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REVIEW

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Migraine and stroke: correlation, coexistence, dependence - a modern perspective

Michał Borończyk[1,2*], Anna Zduńska[3], Julia Węgrzynek-Gallina[4], Olga Grodzka[3,5], Anetta Lasek-Bal[1,2] and Izabela Domitrz[3]

Abstract

Background Migraine is a chronic neurological condition that has a well-documented, yet not fully understood connection to stroke, particularly in patients who experience migraine with aura (MA). Although migraine can rarely be directly related to stroke, in the form of migrainous infarction, it serves as an independent risk factor, particularly when combined with other factors such as smoking or hypertension. This study will thoroughly review and summarize the existing literature regarding the relationship between migraine and stroke.

Main text Several key processes are common to both stroke and migraine. These include cortical spreading depression, particularly in MA, endothelial dysfunction, which activates local inflammatory responses, and vasculopathy, which often appears as white matter hyperintensities on neuroimaging. Furthermore, microRNAs also play a significant role in the pathogenesis of both migraine and stroke by targeting genes such as CALCA, which regulates calcitonin gene-related peptide, a factor involved in the pathophysiology of both conditions. There are also several genetic links between migraine and stroke, including both monogenic diseases and common risk loci. Moreover, various conditions are linked to both migraine and stroke, including patent foramen ovale (PFO), atrial fibrillation, carotid artery dissection, platelet dysfunction, dyslipidemia, obesity, hyperhomocysteinemia, and elevated estrogen levels, such as in combined hormonal contraceptives. Notably, PFO is often found in patients who have experienced a cryptogenic stroke, as well as in those with MA. While microemboli associated with PFO may provoke ischemic events and migraine attacks, the effectiveness of PFO closure in alleviating migraine symptoms has produced varying results. Migraine is linked to worse outcomes after ischemic stroke, including larger stroke volumes and poorer functional outcomes, while the connection between migraines and hemorrhagic stroke is less understood. Furthermore, migraine may serve as a stroke mimic (condition presenting with symptoms similar to ischemic stroke) or a stroke chameleon (unrecognized stroke misdiagnosed as migraine), leading to significant diagnostic and treatment errors.

Conclusions The interplay between migraine and stroke is complex, involving shared pathophysiology and overlapping risk factors. While migraine can serve as both a cause and a risk factor for stroke, the precise mechanisms remain unclear, warranting further research to clarify their connection and enhance clinical management.

Keywords Migraine, Stroke, Migrainous infarction, Stroke mimic, Patent foramen ovale

*Correspondence:
Michał Borończyk
mboronczyk@onet.pl

Full list of author information is available at the end of the article

Introduction

Migraine is a very common neurological disease with a chronic course and unclear pathogenesis. The condition is characterized by paroxysmal headaches with autonomic symptoms and, in some patients, focal neurologic deficits. It affects approximately 14% of the global population. The prevalence of migraine is significantly higher in females and generally increases with age, peaking in the 40 to 44 age group before declining in the elderly [1, 2]. Migraine has a profound impact, diminishing quality of life and placing a substantial financial burden on society. Notably, according to the Global Burden of Disease 2019, migraine is the second leading cause of disability overall and the leading cause among young women [3]. Clinically, migraines are often underdiagnosed and undertreated [4, 5]. Economically, the burden of migraines includes both direct medical costs for diagnostics and treatment, as well as indirect costs associated with lost productivity among the workforce [6]. Although, the relationship between stroke and migraine is well-established and extensively discussed in academic literature, many questions about this connection still arise [7, 8]. In light of this, in this study we want to provide a comprehensive literature review that integrates the most recent findings in this field.

Patients with migraine, particularly those experiencing migraine with aura (MA), often exhibit hyperintense changes in the brain, primarily in the posterior fossa [9]. These changes can be classified as either vascular in nature, resembling silent stroke foci or silent infarcts, or non-vascular, categorized as deep white matter lesions [9, 10].

A patient with a long history of migraine who experiences an ischemic stroke (IS) during a MA attack should be evaluated to determine whether it is a migraine-related cerebral infarction. This phenomenon is defined as a stroke occurring during a migraine attack and linked to migraine pathophysiology, and should be distinguished from strokes unrelated to migraine [11]. Bogousslavsky et al. found the occurrence of migraine-related cerebral infarction in 10.4% of patients with IS under the age of 45 [7]. Donaghy et al. observed a higher incidence of migraine-related cerebral infarction in a group of women aged 20 to 44 years who met additional conditions, such as: migraine attacks were MA attacks from the beginning, the frequency of attacks reached at least 12 per year, and migraine had been experiences for at least 12 years [12]. Similar results were recently presented by Kurth et al., who stated that there was an association between stroke and the frequency of MA attacks in young women, and that women with infrequent migraine attacks were not at increased risk of stroke [13].

While the overall risk of stroke among migraine sufferers is low, accounting for less than 1% of all strokes in patients under 45 years of age [14], emerging evidence suggests that migraine, especially MA, may increase the risk of cryptogenic IS in young individuals. This association is particularly notable in the presence of confounding factors such as cigarette smoking, the use of oral contraceptives [15], and hypertension [16]. These factors can complicate the discussion of whether migraine is a risk factor or merely a coexisting condition. Nevertheless, Bousser et al. proposed that migraine should be considered an independent risk factor for stroke in young women but not necessarily in the broader population [17]. Furthermore, studies indicate that the risk of migraine-related cerebral infarction may decline with advancing age, potentially due to changes in hormonal and metabolic profiles over time [18]. Another possible contributor to the increased stroke risk in migraineurs is the higher prevalence of hyperlipidemia in this population [19]. However, as noted by Olesen et al., distinguishing between migraines that precede stroke and migraine-like headaches caused by IS remains critical, as the latter appears to be more common, especially in young individuals [20]. These findings underscore the complexity of the relationship between migraine, age, gender, and comorbid conditions in influencing stroke risk.

This study aimed to conduct a comprehensive summary of the existing literature on the relationship between migraine and stroke.

Materials and methods

Search strategy

A comprehensive research review was conducted to find peer-reviewed articles on migraine and stroke using scientific databases such as PubMed, Medline, and related cited publications, covering the period from their inception up to January 24, 2025. Additional bibliography searches were performed using references from Google Scholar. The main searches were conducted from the 1st to the 30th of October, while supplementary searches took place from 16th to 24th of January 2025, as part of the review process. The searches utilized a combination of free-text synonyms and MeSH/Emtree headers for keywords and phrases related to migraine and stroke (e.g., migraine & stroke & endothelial dysfunction; migraine & stroke & platelets; migraine & stroke & oxidative stress; migraine & stroke & PFO; migraine & stroke & CGRP; migraine & stroke & microRNA, etc.), according to the article sections.

Eligibility criteria

Inclusion criteria for this article include studies on all types of migraine and/or stroke, primarily involving adult patients aged 18 years and older, as well as in specific cases involving pediatric patients. The project's exclusion

criteria are articles not published in English, articles classified as conference abstracts, and articles presenting overlapping participant data.

Study selection

The retrieved abstracts/articles were analyzed by two teams (stroke experts and migraine experts) after duplicates were removed. Disagreements were resolved by discussion.

Results of searching

After screening 314 potentially relevant citations, initially, 257 articles were considered in our review. Finally, we decided to include and cite 235 articles that best matched our objectives.

Migraine pathogenesis from the perspective of a migraine-stroke correlation

Although discussions concerning migraine pathogenesis have been ongoing for quite a while now, there are still many uncertainties [21–23]. Two main theories that have arisen from debates throughout the years concern the vascular and neural mechanisms involved in migraine pain development [24]. The former has long been recognized, with vasoconstriction believed to cause aura symptoms in MA and vasodilation responsible for the pulsating pain [25]. The vascular theory was considered the leading one until the discovery of calcitonin gene-related peptide (CGRP), which encouraged the use of neural theory [24–26]. CGRP is a vasodilator released from nerve fibers in the trigeminal system, acting on meningeal and cerebral arteries as well as within the trigeminal ganglion. Its close association with the trigeminal ganglion, along with studies confirming its role in migraine, strongly supports its involvement in neural theory [27]. Furthermore, different explanations are also suggested for a migraine-stroke correlation, including cortical spreading depression (CSD), endothelial dysfunction (ED), neurogenic inflammation, or patent foramen ovale (PFO) [28, 29]. The role of vasculature thus, plays a central role in all leading theories. In Fig. 1, we

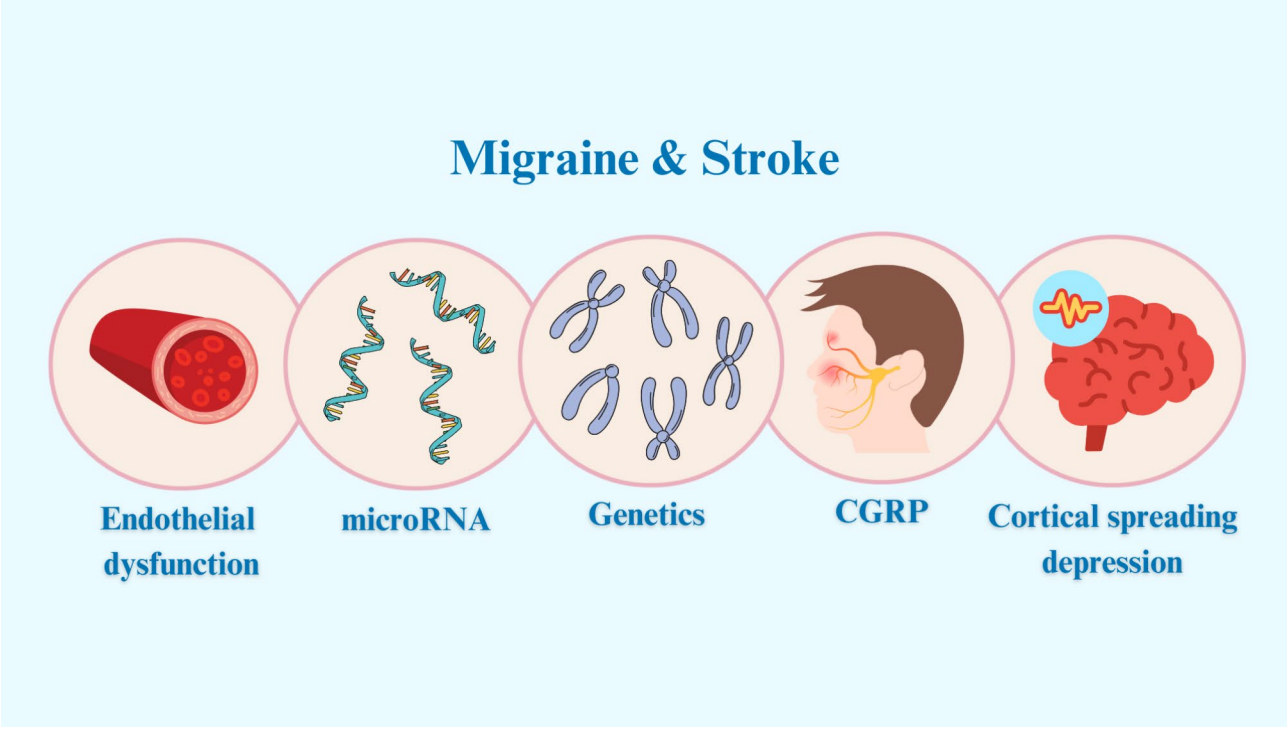

Fig. 1 Common pathophysiological pathways shared by migraine and stroke. (**1**) Endothelial dysfunction affects vascular reactivity and balance. Factors such as platelet activation, oxidative stress, and elevated biomarkers of endothelial dysfunction, like endothelial microparticles and von Willebrand factor, are associated with increased prothrombotic activity and vascular issues in migraine patients. (**2**) MicroRNAs play a role in regulating gene expression and the concentrations of individual miRNAs change in both migraine and stroke. Certain miRNAs can be biomarkers for diagnosis, treatment response, and potential therapeutic targets in both conditions. (**3**) Genetic predispositions include monogenic disorders such as CADASIL and hemiplegic migraine, along with common risk loci identified through GWAS. (**4**) CGRP, a neuropeptide with vasodilatory effects, is elevated during migraines and contributes to migraine-related pain and stroke-related neuronal damage. (**5**) CSD is an electrophysiological phenomenon linked to changes in neurotransmitters and cerebral blood flow. It is thought to connect migraines, especially those with aura, to small cortical infarctions. CSD triggers the symptoms associated with aura and may be related to IS. The oligemia induced by CSD results in a modest reduction in cerebral blood flow, which can lead to ischemia in tissues that are genetically or metabolically predisposed

provide a graphical summary of the common pathophysiological processes associated with both migraines and strokes.

Migraine aura and its pathophysiology

Cortical spreading depression is defined as an electrophysiological phenomenon with an impact on neurotransmitters, ionic balance, and cerebral blood flow [30]. In research conducted by Øygarden et al. on a large group of migraine and non-migraine patients (196 and 720 individuals, respectively), migraine was shown to be associated with small cortical infarctions [31]. Researchers suggested CSD as a linking element. The exact role of CSD in migraine is to trigger aura symptoms by causing minor disruptions in normal brain physiology. However, the connection between stroke and CSD remains less understood [32]. Sueiras et al. analyzed cortical depolarization in patients with traumatic brain injury and cerebral artery infarction [33]. In the infarction group, the percentage of CSD presence reached almost 60%. Therefore, the CSD phenomenon, typically linked to migraine, has also been suggested to be associated with IS.

In experimental conditions, increased susceptibility to migraine-triggering spreading depolarization (SD) has been observed in migraine-prone brains, providing a potential mechanism for increased brain susceptibility to ischemia and stroke risk in migraineurs [34]. Recurrent, slowly spreading peri-infarct depolarizations resembling CSD are generated in focal cerebral ischemia [35]. During a migraine, CSD triggers a transient increase in blood flow to brain tissue lasting 1–2 min, increasing energy, oxygen, and glucose consumption. This is followed by a period of hypoperfusion lasting 1–2 h [36]. Based on positron emission tomography studies, CSD-induced oligemia is estimated to account for a 12–17% reduction in cerebral blood flow. This reduction is not sufficient to cause stroke unless there is a genetic or metabolic predisposition of the tissue itself to damage [37]. In addition to CSD, another probable cause of hypoperfusion is cerebral vasospasm. Repeated occurrence of CSD due to migraine attacks may reduce the overall resistance of neurons and accelerate the onset of ischemia [36].

Migraine and CSD also share common triggers, such as microembolic occlusion of small cerebral arteries, which can trigger CSD, migraine, and even stroke [34]. SD occurs in the ischemic penumbra during stroke, superposed on low perfusion levels. Ischemia-induced changes in brain tissue homeostasis in stroke reverse the typical SD blood flow response from spreading hyperemia to spreading ischemia, thereby facilitating neuronal damage [38].

Endothelial dysfunction

The important role of the endothelium, the inner layer of blood vessels, is to modulate vascular tone due to the synthesis and release of relaxing mediators, including specific dilating factors [39]. Moreover, another function is to inhibit the adhesion of platelets and leukocytes to the vascular surface and maintain a balance of profibrinolytic and prothrombotic activity [40]. Two main components contribute to ED: impaired vascular reactivity and endothelial activation—an inflammation-induced process that can trigger platelet activation, aggregation, coagulation, and clot formation, while also suppressing antithrombotic substances [41]. ED has been linked to both migraine and stroke [42], and also has been suggested as an early biomarker of vascular pathology in migraine [43].

Role of platelets activation

Platelets aggregate in response to exposure to damaged endothelium and high shear stress conditions [41]. In addition, platelets contain serotonin, and only a small amount of it is dissolved in the plasma. It is likely that during the reduction of intraplatelet serotonin, observed in migraine attacks, the level of free serotonin in the plasma increases to the active level. Serotonin is a regulator of pain sensation and plays an important role in the pathogenesis and pharmacotherapy of migraine [44]. In some patients with migraine, mainly with aura, increased platelet activity is observed in vivo, both during the attack and also in the interictal period [45]. Serotonin can activate perivascular pain fibers around extracranial arteries. The action of serotonin is accompanied by the local release of pain mediators, including nitric oxide, prostacyclin, and neuropeptides [44, 46].

Oxidative stress

Oxidative stress arises from excessive free radical production when the system fails to mount an adequate antioxidant response. The brain, with its high oxygen consumption and rich lipid content, is very susceptible to oxidative stress [47]. Oxidative stress is a common factor underlying migraine triggers, capable of disrupting the biochemical integrity of the central nervous system and contributing to neuronal dysfunction in the brain of migraine patients [48]. The pathophysiological processes underlying IS also include oxidative stress, excitatory amino acid toxicity, ionic disturbances, increased apoptosis, and inflammation, leading to IS-induced brain damage [49].

Biomarkers of endothelial dysfunction

Biomarkers of ED during CSD in migraine include inflammatory cytokines such as endothelial microparticles (EMP), endothelial progenitor cells (EPC),

high-sensitivity C-reactive protein (hs-CRP), and endothelin-1 (ET-1), which exhibits prothrombotic effects by attracting leukocytes to sites of inflammation and inhibiting nitric oxide synthesis and vasoconstrictor effects [50]. Patients with MA may have increased levels of circulating EMP compared with controls [37]. The extent of ED correlates with the amount of circulating EMPs, which are an indicator of endothelial activation. Prothrombotic physiological changes in the brain endothelium may be induced by aura-related oligemia or oxidative stress. It appears that aura may accelerate the release of inflammatory cytokines, which then activate the endothelium, leading to increased coagulation and thrombosis-induced ischemia, and ultimately to aura or stroke, depending on the severity of the process [41].

Moreover, an important plasma biomarker of ED is von Willebrand factor (vWF), which activates platelet glycoprotein IIb/IIIa receptors, causing platelet adhesion and aggregation [51]. Significantly higher vWF antigen and vWF activity were observed in people with migraine and a history of stroke compared to the control group. These parameters were also significantly higher in people with migraine but without a prior stroke [52]. Another marker of ED is ET-1, which has potent vasoconstrictor activity on smooth muscle cells but also binds to ET-1 receptor type B receptors on the endothelium to induce nitric oxide-dependent vasodilation [53]. The role of ET-1 in migraine has not been clearly defined. Few studies have shown an increase in ET-1 levels in migraine patients in the interictal period [40]. In addition, ET-1 and its receptors are expressed in certain neurons within the trigeminal ganglia [53]. However, intravenous infusion of ET-1 did not induce aura or headache in patients with MA [54]. In addition, migraineurs have reduced levels of circulating EPCs, a nonspecific marker of vascular function that is inversely associated with cardiovascular disease risk, suggesting that EPCs may be a link between migraine and cardiovascular risk [55]. It should be emphasized that ED of arterial vessels is one of the key events in atherosclerosis, preceding the development of macroangiopathy and microangiopathy, for example, in patients with stroke [40].

CGRP

As previously reported, CGRP plays a key role in linking the neuronal and vascular components of migraine headaches. It is a regulatory neuropeptide and a potent microvascular vasodilator, released from peripheral afferent fibers of the trigeminal nerve. The importance of CGRP in the pathophysiology of migraine is strongly supported by various research results [56]:

I. CGRP levels are elevated in migraineurs during and between migraine attacks,
II. CGRP is reduced after migraine abortive and prophylactic treatment,
III. CGRP administration itself can induce migraine-like headaches,
IV. CGRP antagonists and monoclonal antibodies against CGRP are effective therapies for migraine.

As a result of IS, a necrotic scar forms, which, among other effects, impedes lymphatic flow and prolonges ion trapping time in the infarct core. This, in turn, may lead to the accumulation of ions such as potassium and glutamate. Elevated potassium levels stimulate nociceptive fibers of the trigeminal nerve, triggering the release of CGRP, among other substances [57].

The subtle role of microRNAs

MicroRNAs (miRNAs) have recently gained much attention due to the 2024 Nobel Prize in Physiology or Medicine awarded to Victor Ambros and Gary Ruvkun for their discovery [58–60]. For the last three decades, miRNAs have been found in many fields of medicine. They regulate diverse cell processes based on their ability to inhibit protein synthesis [61, 62]. Neurology is among the many medical disciplines where miRNAs are gaining influence [63–65], particularly in conditions such as migraine and stroke [66, 67]. Moreover, limited research suggests that specific miRNAs may be similarly dysregulated in both migraine and stroke [68].

Numerous studies have demonstrated that the expression profiles of various miRNAs are altered in patients following ischemic and hemorrhagic strokes [69–71]. Notably, these miRNAs may serve as important predictors of poor outcomes following IS. For instance, Fernández-Pérez et al. identified five specific miRNAs that were consistently correlated with poor outcomes three months after a stroke [72]. Additionally, a separate study found a significant association between miRNA-197 expression and stroke risk in individuals over the age of 60 [73]. Furthermore, another study revealed that elevated levels of miRNA-125b-5p might be linked to radiological complications, such as edema or hemorrhagic transformation, following thrombolytic therapy for IS [70]. Recent studies carried on rats have underscored the therapeutic potential of miRNA-7, which may help reduce ischemic injury, restore neuroprotection, and improve motor function [74, 75]. Consequently, miRNAs, as key regulators of gene expression, hold considerable promise as therapeutic agents for IS, particularly through mechanisms such as thrombosis reduction, blood-brain barrier preservation, inflammation modulation, and angiogenesis promotion [76].

MicroRNAs in migraine have been examined in a multidimensional manner in preclinical and clinical trials concerning migraine diagnosis [77–79], therapy [80],

or treatment response [81, 82]. One of the explanations for their role is targeting genes crucial for migraine pain development and, therefore, inhibiting their translation and protein synthesis. This theory is strongly supported by a study conducted by Zhai et al. showing decreased levels of miR-30a in migraine patients compared to healthy controls [83]. One of the target genes for the examined miRNA is CALCA, which encodes CGRP, a key protein in migraine pain pathogenesis. In migraineurs, lower miR-30a expression reduces inhibition of CGRP synthesis, leading to elevated CGRP levels, as observed during migraine attacks.

Much research has focused on miRNAs' diagnostic value, showing different expressions in migraine patients in comparison to controls. In a study conducted by Gallardo et al., participants with migraine diagnoses were compared to healthy individuals without a family history of migraine [77]. Three miRNAs; miR-342-3p, miR-532-3p, and miR-758-5p, differed significantly between study groups, suggesting their potential use in migraine diagnosis. In another study conducted in Taiwan, two other miRNAs were found to distinguish migraine patients from the control group: miR-126 and miR-155 [78]. The latter was also analyzed by Greco et al., comparing not only migraine patients to healthy individuals but also chronic migraine to episodic migraine [79]. The expression of miR-155 was the highest in chronic migraine patients and the lowest in the control group. Therefore, the study showed a potential role in migraine diagnosis, including differentiation between migraine types.

Beyond diagnosis, miRNAs have been studied as predictive biomarkers of treatment response. Ornello et al. conducted miRNA profiling before and after CGRP-targeting therapy, identifying a broad set of miRNAs with significantly altered expression following erenumab treatment [81]. Another research group analyzed the levels of miR-34a-5p and miR-375 in the serum and saliva of participants with MA [82]. The expression of these miRNAs was lower in individuals treated with non-steroidal anti-inflammatory drugs and magnesium compared to those who did not receive acute treatment.

Finally, therapies based on miRNAs' agonists or antagonists may influence the future of migraine treatment. Those examinations have been conducted mainly on animal models so far, but with promising results. In a study conducted by Wen et al., miR-155-antagomir alleviated neuroinflammation in a mouse migraine model, showing an assumed advantage in migraine treatment [80]. The role of miRNAs requires more research; however, there is much to suggest they may influence migraine management.

Genetics and epigenetics

There is increasing evidence supporting a shared genetic foundation between migraine and stroke from multiple perspectives [84–86]. Notably, several monogenic disorders associated with vascular dysfunction also include migraine or migraine-like symptoms as part of their clinical spectrum. One such example is cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a small vessel disease caused by a mutation in the NOTH3 gene. This gene encodes a transmembrane receptor expressed on vascular smooth muscle cells, and its dysfunction leads to vascular disease. Typical symptoms of CADASIL include MA (predominantly) or MO, transient ischemic attacks, recurrent IS, psychiatric disturbances, and cognitive impairment [84, 85, 87]. The prevalence of MA in CADASIL is estimated to be between 20 and 40% [84]. Other vascular diseases in which migraine may occur, include retinal vasculopathy with cerebral leukodystrophy (RVCL), hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL), hereditary hemorrhagic telangiectasia, and mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) [85].

One particular monogenic disorder is hemiplegic migraine (HM), in which migraine is the primary symptom, often accompanied by motor weakness. This condition may also involve impaired consciousness, cerebellar ataxia, and intellectual disability. HM can occur sporadically or as familial HM, which follows an autosomal dominant inheritance pattern [88]. Regarding familial HM, evidence from both animal and human studies highlights the role of CSD as a shared mechanism linking migraine and IS [31, 33, 34]. What is more, a similar mechanism has been observed in CADASIL [85].

Furthermore, genome-wide association studies (GWAS) have provided valuable insights by identifying common genetic variants linked to the susceptibility of both migraine (MA and MO) and IS, along with its subtypes, including large artery atherosclerotic and cardioembolic strokes [85]. For example, a large-scale meta-analysis by Malik et al., conducted through the International Headache Genetics Consortium and METASTROKE, examined genome-wide risk loci for these phenotypes and assessed the shared genetic risk between migraine and IS [86]. Their findings showed that MO exhibited a much stronger overlap with IS and its subtypes than MA. The most notable overlap was found between MO and large artery stroke, as well as between MO and cardioembolic stroke. This suggests that migraine may independently increase the risk of stroke occurrence. Further building on these results, additional researchers have investigated the causal relationship between migraine and IS, including its various

subtypes [89]. However, in one GWAS, no causal effect of migraine on IS was observed. On the other hand, Siewert et al. reported the genetic correlation between migraine and major risk factors for stroke, such as heart disease, type 2 diabetes, blood lipid levels, and blood pressure [90]. Additionally, Daghlas et al. observed a genome-wide genetic correlation between carotid artery dissection (CAD) and migraine, particularly MO, further supporting the hypothesis of a shared genetic basis [91]. Another study found that migraine is associated with poorer functional outcomes after IS [92]. These findings highlight the shared genetic links between migraine and stroke. However, further research is necessary to fully understand the connections and underlying mechanisms.

Migraine as a risk factor for stroke

In a recent meta-analysis including more than 1 million people, migraine was associated with an increased risk of stroke (hazard ratio (HR): 1.42). Furthermore, the presence of aura increased stroke risk and all-cause mortality [93]. Similarly, in a meta-analysis of 21 observational studies of the association between migraine and IS, MA was independently associated with a 2-fold increased risk of IS, even when adjusting for other stroke risk factors [94]. The risk of IS was higher in people who had active migraine (recent attacks), in those who experienced > 12 migraine attacks per year [95], and in younger and female individuals, especially with MA [96]. Figure 2 outlines the key clinical risk factors shared by stroke and migraine. Below, we provide a detailed description of each of these conditions, which may be significant in understanding the relationship between migraines and strokes.

Platelet dysfunction

Reduced platelet membrane fluidity has been found in migraine patients, and platelet membrane abnormalities are evident in changes in the number and expression of fibrinogen receptors and increased expression of platelet glycoprotein IIb [45]. Platelet activation and aggregation observed during and between migraine attacks likely occur due to neurogenic inflammation characterized by the release of various neuropeptides. These neuropeptides include pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38), CGRP, platelet-activating factor (PAF), and other proinflammatory cytokines that can cause excessive platelet aggregation. This may increase the risk of intravascular platelet aggregation or mural thrombus formation, which can lead to stroke [97].

The involvement of platelet aggregation in many migraine patients is supported by reports of increased platelet activity during attacks and the beneficial effects of antiplatelet drugs [98]. Clinical studies have shown that patients with polycythemia vera and essential thrombocythemia had severe headaches and migraines, and it has been suggested that MA may be related to polycythemia and thrombocytosis, as both conditions are associated with an increased risk of IS [57]. Studies have also shown increased levels of procoagulants such as antiphospholipid antibodies, tissue plasminogen activator antigens, and vWF in migraineurs, supporting the link between migraine and stroke risk [99]. The effect of clopidogrel on the occurrence of migraine attacks may support the hypothesis regarding the potential role of platelet activation and prothrombotic state in the pathogenesis of migraine [100]. PAF may be a potential contributor to platelet activation and aggregation, possibly via activation of the trigeminovascular system [101].

Homocysteinemia

Homocysteine is associated with an increased risk of premature vascular disease and thrombosis and has been shown to be elevated in migraine patients. Homocysteine may play a role in migraine as a result of oxidative damage to the vascular endothelium. Elevated serum levels have been shown to be responsible for a hypercoagulable state supported by elevated vWF or prothrombin activation [102]. Moreover, higher plasma homocysteine levels were observed in patients with PFO [103].

Estrogens and combined hormonal contraceptives

Hormonal influences, particularly estrogen fluctuations, are associated with migraine pathogenesis and stroke risk, highlighting the need for tailored interventions for women [50]. Migraine attacks have been shown to be associated with a drop in estrogen levels in the late luteal (premenstrual) phase of the menstrual cycle, and migraine headaches are more severe, debilitating, and frequent during the menstrual breaks of the reproductive cycle [104]. Cardiovascular disease is less common in premenopausal women than in men of the same age but increases exponentially in postmenopausal women. Estrogen therapy and aging directly affect endothelial function and the release of endothelium-derived factors, which in turn modulate platelet aggregation and smooth muscle responses. Thus, an estrogen-rich state may shift the burden of cardiovascular risk into later life, in part by modulating the platelet secretion profile [105].

Studies have shown that taking combined hormonal contraceptives (CHCs) may increase the risk of stroke by up to seven-fold in women with MA but to a much lesser extent in MO (OR = 6.1 for stroke in women with MA and 1.77 in women with MO who used CHCs in the 3 months before stroke) [106]. Estrogens influence serotonin release by reducing its uptake and degradation while increasing production [107]. In addition, estrogen-containing oral contraceptives may precipitate aura with migraine headaches in patients who have not previously experienced aura, and migraines may also occur for the

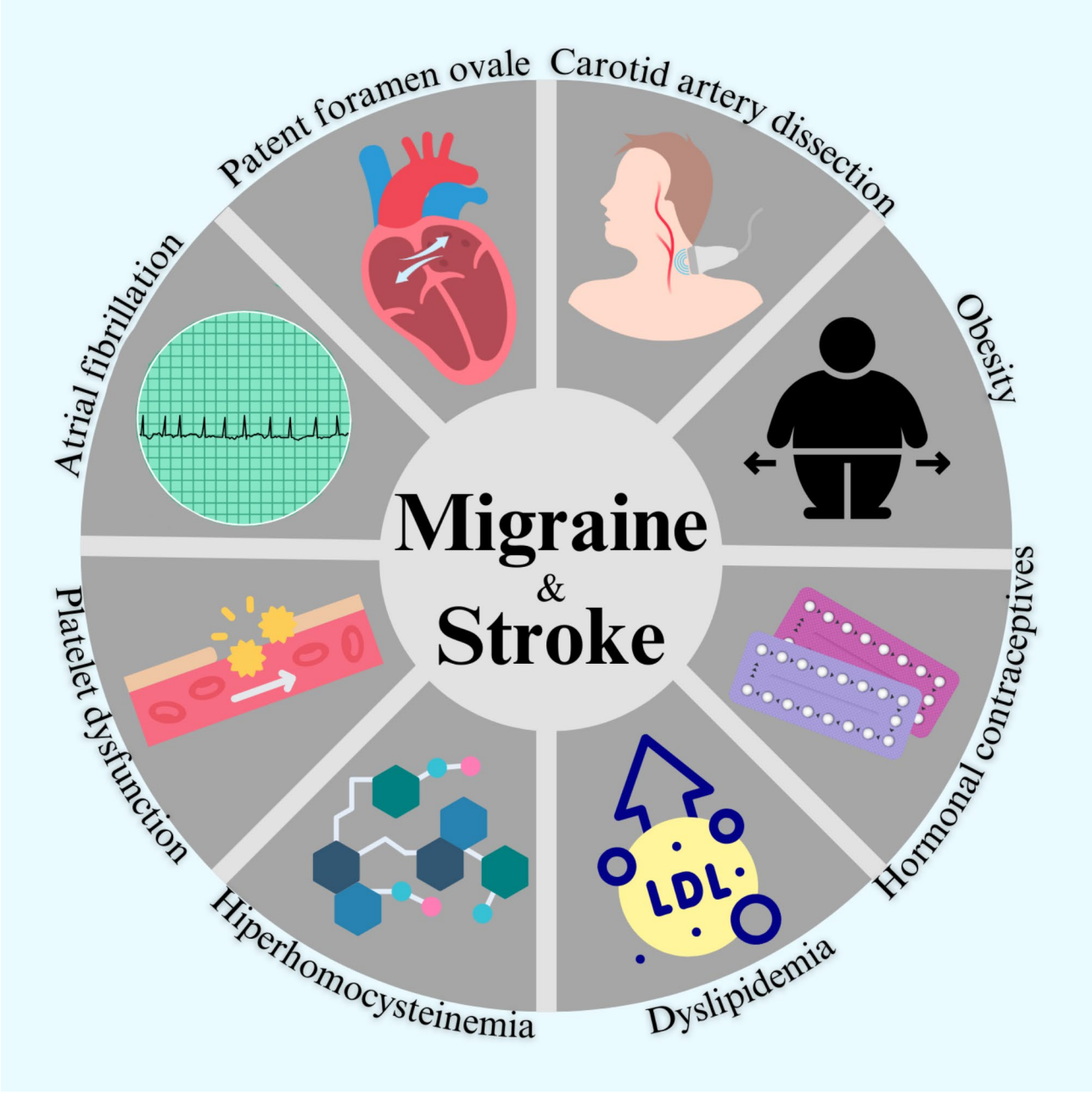

Fig. 2 Clinical risk factors contributing to the pathogenesis of migraine and stroke. (**1**) AF: may lead to the formation of microemboli in the left atrium which may transfer to brain and cause CSD, the pathophysiological basis of MA. (**2**) Patent foramen ovale: microemboli passing through a PFO can cause ischemia, cortical excitability, and trigger migraines by inducing CSD. They also transiently block microcirculation, leading to hypoxia and promoting clotting, inflammation, and further ischemia. (**3**) CAD: leads to ED and to create clinically silent circulating microemboli that may cause ischemia or CSD. (**4**) Obesity: significantly increases the risk of stroke due to elevated vascular risk. The extraovarian production of estrogen and estradiol in adipose tissue may explain the high incidence of MA in these patients. (**5**) Hormonal contraceptives: Potential mechanisms may involve estrogen-mediated coagulation, which induces platelet aggregation and can lead to the formation of microemboli, subsequently causing regional hypoperfusion, triggering CSD, and leading to increased MA and stroke risk. (**6**) Dyslipidemia: Elevated cholesterol levels, especially LDL-C, increase the risk of vascular diseases, including stroke, and also increase the frequency and severity of migraine attacks. (**7**) Hiperhomocysteinemia: elevated levels of homocysteine in the serum have been linked to an increased tendency for hypercoagulable state. (**8**) Platelet dysfunction: PAF may contribute to platelet activation and aggregation, potentially linked to polycythemia and thrombocytosis, which are associated with increased ischemic stroke risk and MA

first time in women taking CHCs [108]. Aura may be related to increased estrogen levels. Possible mechanisms include estrogen-induced coagulation, which can lead to microemboli that result in regional hypoperfusion. This, in turn, generates CSD. Estrogen may also induce platelet aggregation, triggering the release of serotonin and nitric oxide [57]. Estrogen withdrawal is associated with MO, high levels of estrogen are associated with MA. Under normal conditions, estrogen has a neuroprotective effect against acute stroke (e.g. by enhancing cerebral reperfusion after ischemia and limiting vascular ED), but at moderate and high concentrations it can lead to emboli that can eventually lead to IS [109].

Studies indicate that the risk of IS in women suffering from migraine increases significantly in combination with other risk factors (3–9-fold in the case of smoking, 4–8-fold in the case of CHCs use and 10-fold in the case of both factors) [110].

Platelets in women show increased aggregation compared with platelets in men, and pretreatment with estradiol increased thrombin-induced platelet aggregation [111]. Estrogen receptors are found in the trigeminal nucleus in humans, and cyclical changes in estrogen levels may influence the release of CGRP [112].

Lipid disorders

The association between dyslipidemia and vascular risk is well-known [113]. Many studies have shown increased total cholesterol levels in migraineurs compared with controls. In some studies, increased cholesterol levels were only found in the MA [114, 115], in other studies, there were no significant differences depending on the type of migraine [116]. Moreover, a correlation was demonstrated between the lipid profile and the number and severity of migraine attacks. In migraine patients with frequent and severe headache attacks, the level of total cholesterol and low-density lipoprotein cholesterol (LDL-C) was higher than in patients with mild attacks [117]. It was also shown that in migraine patients with white matter changes in magnetic resonance imaging (MRI), triglyceride levels were higher and high-density lipoprotein cholesterol (HDL-C) levels were statistically lower than in patients without white matter changes [118]. A recent meta-analysis of studies examining lipid levels in migraineurs found higher levels of total cholesterol, LDL-C, and triglycerides in migraineurs, while HDL-C did not differ between migraineurs and controls. However, no significant differences were found between migraineurs with and without aura [113]. In a study conducted by Ulusoy et al., MHR levels (monocyte to HDL ratio) were measured in migraine patients, which were found to be higher than in the control group and were correlated with pain intensity (visual analog scale (VAS) and migraine-related disability (MIDAS scale)) [118]. At the same time, no association between migraine and subclinical atherosclerosis has been demonstrated [119].

Obesity

Obesity is considered to be one of the most important modifiable risk factors for IS [120]. The risk of episodic migraine is greater in obese people, with the strongest associations occurring in people under 50 years of age [121]. Migraine is associated with an increased incidence of elevated body-mass index (BMI). The unusually high incidence of MA in morbidly obese patients may be due to extraovarian production of estrogen and estradiol in adipose tissue [122]. Most studies have not shown any relationship between the concentration of adiponectin, secreted from subcutaneous fat tissue, and migraine [123]. One the study by Peterlin et al. did showed that adiponectin can be a marker of acute treatment response in migraine patients, however the study was conducted on just a small group of patients [124]. Some studies have shown a protective role of adiponectin in IS, while in other studies there were no significant differences in adiponectin levels in stroke patients and the control group [125]. It should be emphasized that in population studies, obesity is considered to be one of the main factors responsible for the transformation of migraine from episodic to chronic [126].

Atrial fibrillation

Latterly, a link between MA and atrial fibrillation (AF) has been suggested. Since AF is a risk factor for stroke, this may be a pathophysiological link between MA and stroke [127]. In recent studies, IS and AF was found to be more common in patients with MA compared with those with MO [128]. Additionally, severe MA has been found to significantly increase the risk of developing AF in women [129], while AF is a frequent cause of IS in young adults suffering from MA [130]. However, no direct causal relationship has been established between the increased incidence of AF and IS in patients with MA [127].

Evidence of AF occurring during migraine attacks is limited, with only a few case reports documenting patients experiencing AF specifically during these attacks, often accompanied by vomiting [127]. The exact mechanism linking migraine and AF remains unclear. Potential explanations include arrhythmias caused by autonomic dysfunction during migraine attacks or microembolisms associated with AF that may lead to CSD, which is the underlying pathophysiology of MA [37]. AF is thought to be associated with MA partly because patients with MA tend to have more vascular risk factors than those with MO. These vascular risk factors may lead to structural cardiac abnormalities, which could result in AF. It is also

possible that AF could trigger migraine auras, as microemboli have the potential to induce CSD [127].

Autonomic dysfunction has been shown to be involved in both migraine [131] and AF [132]. The central autonomic network, along with peripheral sympathetic and parasympathetic pathways, is involved in generating headaches and cranial autonomic symptoms associated with migraine [131]. During a migraine aura, there is a SD in the cerebral cortex. When this spreading neuronal excitation, followed by depression, impinges on the insular cortex - which is crucial for pain perception and the central autonomic nervous system regulation - autonomic control of the cardiovascular system can be disrupted [133, 134]. Therefore, CSD during migraine attacks may contribute to dysfunctions in both autonomic control and AF [133].

In a study on the comprehensive assessment of vascular and non-vascular risk factors associated with migraine, AF was not significantly associated with migraine [135]. There was also no association between migraine and the subsequent risk of developing AF in a 9-year follow-up study of migraine patients [136]. However, there are case reports of patients with an attack of AF during a migraine headache [127]. At the same time, patients with migraine and AF have fewer migraine attacks after ablation therapy for AF, but transient migraine-like headaches have also been reported after ablation. The results of studies on the effect of catheter ablation for AF on the induction or modification of the intensity and frequency of migraine attacks are contradictory and are probably also confounded by anticoagulant therapy [137]. Furthermore, no genetic association was found between migraine and AF in az GWAS [138].

Carotid artery dissection

Carotid artery dissection accounts for up to one in five cases of stroke in young individuals, and several studies have indicated the existence of a relationship between CAD and migraine, particularly in MO [135, 139]. One study found that CAD was the most common cause of stroke in individuals with MO, accounting for 15% of cases, and the third most common cause among those with MA, accounting for 10% [130]. Furthermore Metso et al. reported that migraine was more common in patients with stroke and CAD compared to patients with stroke of other causes [140]. Several risk factors contribute to CAD, including hypertension, migraine (especially MO), neck trauma, and recent infections (particularly intracranial or systemic infections). Interestingly, hypercholesterolemia and being overweight seem to have a protective effect against dissection [91, 139–142]. Moreover, in patients with migraines who have experienced CAD, various changes in migraine patterns have been observed. These include a reduction in the frequency of migraine attacks, a decrease in pain intensity, and in 14.9% of cases, the complete cessation of migraine headaches [143]. Potential mechanisms underlying the association between migraine and CAD may also be related to clinically silent circulating microemboli, which have been detected in patients with CAD and which may cause ischemia and trigger SD/migraine attacks, and ED [38]. Biomarker studies have suggested a common involvement of matrix metalloproteinases and methylene tetrahydrofolate reductase (MTHFR) metabolism in migraine and CAD [144]. Furthermore, a genetic-level association (genome-wide genetic correlation) has been demonstrated between CAD and migraine, particularly MO [91].

Patent foramen ovale

Patent foramen ovale is identified in up to 65% of young patients who experienced cryptogenic stroke [145]. Numerous studies report that PFO is significantly more common in stroke patients with migraines compared to those without migraines. This association is particularly pronounced in cases involving MA, as well as in cryptogenic strokes [46, 146]. For instance, a study by West et al. revealed that among patients with cryptogenic strokes and migraines with frequent aura, the prevalence of PFO reached as high as 93% [46]. Furthermore, another study found that high-risk PFO was identified as the primary cause of stroke in young individuals with MA, accounting for 17% of such cases [130]. Additionally, it seems that patients with PFO who suffer from IS exhibit a higher incidence of MA [145, 147].

Patent foramen ovale facilitates acute ED, leading to a pro-inflammatory and pro-thrombotic state, by transferring microbubbles (occurring after diving and during medical procedures such as coronary artery bypass surgery and hemodialysis) into the arterial circulation. This is considered a risk factor for vascular disease [148]. In a study by Lantz et al., patients with cryptogenic stroke and PFO showed a high rate of ED, which did not change after PFO closure, although the patients had no cardiovascular risk factors [42]. Genetic defects in MTHFR have also been linked to atrial septal abnormalities, including PFO, which are associated with ED and may predispose individuals to cryptogenic stroke [149].

The relationship between PFO and stroke occurrence in individuals with migraines, particularly MA, has been the subject of considerable scholarly debate. It remains unclear whether PFO is a causal factor for stroke in these patients or merely a coincidental finding that influences these conditions in distinct ways [150]. In a study by Gollion et al., a significant association between potentially causal PFO and MA in young adults experiencing cryptogenic stroke was identified (OR: 3.24, 95% CI: 1.45–7.2) [151]. In contrast, two additional studies indicated no

such association between MA and PFO [145, 152]. The discrepancies observed in these studies may arise from the necessity to differentiate between potentially causal PFO - which is characterized by a large shunt or the presence of an atrial septal aneurysm (ASA) - and PFO that does not relate to stroke, which is often an incidental finding and unlikely to contribute to stroke risk [153]. Furthermore, research by Altamura et al. indicated that the presence of high-risk PFO in patients with MA did not significantly elevate the likelihood of stroke occurrence in the future [146].

Right-to-left shunting (RLS) and associated ASA have been shown to make PFO a potential factor in stroke as well as MA [154]. Microemboli from the venous circulation may pass through the PFO, causing ischemia, cortical excitability, and subsequent CSD and/or triggering a migraine attack [155]. Microemboli can transiently occlude microcirculation, causing small foci of cerebral hypoxia/ischemia. They can also provide a basis for platelet clotting and activation, and release proinflammatory factors from the occluded microvessel wall and trapped blood cells, which further contribute to ischemia [154]. Paradoxical emboli appear to have a tendency to move into the posterior circulation, an area that is hypoperfused during a MA attack [156]. The more frequent occurrence of paracortical FLAIR hyperintensities in migraine patients with PFO compared with those without PFO may support the presence of microemboli [157]. The theory of microemboli occurrence is supported by the higher frequency of microembolic signals detected via transcranial Doppler ultrasound in individuals with severe aura symptoms, such as speech and memory disorders (29.4%), compared to those with typical visual aura (3.2%) and healthy controls (5.9%) [158].

Research on the relationship between PFO morphology, the size of the RLS, and migraine severity has again produced somewhat inconclusive results. In a study by Martinez-Majander, it was revealed that the prevalence of MA in stroke patients increased with the size of RLS in those with PFO: 29.2% for patients with no shunt, 37.9% for those with small RLS, 46.7% for moderate RLS, and 49.4% for severe shunts [145]. Furthermore, another study compared the characteristics of PFOs in patients with migraines and those with embolic stroke of undetermined source (ESUS), and showed that, in ESUS patients, the PFOs were higher, and RLS during Valsalva maneuver was observed more frequently [159].

Previous studies suggest that closure of PFO as a secondary prevention after stroke can reduce migraine symptoms, especially in patients with MA [160–164]. For instance, a questionnaire-based study involving patients post-PFO closure found that 80.9% of individuals who previously experienced migraines reported either a decrease in severity or complete resolution of their symptoms [161]. Additionally, a long-term prospective study found that 87.0% of patients who underwent PFO-closure for stroke prevention experienced at least a 50% reduction in migraine severity, while 48% achieved complete remission. The improvement was more pronounced in patients with MA [160]. However, contrasting results were observed in the CLOSE-MIG randomized trial, which compared the effectiveness of PFO closure to antiplatelet therapy among a subgroup of patients with migraines. This study found no significant differences between the two groups regarding the average annual frequency of migraine attacks, the cessation of attacks, migraine-related disability after two years, or the use of preventive migraine medications during the observation period. This lack of difference was consistent for both patients with any type of migraine and those with or without aura. The significance of this finding lies in its origin from a randomized prospective trial, as opposed to observational studies like most of the aforementioned research [165]. Similar results were reported in other trials that did not meet their primary endpoints; however, these studies did observe a significant reduction in aura attacks among patients with MA [166, 167].

Insight into the migraine-stroke correlation through MRI and vasculopathies

Neuroimaging studies often reveal white matter hyperintensities (WMH) or white matter abnormalities (WMA), silent infarct-like lesions (ILL), and ischemic lesions (stroke) [168]. Hyperintense changes in the white matter of the brain may indicate concomitant structural or biochemical abnormalities in the vessels. Ultrastructural examination of the vessels of the skin and skeletal muscles revealed various pathological changes in the microvessels in 80% of patients with clinically diagnosed migraine and hyperintense changes in the white matter on MRI imaging, indicating microangiopathy [169].

WMA are typically visible on T2 and FLAIR magnetic resonance images and are assumed to consist of gliosis, demyelination, and axonal loss, probably due to microvascular damage [170]. Women with migraine, with or without aura, have a high risk of white matter changes, which increases with attack frequency [171]. In people with migraine, the probability of detecting WMAs on conventional brain MRI is 2 to 4 times higher compared to healthy controls [170]. A study conducted in a group of 263 migraine patients showed that the majority of migraine patients (63.9%) had WMH on T2 and FLAIR imaging, with the greatest intensity of changes in the frontal lobes, the changes were mostly distributed bilaterally (61%) [157]. WMHs may reflect minor brain damage caused by reduced local perfusion [172].

Migraine patients also have an increased risk of subclinical cerebellar infarcts, which increases with the

frequency of attacks and is particularly evident in the MA group, the majority of these infarcts being located in the border zone of the cerebellar arteries [173]. At the same time, migraine patients, despite the increased frequency of ischemic cerebellar changes, demonstrate normal cerebellar functions in cerebellar tests [174]. Similarly, middle-aged women with active MA had an increased risk of late cerebellar infarct-like changes on MRI compared with those without migraine [10]. A follow-up study conducted 9 years later showed progression of deep WMLs in women with MA, but no increase in the number of infarct-like lesions in the posterior circulation [175]. Similarly, a recent meta-analysis of population-based and clinical studies found that MA was significantly associated with silent cerebral infarction and silent cerebellar infarction, whereas population-based studies alone found no association between migraine and silent cerebral infarction, probably due to the small number of available studies [176].

In summary, MRI scans suggest an increased risk of infarcts and WMH in migraineurs, but the relationship between the severity or duration of migraine and the severity of structural brain abnormalities is inconsistent [95].

MRI changes in the form of unilateral hyperintense cortical signal in T2-weighted and FLAIR sequences with gyral enhancement, usually involving the temporoparietal-occipital region, occur in the syndrome of stroke-like migraine after radiotherapy (SMART). This is a reversible neurological complication, in the form of migraine headache, seizures and subacute focal neurologic deficits, which appears several months or years after radiotherapy for brain tumors [177].

The suggested association of migraine and stroke may also be supported by genetic factors, which may play a role, since migraine and stroke occur in such rare vasculopathies as CADASIL, RVCL and MELAS [128, 178]. The characteristic features of CADASIL on MRI are white T2 and FLAIR hyperintensities, often involving the external capsule and temporal pole, multiple lacunar infarcts and microbleeds [179]. In the case of RVCL, the lesions visible on MRI may mimic tumors with a pronounced mass effect, contrast-enhancing, sometimes with vasogenic edema, and there may also be additional WMH without contrast enhancement [180]. In the case of MELAS, at the time of a stroke-like attack, brain MRI findings suggest ischemia or edema, in the form of high signal areas on FLAIR and diffusion-weighted image (DWI), which are similar to the changes seen in cerebral infarction, but their distribution is not consistent with the vascular territory and these changes occur mainly in the posterior brain regions [181]. Gene mutations in the above-mentioned vasculopathies probably increase the susceptibility to stroke by facilitating ischemic depolarization [182].

Migrainous infarction

In rare cases, a migraine aura attack can develop into a migrainous infarction (MI), which according to the International Classification of Headache Disorders, 3rd ed., occurs in a patient with MA and is typical of previous attacks, except when one or more aura symptoms last > 60 min and neuroimaging shows ischemic infarction in the relevant area [11]. MI is considered a rare complication of migraine: 0.5-1.5% of all IS. A prospective study found that most patients with MI experienced prolonged aura symptoms, primarily visual aura. A total of 70.6% of patients had acute ischemic changes in the posterior circulation [183], consistent with Nordic multicenter study [184]. In younger patients, MI may range as much as 10–14% and shows predominant involvement of the posterior circulation, with the majority occurring in young women with MA [57]. The prognosis after the MI seems to be good, as most patients recover, and the frequency of migraines decreases [185]. The most common risk factors for MI were CHCs, current smoking, hyperlipidemia and PFO, while diabetes and hypertension were rare [184]. During MI, trigeminal nerve fibers are activated, which leads to the release of CGRP, which acts on, among others, brain endothelial cells and platelets, thus increasing the release of PAF, which is a strong inflammatory mediator and is involved in platelet aggregation and tissue ischemia [101].

Migraine and cryptogenic stroke

Numerous studies have identified migraine as an independent prognostic factor for the occurrence of IS in young adults [128, 186], and particularly strong association has been noted between migraine and cryptogenic stroke [186–189]. A study by Altamura et al. reported that among stroke patients with a history of MA, the presence of visual aura and shorter aura duration were predictors of stroke occurrence [146]. Notably, patients with migraine who experience a stroke tend to have fewer traditional cardiovascular risk factors compared to those without migraine [130, 189, 190]. However, patients with both migraine and stroke more frequently exhibit AF [128, 130]. A study by Gollion et al. demonstrated an association between the occurrence of migraine in young post-stroke individuals and AF (OR: 5.08; 95% CI: 1.24–21.92) [130]. These findings suggest that AF may mediate the association between migraine and cryptogenic stroke.

Women with migraine appear to be more susceptible to cryptogenic stroke compared to men [188, 191–193]. This increased risk can be attributed to several factors. Firstly, women are three times more likely than men to experience migraines, and this higher prevalence

contributes to an elevated stroke risk, particularly when combined with states of high estrogen levels. Additionally, the use of oral contraceptives and hormone replacement therapy further exacerbates the stroke risk [192, 193]. Furthermore, pregnant women with migraines are also at an increased risk for both ischemic and hemorrhagic stroke [194, 195]. In women, MA has been linked to endothelial activation, hormonal contraceptive use, pregnancy, and thrombosis, suggesting that some auras may result from ischemia caused by microembolism or thrombosis. Consequently, this may increase the risk of stroke, particularly in younger women [192].

However, it should be recognized that in most epidemiological studies, headache information was collected retrospectively, and cerebrovascular events can induce headache patterns similar to migraines, with such incidents occurring in up to 44% of stroke patients [89, 190]. Therefore, it's not clearly understood whether the correlation between stroke and migraine should be interpreted as a definitive causal relationship [89]. This hypothesis is further supported by results from Mendelian randomized studies that examined patients with genetic variants linked to migraine and stroke. Researchers were unable to establish a causal relationship between migraine at all, MA or MO, and IS overall (OR: 0.935; 95% CI: 0.851–1.027), or its subtypes and post-stroke outcomes [89, 196]. However, recent studies indicate a possible correlation between MA and the susceptibility to early-onset IS [197].

Migraine and stroke in posterior circulation

Migraines, particularly MA, have been linked to an increased risk of stroke within the posterior (vertebrobasilar) circulation. This association may stem from genetic and vascular factors affecting blood flow in this region, which supplies brain areas more vulnerable to migraine-related vascular disruptions. While the exact mechanisms underlying this connection remain under investigation, current evidence indicates that MA, especially in young women, may significantly elevate the risk of stroke in the posterior vasculature [184, 198].

Research indicates a significant association between polygenic risk scores for migraines and strokes occurring in the posterior circulation [199]. In a study by Visocnik et al., it was observed that headaches triggered by CGRP result in a notable decrease in the mean arterial velocity of the posterior cerebral artery, affecting both migraine patients and control subjects. However, the response observed in individuals with migraines was markedly diminished. Furthermore, hemodynamic changes in the posterior circulation arteries were found to be related to both migraine occurrences and the physiological response to CGRP [200]. An additional study highlighted that the vasodilatory effects of CGRP are particularly pronounced in migraine patients, particularly in those experiencing MA [201].

Moreover, the literature has described a correlation between migraines and the fetal-type posterior cerebral artery phenotype in patients who have suffered an IS [202]. Furthermore, the presence of RLS in individuals with MO may contribute to white matter integrity alterations, particularly in the posterior circulation [203]. This growing body of evidence highlights the importance of investigating the vascular mechanisms that may elucidate the relationship between migraines and the risk of stroke, especially within the context of posterior circulation.

Migraine and outcomes after stroke

According to the available literature, it appears that reports predominantly indicate that migraine patients, particularly MA, are at a higher risk of poorer outcomes following IS. In one meta-analysis, MA was shown to be associated with increased cardiovascular mortality (HR: 1.27; 95% CI: 1.14–1.42), however, this analysis did not differentiate outcomes for patients following a stroke or myocardial infarction [204]. Another study reported worse prognosis only among men with migraine (modified Rankin Scale (mRS) 3-6 RR: 1.5; 95% CI: 1.0-2.1), while no such association was observed in women (mRS 3-6 RR: 1.1; 95% CI: 0.7–1.5) [186]. Additionally, a Mendelian randomization study demonstrated that genetic predisposition to migraine is associated with poor functional outcomes (mRS 3–6) after IS (OR for poor outcome per doubling of migraine odds: 1.22, 95% CI: 1.02–1.45) [92]. Furthermore, it seems that young patients with a history of migraine and stroke had a larger stroke volume (median 5.9 cm^3 vs. 2.6 cm^3), with the largest volume observed in those with aura (median 9 cm^3) [205]. However, a study by Oliveira et al. did not find differences in stroke volume, the presence of penumbra, or stroke prognosis in patients with migraine, although the cohort of migraine patients was relatively small [206], similar to a study by Mulder et al., that did not demonstrate more severe stroke progression or differences in treatment outcomes; migraine patients represented only slightly more than 7% of the study group, and there was no differentiation between patients with and without aura [207].

Hemorrhagic stroke and migraine

Multiple meta-analyses suggest that patients with migraines have a higher risk of experiencing hemorrhagic stroke (HS) [204, 208]. However, some studies do not confirm a causal link between these two conditions [196]. In a study by Gaist et al., patients with intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH) were evaluated for the presence of migraines, but no association was found [209]. One possible reason for

these discrepancies could be that many studies linking HS and migraines did not distinguish between ICH and SAH in their outcome assessments. Additionally, some studies do not report separate results for MA and MO. Furthermore, existing research has given limited attention to the activity and duration of migraine episodes [210]. These factors contribute to the ongoing uncertainty regarding the relationship between HS and migraines, underscoring the need for large-scale, well-designed randomized trials to address this issue thoroughly.

Additionally, it should be noted that migraine-like attacks may be associated with intracranial arteriovenous malformations (AVM), often located in the occipital lobe or pons [211–213]. AVM can manifest as unilateral headaches that resemble migraines, including those with aura [211, 213]. These AVM may lead to chronic migraine symptoms, causing a progression from unilateral to bilateral headaches over time [212, 213]. What's more, these vascular abnormalities can result in ICH, particularly among young individuals, which is the most common cause of ICH in this patient group. Consequently, this may suggest a seeming relationship between ICH and migraine [214].

Migraine as a stroke mimic

Stroke mimic (SM) is a condition manifesting with a clinical presentation similar to IS, leading to overdiagnosis [215–217]. Since rapid diagnosis and treatment decisions are critical in cases of IS [218, 219], misdiagnosis may lead to complications and generate unnecessary costs [220]. The estimated rate of false-positive diagnoses in these cases is approximately 7.3% [215, 216, 221].

A 10-year evaluation of acute stroke and SM cases showed that acute migraine poses the most common SM, with a prevalence of 14.7% of cases [215]. Due to its similarity to ischemia symptomatology, mainly cases of MA, a wide range of aura types may be confusing and contribute to diagnostic errors [222]. Aura symptoms typically last between 5 and 60 min, whereas motor symptoms can persist for up to 72 h. Although these symptoms often occur before a headache, there are instances where an attack with aura is followed by a less severe headache or even no headache at all. Additionally, the clinical presentation of aura can vary [11], which may lead to confusion. Visual, retinal, sensory, brainstem, speech, or motor symptoms resemble the symptoms of IS, especially when they co-occur. It was observed that sensory and brainstem auras in SMs were often followed by motor, visual, or speech/language auras [222, 223]. Moreover, the symptoms of brainstem aura can closely resemble those of a stroke, particularly when vertigo is accompanied by other brainstem symptoms such as veering, drowsiness, nystagmus, confusion, and tinnitus [217, 223]. In rare cases, there may be decreased consciousness and general weakness caused by hyperventilation, even without a migraine aura [223].

Another relevant issue is HM, which manifests with headache and motor weakness, which usually last less than 72 h but in some patients may persist for weeks [11]. It is a rare condition, with an estimated overall prevalence of 0.01%. It is especially significant as a potential cause of pediatric stroke mimicry, given its onset during adolescence [224–226]. HM can be classified into two types: familial, which has a positive family history of similar attacks, and sporadic, which is more challenging to diagnose [227].

Factors predicting migraine SMs include age, absence of cardiovascular disease, and a lower score on the National Institute of Health Stroke Scale (NIHSS), all of which are consistent findings across various studies [221–223]. However, reports on the influence of gender on migraine SMs remain inconsistent. Some studies indicate a higher prevalence of migraine SMs among females [220, 222], while others find no significant difference [224]. Similarly, regarding the patients' migraine history, Park et al. reported that it was present in only 47.2% of subjects [223]. A meta-analysis by Macias-Gómez et al. found that only 50% of patients had a prior diagnosis of migraine, yet up to 79.4% of them fulfilled the diagnostic criteria of migraine at the time of code stroke [222]. Additionally, several studies have focused on the frequency of aura symptoms. Although the most common aura is thought to be visual, occurring in over 90% of patients [11], analyses of migraine SMs have indicated that sensory symptoms are more prevalent (66,68). Furthermore, loss of sensation was described as a significant risk factor of mimics in a Norwegian stroke trial [228]. It is estimated to occur in 73.5% of patients with migraine SMs [222].

A subsequent important topic of discussion is the role of neuroimaging in clinical practice [221–223, 226]. Brain computed tomography (CT) and CT angiography are widely used in routine clinical practice and are useful for treatment selection in patients presenting with large vessel occlusion. Studies have not shown evidence of any vascular disease potentially related to the symptoms of patients with migraine [221, 223, 226]. Perfusion CT is compatible with normal perfusion [221–223], however, it can provide additional information in some cases when used in combination with conventional MRI and CT. This combination may assist in detecting SMs in patients who present with acute onset of focal neurologic deficits [222, 226]. A novel MRI sequence known as arterial spin-labeled is considered a useful option to expedite accurate diagnosis [226].

An alternative method for predicting SMs is the use of clinical scales based solely on a patient's history and examination findings. These scales can improve the

identification of SMs during the decision-making process for intravenous thrombolysis, especially when the evaluation is conducted by an emergency physician, neurologist, and with non-contrast CT [229–232]. The FABS prediction tool exemplifies this approach, consisting of six essential variables, each contributing one point when present [232]. The variables included are absence of facial droop, a negative history of AF, age < 50 years, systolic blood pressure < 150 mmHg at presentation, a history of seizures, and isolated sensory symptoms without weakness at presentation. A higher score indicates a greater likelihood of SMs. The authors assessed that FABS ≥ 3 could identify patients with SM with 90% sensitivity (95% CI, 86-93%) and 91% specificity (95% CI, 88-93%) [232]. Other commonly known prediction tools include the simplified FABS, Telestroke Mimic Score, and Khan Score. All of these tools are based on similar variables with minor modifications and different methods of scoring [229–232]. Comparisons of these four prediction tools indicate that the Telestroke Mimic Score has the highest sensitivity, while the Khan Score exhibits the strongest specificity. All four scores demonstrate high positive predictive values (ranging from 88.1 to 97.5%) but low negative predictive values (ranging from 4.7 to 32.3%). A novel decision tree, that utilizes only age, the presence of migraine, and psychiatric history, has shown improved predictive performance [229, 233]. Nevertheless, another source has indicated that none of these tools can effectively identify SMs with sufficient accuracy for consistent clinical application [233]. Thus, further research and reasonable clinical judgment are needed to assess the likelihood of SMs at presentation.

Migraine as a stroke chameleon

An opposing phenomenon to SM is known as stroke chameleon (SC). This occurs when cerebral ischemia is unrecognized and initially diagnosed as migraine. Therefore, SC cases are considered as false negatives [216]. It is estimated that roughly 9% of cerebrovascular events are initially overlooked in emergency departments [221]. This is significant, as these patients have higher disability and mortality rates within 12 months [234]. The risk of misdiagnosis increases when the presented neurologic complaints are mild, nonspecific, or transient. Younger patients with a lower cerebrovascular risk profile are more frequently misdiagnosed as SCs [221, 234].

Stroke chameleons may be considered from several perspectives. First, a headache can be a symptom of IS. In a study analyzing over 2000 patients, 27% reported having a headache at the onset of their stroke [235]. Conversely, ischemic cerebral events can trigger a headache that resembles a migraine, leading to misinterpretation [11, 221]. According to the definition by the International Headache Society (IHS), a de novo secondary headache type occurs "in close temporal relation to another disorder that is known to cause headache" [11]. Another issue is mentioned above MI, which refers to a situation where ischemia symptoms manifest during a MA attack. The clinical presentation in these cases must correlate with an ischemic brain lesion located in the corresponding territory, as identified by neuroimaging [11].

Stroke chameleons present a significant diagnostic challenge during clinical assessment. It may be helpful in differential diagnosis to define the time distance and order of the neurological symptoms [216]. Since migraines can present both as SCs and SMs, it is crucial to conduct a detailed analysis of clinical symptoms and radiological findings to avoid complications [220, 234] and to provide the best possible care for patients. Awareness of the complex nature of migraines is essential for making accurate diagnoses.

Final considerations and practical guidance for patients

Although migraine-like headaches caused by IS (particularly in young adults) are more common than strokes triggered by migraine, specific factors in patients with migraines increase the risk of acute cerebral ischemia. In any patient presenting with both migraine and stroke, a shared pathomechanism should be considered. This is particularly relevant in younger patients, where migraines are common and strokes are rare.

Important risk factors for stroke in young women with migraines include smoking, the use of oral contraceptives, arterial hypertension, and lipid disorders. Recognizing these allows healthcare providers to formulate a preventive strategy which should be discussed with the patient. It is important to highlight that these factors are modifiable, offering opportunities for targeted interventions.

Limitations

Our study has several limitations that should be acknowledged. First, we excluded articles published in languages other than English, which may have limited the scope of our research. Second, we may have missed valuable studies indexed in databases other than those we searched. Moreover, potential bias may stem from the lack of systematic rigor in the search methodology and the heterogeneity of the included article types.

Summary

The relationship between migraine and stroke is still too complicated, this study only addresses the most important issues, which can be summarized as follows:

I. The exact mechanism by which migraine causes stroke is not fully understood. However, vasoconstriction and changes in cerebral blood flow are believed to play a central role.
II. Migraine may act as both a potential cause of stroke and a consequence (sequela) of it. While these conditions often occur independently, shared underlying mechanisms may contribute to their coexistence.
III. In every patient with the coexistence of migraine and stroke, a common pathophysiology for both diseases should be suspected. This is especially true for young patients, in whom migraine is common and stroke is rare.
IV. Women of reproductive age may have an increased risk of stroke, primarily due to a high prevalence of MA. This risk is further elevated when combined with other stroke risk factors such as smoking, the use of oral contraceptives, or pre-existing hypertension. Consequently, this group is likely to display the greatest number of coexistent risk factors.
V. New studies are needed to explain both the mechanisms of migraine-related cerebral infarctions and to assess their actual frequency.
VI. Female migraine patients, particularly those with MA, are at a higher risk of poorer outcomes following IS than patients without migraine.
VII. Some patients with migraine (with or without aura) have an increased risk of posterior cerebral infarction and subclinical changes in deep white matter.
VIII. Migraine can resemble stroke symptoms (stroke mimic), and stroke can resemble a migraine attack (stroke chameleon).

Abbreviations

AF	Atrial fibrillation
ASA	Atrial septal aneurysm
AVM	Arteriovenous malformations
BMI	Body-mass index
CAD	Carotid artery dissection
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CGRP	Calcitonin gene-related peptide
CHC	Combined hormonal contraceptive
CI	Confidence interval
CSD	Cortical spreading depression
CT	Computed tomography
DWI	Diffusion-weighted image
ED	Endothelial dysfunction
EMP	Endothelial microparticles
EPC	Endothelial progenitor cells
ESUS	Embolic stroke of undetermined source
ET-1	Endothelin-1
GWAS	Genome-wide association studies
HDL-C	High-density lipoprotein cholesterol
HIHRATL	Retinal arteriolar tortuosity and leukoencephalopathy
HM	Hemiplegic migraine
HR	Hazard ratio
HS	Hemorrhagic stroke
Hs-CRP	High-sensitivity C-reactive protein
ICH	Intracranial hemorrhage
ILL	Infarct-like lesions
IS	Ischemic stroke
LDL-C	Low-density lipoprotein cholesterol
MA	Migraine with aura
MELAS	Mitochondrial encephalomyopathy, lactic acidosis and stroke
MI	Migrainous infarction
MIDAS	Migraine-related disability scale
miRNA	microRNA
MO	Migraine without aura
MRI	Magnetic resonance imaging
MTHFR	Methylene tetrahydrofolate reductase
NIHSS	National institute of health stroke scale
OR	Odds ratio
PAF	Platelet-activating factor
PACAP-38	Pituitary adenylate cyclase-activating polypeptide 38
PFO	Patent foramen ovale
RLS	Right-to-left shunt
RVCL	Retinal vasculopathy with cerebral leukodystrophy
SAH	Subarachnoid hemorrhage
SC	Stroke cameleon
SD	Spreading depolarization
SM	Stroke mimic
SMART	Stroke-like migraine after radiotherapy
VAS	Visual analog scale
vWF	Von willebrand factor
WMA	White matter abnormalities
WMH	White matter hyperintensities

Author contributions
MB was responsible for 2, 4.7, 4.8, 7-10 sections, Figures preparation, formatting and general manuscript preparation, AZ was responsible for 4-4.6, 6 sections, reviewed the main manuscript text, JWG was responsible for 3.5, 11, 12, 14 sections and reviewed the main manuscript text, OG was responsible for 3-3.3 section and reviewed the main manuscript text, ALB was responsible for general study concept, 2, 3.4, 5, 13 sections, supervised the project and provided critical revisions for the intellectual content, ID was responsible for 1 and 15 sections and general study concept, supervised the project and provided critical revisions for the intellectual content, reviewed the main manuscript text, figure and additional material. All authors have read and agreed to the submitted version of the manuscript.

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Author details
[1]Department of Neurology, Faculty of Health Sciences in Katowice, Medical University of Silesia in Katowice, Ziołowa 45/47, Katowice 40-635, Poland
[2]Department of Neurology, Upper-Silesian Medical Centre in Katowice, Ziołowa 45/47, Katowice 40-635, Poland

[3]Department of Neurology, Faculty of Medicine and Dentistry, Medical University of Warsaw, Bielanski Hospital, Cegłowska 80, Warsaw 01-809, Poland
[4]Department of Neurology, Faculty of Medical Sciences, University Clinical Centre of Medical University of Silesia, Medyków 14, Katowice 40-752, Poland
[5]Doctoral School, Medical University of Warsaw, Żwirki i Wigury 61, Warsaw 02-091, Poland

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