant association between PFO closure and a reduction in the number of migraine days.[e1] However, 4 randomized controlled trials of PFO closure vs medical treatment in patients with migraine failed to meet their primary outcomes.[e2] A more recent patient-level meta-analysis of Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura and Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the Amplatzer Occluder Compared to Medical Management showed a mean reduction in monthly migraine days (−3.1 vs −1.9 days; $p = 0.02$), a mean reduction in monthly migraine attacks (−2.0 vs −1.4; $p = 0.01$), and the number of participants with complete resolution of their migraine (9% vs 1 0.7%; $p < 0.001$). Although these analyses have some limitations (e.g., cohorts with different inclusion criteria and primary outcomes), they suggest that reducing the burden of paradoxical embolism may be associated with lessening migraine phenomena.[e3]

Catheter Ablation and Atrial Fibrillation

Anecdotal case reports and small case series suggest that catheter ablation may be associated with a low risk of new-onset MA in patients with atrial fibrillation.[e4] In general, MA episodes occur within the first week postablation and do not persist in the long term.[e5] In the most extensive study, among 2,069 patients who underwent catheter ablation, 48 (2.3%) reported postprocedural headaches, 22 (1.1%) met the criteria for new-onset definite migraine, and 12 (0.6%) for new-onset probable migraine.[e6] Most patients with definite migraine had complete resolution of symptoms at 1–2 years, suggesting a transient and self-limited postprocedural phenomenon. Possible mechanisms include exposure of the arterial blood to molecules exclusively found in the venous circulation (bypassing pulmonary inactivation) and cerebral microembolism.[e6] These procedures may also cause covert acute brain infarcts, potentially explained by thrombogenic catheters/sheaths, left atrial dysfunction, air embolism, and activation of the coagulation cascade.[e5] Despite these phenomena being reasonably common, they only rarely cause focalizing signs or cognitive impairment.[e7] In the longer term, catheter ablation may improve migraine symptoms.[e5] In a prospective observational study including 40 patients with atrial fibrillation and migraine, 38 experienced significant improvements in their migraines after the ablation procedure.[e5] Although larger and more robust studies are needed, available data support a link between microembolic mechanisms, SD, and MA in patients with atrial fibrillation.

Clinical Vignette Discussion

A full discussion of the case described in Section 1 is presented in the supplementary file. The case analysis addresses the clinical presentation and link between migraine and stroke, potential stroke mechanisms explaining the patient's stroke, and the role of microembolism in the context of current knowledge.

Knowledge Gaps and Future Directions

Ischemic strokes in patients with migraine have multiple and potentially synergic mechanisms. Migraine-related mechanisms can explain a small proportion of migrainous infarctions but can contribute more widely to increase patients' susceptibility to brain ischemia. In the background of increased ischemic vulnerability, patients with migraine can experience ischemic strokes caused by other mechanisms. Studies characterizing migrainous and nonmigrainous strokes in patients with migraine are scarce, probably due to the strict *ICHD-3* challenging recruitment. Future collaborative studies should evaluate the clinical and research implications of the *ICHD-3* classification.

Ischemic stroke risk is higher in patients with MA compared with MO. High migraine frequency,[e8] late-onset MA (≥50 years),[e9] and short-lasted auras[e10] are associated with increased ischemic stroke risk. Other clinical aspects potentially relevant to stroke risk, such as aura types different from visual aura, are poorly understood partially due to their infrequent occurrence. Future strategies may require a comprehensive assessment of additional clinical characteristics associated with increased risk of ischemic stroke to tailor vascular prevention. To date, the best strategy is to identify and treat vascular risk factors.

It is still undefined if and how stroke can be prevented in patients with migraine. It remains to be determined whether an optimized control of vascular risk is associated with lower embolic rates and thus fewer ischemic strokes. Hypercoagulability may be considered a potential target for stroke prevention, mostly among women taking oral contraceptives. However, in patients with migraine, there is no proven benefit for systematically searching for thrombophilia. In addition, it is yet unknown whether migraine preventive treatments aiming at reducing attack frequency can reduce

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stroke risk. In women with migraine and ischemic stroke, there are not well-established specific secondary prevention measures.

The translational model of SD and MA has some limitations. First, experiments on SD were performed in rats or mice, in which the occurrence of aura or migraine cannot be clinically proven. Besides, some studies used animal models carrying the genetic mutations of FHM, with potentially different mechanisms relative to those of sporadic migraine. In addition, microembolism through PFO clinically provokes migraine attacks only in a minority of patients with migraine, even those with aura. Also, there is no direct evidence of SD-like events triggered by microembolism in human subjects. Besides, a cortical phenomenon like SD cannot explain all cases of migrainous infarction, which can affect not only the cerebral cortex but also the cerebellum or the brainstem.[e11] Despite these limitations, some conclusions can be drawn from current evidence. First, microembolism, which PFO favors, is a likely trigger for SD, a proxy of migraine aura. Second, the duration and burden of microembolism may determine the severity of clinical consequences, ranging from transient SD to brain infarcts. Third, increased susceptibility to SD and ischemia may lower the threshold for microembolism-related cerebral ischemia and brain infarcts.

Microembolism is an increasingly recognized mechanism participating in the complex pathophysiology of SD and MA. Because of multiple overlapping pathophysiologic processes, elucidating its exact role is challenging. More experimental and human research is needed for understanding how microembolic mechanisms affect patients with migraine and how they can be tackled. This research is also of fundamental importance for better characterizing MA-related stroke risk.

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