



Migraine and stroke

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Abstract

Migraine is a primary disorder of the brain with peripheral consequences. The prevalence of migraine is as high as 18% in the general populations. The association between migraine and stroke has been well documented in many case-control and cohort studies. This association has been stronger in patients with migraine with aura compared to migraine without aura and dependent on sex, age, frequency of attacks, and oral contraceptive treatment. The mechanisms linking migraine to stroke are complex and not entirely elucidated. Several hypotheses have been proposed to explain this association. In this review we discuss these hypotheses, the epidemiological data, and the role of patent foramen ovale in migraine and stroke. In addition, we discuss the possible role of genetics in the link between migraine and stroke.

INTRODUCTION

The prevalence of migraine is as high as 18% in the general population (1). Migraine is identified as a primary disorder of the brain with peripheral consequences (2). The highest prevalence occurs between the ages of 25 and 55 years with a significant loss in productivity and a substantial increase in health care-related costs (2). Migraine is three times more common in women (1) and is characterized by recurrent attacks of pain and associated symptoms, typically lasting from 4 to 72 hours (3, 4). Migraine may result from a dysfunction of an area of the brainstem that is involved in the modulation of pain, sensory processing, and craniovascular afferents. The two most important migraine types are migraine without aura (Mw/oA) and migraine with aura (MwA). Aura is the only distinguishing feature between both subtypes while pain and associated symptoms are similar (5).

The association between migraine and cardiovascular disease (CVD) has been studied for a long time. Despite recent evidences linked migraine with a broader range of CVD including angina, myocardial infarction, coronary revascularization, claudication, and cardiovascular mortality (6), the stronger and most explored association remains with ischemic stroke (7). Few studies investigated the association between migraine and hemorrhagic stroke providing conflicting and inconsistency results (8, 9), without achieving any definite conclusion about the possible association. In this review we focus on the association between migraine and ischemic stroke (IS).

Ischemic stroke is a major healthcare problem worldwide, ranking as the third leading cause of death in the Western countries (10). Moreover, IS is also a leading cause of disability, with 20% of survivors requiring institutional care after 3 months of stroke onset and 15% to

30% being permanently disabled (10). Migraine is considered *Less Well-Documented or Potentially Modifiable Risk Factor* for CVD according to the American Heart Association (AHA) guidelines for primary prevention of IS (10). Therefore, clear understanding of the association between migraine and IS and the mechanisms underlying this association will help develop new preventive strategies in this subpopulation of patients at risk of IS.

Migraine as Risk factors for Stroke: Epidemiological Studies

The association between migraine and IS has been well documented in many case-control and cohort studies. Table 1 lists most relevant studies on the association between migraine and IS and/or ischemic vascular events. In 12,750 African-American and white men and women enrolled in the Atherosclerosis Risk in Communities Study (ARIC) (11) MwA was strongly associated with IS symptoms (odds ratio [OR] 5.46, 95% CI: 3.64 to 8.18), transient ischemic attack (TIA) symptoms (OR 4.28, 95% CI: 3.02 to 6.08), and verified IS events (OR 2.81, 95% CI: 1.60 to 4.92). Other headaches with aura as defined by the modified International Headache Society diagnostic criteria were also significantly associated with IS (OR 3.68, 95% CI: 2.26 to 5.99) and TIA symptoms (OR 4.53, 95% CI: 3.08 to 6.67). In contrast, the associations for Mw/oA and other headaches without aura were not significantly associated with IS or TIA. Similar findings were found in a study conducted in 39,754 individuals enrolled in the Women's Health Study (12). Mw/oA had no association with an increased risk of any type of stroke. Instead, patients with MwA had increased adjusted hazards ratios (HRs) of 1.53 (95% CI, 1.02 to 2.31) for all stroke and 1.71 (95% CI, 1.11 to 2.66) for IS, but not for hemorrhagic stroke. Interestingly, patients with MwA younger than 55 years had a greater increase in risk of stroke. These results were also confirmed in a subgroup of the same cohort population after adjustment for major vascular risk factors (age, blood pressure, antihypertensive medication, diabetes, body mass index, smoking, alcohol consumption, menstrual status, hormone levels, oral contraceptive use and cholesterol) (13). In a case-control study performed in 86 women with IS and 214 controls aged 20–44 years, the adjusted risk of IS was significantly associated with migraine of more than 12 years duration, initial MwA, and particularly if attacks were more frequent than 12 times per year (14). The association between migraine and IS was also showed in men. A prospective cohort study of 20,084 men aged 40 to 84 years participating in the Physicians' Health Study found that men who reported migraine had a adjusted HR of 1.12 (95% CI, 0.84 to 1.50) for IS (15). However, previous large epidemiological studies conducted in both sexes did not find significant association between migraine and IS in people older than 60 years of age (16, 17).

A systematic meta-analysis conducted on 14 case-control studies with an age of the participants among studies ranged from 15 to 84 years showed the relative risks (RR) for people with MwA and Mw/oA of 2.27 (95% CI, 1.61

to 3.19) and 1.83 (95% CI, 1.06 to 3.15), respectively (18). This risk did not differ when analysis was stratified by age. In this study, women using oral contraceptives had an approximately eightfold increase risk of IS compared to non-users. Recently, another systematic meta-analysis conducted on 9 studies reported a pooled RR of 1.73 (95% CI, 1.31 to 2.29) for the association between migraine and IS (19). Additional analyses indicated a significantly higher risk among individuals with MwA (RR 2.16, 95%CI, 1.53 to 3.03) compared to those with Mw/oA (RR 1.23, 95%CI, 0.90 to 1.69). The risk was greater among women, those younger than 45 years of age, with history of smoking and use of oral contraceptives.

Overall, these findings demonstrated a significant association between MwA and IS. This association is dependent on sex, age, frequency of attacks, and oral contraceptive use. The associations between migraine and silent cerebral infarction and white matter lesions (WML) have also been reported. A study using magnetic resonance imaging (MRI) showed that the patients with migraine had a higher prevalence of silent infarct in the cerebellar region of the posterior circulation territory than controls (OR 7.1; 95% CI, 0.9 to 55). This association was more pronounced among women (OR 2.1; 95% CI, 1.0 to 4.1) than men. The risk is greater in patients with MwA and those with the frequent attacks (20).

Possible Mechanisms linking Migraine to Stroke

The mechanisms linking migraine to IS are complex and not entirely elucidated. Several hypotheses have been proposed, including 1) migraine may directly lead to IS; 2) migraine may interfere with an existing local vascular lesion in the brain; 3) migraine and IS share the same inflammatory and noxious mechanisms; 4) medications for migraine may cause IS; and 5) the presence of patent foramen ovale (PFO) may be a link between migraine and IS (7).

In a study conducted in a population-based cohort from Netherlands, the Genetic Epidemiology of Migraine (GEM) study, patients with MwA had the higher prevalence of modifiable and non-modifiable vascular risk factors including hypertension, smoking, alcohol consumption, diabetes, and hyperlipidemia, compared to those without migraine (21). Moreover, the common comorbidities between migraine and IS could play an important role. Obesity is a well-established risk factor for CVD. Patients with high frequency episodic migraine have a higher body mass index (BMI) compared to controls (22). These shared factors may predispose patients to migraine as well as to IS.

Reduction in cerebral blood flow (CBF), cerebral blood volume (CBV), especially in the posterior circulation, is one of the most reported mechanism linking migraine to IS. Figure 1 shows the most relevant factors leading to reduction in CBF and CBV. In patients with a migraine headache, global CBF and CBV are reduced during the headache phase (23). These reductions may be associat-

TABLE 1
The most relevant studies on the association between migraine and ischemic stroke and/or ischemic vascular events.

Patients / Healthy controls	Gender	Country	Association between migraine and ischemic stroke and/or ischemic vascular events		References
			MwA	MwoA	
12.750	M/F	USA	IS symptoms (OR 5.46, 95% CI: 3.64 to 8.18) TIA symptoms (OR 4.28, 95% CI: 3.02 to 6.08) IS events (OR 2.81, 95% CI: 1.60 to 4.92)	not significant	¹¹ Stang et al., 2005
39.754	F	USA	Total Stroke (HRs 1.53, 95% CI 1.02 to 2.31) Ischemic Stroke (HRs 1.71, 95% CI 1.11 to 2.66)	not significant	¹² Kurth et al., 2005
27.840	F	USA	major CVD (HRs 2.15, 95% CI: 1.58–2.92; <i>P</i> = .001) Ischemic Stroke (HRs 1.91, 95% CI: 1.17–3.10; <i>P</i> = .01) Myocardial infarction (HRs 2.08, 95% CI: 1.30–3.31; <i>P</i> = .002) Coronary Revascularization (HRs 1.74, 95% CI: 1.23–2.46; <i>P</i> = .002) Angina (HRs 1.71, 95% CI: 1.16–2.53; <i>P</i> = .007) Ischemic CVD Death (HRs 2.33, 95% CI: 1.21–4.51; <i>P</i> = .01)	not significant	¹³ Kurth et al., 2006
86/214	F	UK	Ischemic Stroke (OR 12., 95% CI: 0.89 to 168.4)	n.d.	¹⁴ Donaghy et al., 2002
20.084	M	USA	n.d.	n.d.	¹⁵ Kurth et al., 2007
200/100	M/F	Israel	not significant	n.d	¹⁷ Mosek et al., 2001
metanalysis 14 studies	M/F	–	Ischemic Stroke (RR 2.27, 95% CI: 1.61 to 3.19)	Ischemic Stroke (RR 1.83, 95% CI: 1.06 to 3.15).	¹⁸ Erminan et al., 2005
metanalysis 25 studies	M/F	–	Ischemic Stroke (RR 2.16, 95% CI: 1.53 to 3.03)	Ischemic Stroke (RR 1.23, 95% CI: 0.90 to 1.69)	¹⁹ Schurks et al., 2009

Abbreviations: M: male; F: female; OR : odds ratio; HRs :adjusted hazards ratios; CI: confidence interval; RR: relative risk

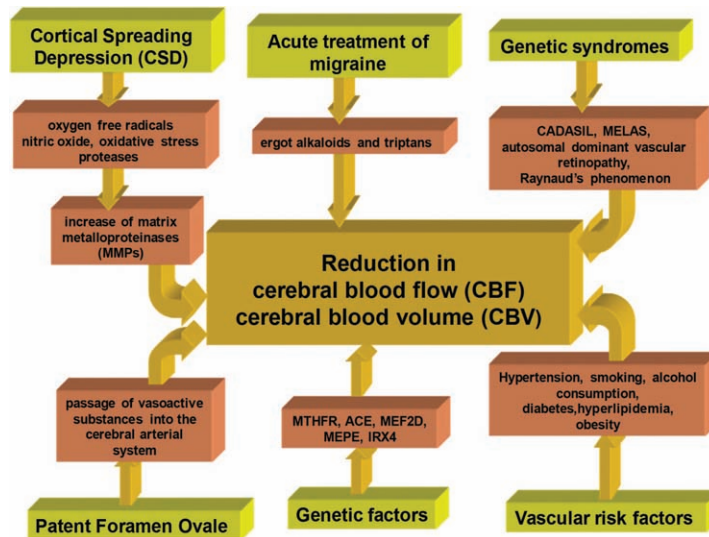


Figure 1. Factors leading to reduction in cerebral blood flow, and cerebral blood volume.

MTHFR: methylenetetrahydrofolate reductase; *ACE*: angiotensin-converting enzyme; *MEF2D*: myocyte enhancer factor 2D; *MEPE*: matrix extracellular phosphoglycoprotein; *IRX4*: iroquois homeobox 4.

ed with existing vascular pathologies, typical of patients with migraine, such as vertebral artery hypoplasia (24), and together may increase the risk of IS. Reduction of cerebral vasoreactivity in patients with migraine was also shown in a study testing the effect of vascular agents such as 5-hydroxytryptamine (5-HT) on CBF (25). Moreover, cortical spreading depression (CSD), that is the presumed substrate of aura, may predispose to vascular event by reducing CBF and by increase inflammation (26). During CSD, oxygen free radicals, nitric oxide, and proteases were released in large amounts, leading to an increase of matrix metalloproteinases (MMPs) that are known to play a pivotal role in pathogenesis of stroke (27).

Recently, an intriguing proposal on the role of the oxidative stress as the possible link between migraine and CVD and IS has been postulated (28). Oxidative stress induces impairment of arterial function including alteration of flow-mediated dilation, increase in inflammation, and leads to a prothrombotic status, all established risk factors for vascular events (29). Oxidative stress has been directly associated with migraine pathophysiology (30), and is more pronounced in patients with MwA that are more susceptible to IS (31). Other vascular factors such as the number of circulating endothelial progenitor cells (EPC) may also play an important role in the association between migraine of IS. EPC is considered a surrogate biological marker of vascular function and diminished EPC are associated with higher risk for vascular events (32). Abnormalities in EPC levels and functions have been found in migraine patients (33).

The most used drugs for the acute treatment of migraine are cranial vasoconstrictors (ergot alkaloids and triptans). However, these drugs may cause vascular side effects including IS due to these properties (34). A retrospective case – control study using data from the PHARMO Record Linkage System demonstrated that the overuse of

triptans and ergotamina increased the risk of ischemic events (35). New therapeutically strategies to treat migraine and avoid these complications are warranted.

Patent Foramen Ovale (PFO), Migraine, and Ischemic Stroke

PFO is a common remnant of fetal anatomy, which is found in 15–25% of all healthy people (36) (Figure 2). PFO has been identified as an important etiology of IS in young, especially when combined with atrial septal aneurysm (ASA) (37). However, the causative relationship between presence of PFO and IS is unclear and the true existence of this relationship has been widely debated (38). An association between PFO and migraine has been identified in many studies (39). A study aimed to investigate the prevalence of PFO in a consecutive unselected cohort of 141 migraine patients and compare it with a group of 130 young and 200 elderly ischemic stroke patients, found that the prevalence of PFO was 52% in MwA patients, 34% in Mw/oA patients, 34% in young stroke patients and 21% in elderly stroke patients ($P < 0.001$). The difference between MwA and Mw/oA patients was significant (40). In addition, a study conducted on 215 patients, demonstrated that the percutaneous closure of PFO significantly reduced the frequency of migraine attacks by 54% in patients with MwA and by 62% in patients with Mw/oA, suggesting a possible role of PFO in the migraine pathophysiology (41).

The mechanism linking the PFO with migraine has been hypothesized to depend on paradoxical embolism originated from right-to-left shunts via PFO that may allow passage of higher concentrations of vasoactive substances into the cerebral arterial system (39). In the Northern Manhattan Study (NOMAS), a large population-based, stroke patients with larger PFOs had more embolic infarct lesions on brain imaging than those with small

PFOs, suggesting that larger PFOs may be more likely to cause paradoxical embolization (42).

Despite the evidence linking PFO and migraine in case-control studies and initial PFO closure non-randomized clinical trials, several newer studies did not confirm these results. In the Migraine Intervention With STARFlex Technology (MIST) trial (43), a prospective, multicenter, double-blind, sham-controlled trial, no significant difference was observed in the refractory migraine headache cessation between implant and sham groups. Further well-designed trials are necessary to address unresolved issues related to PFO/stroke and PFO/migraine, and to identify the patients who would most likely benefit from PFO closure. Several randomized trials of transcatheter PFO closure versus medical management are currently underway in the United States and Europe (44).

The evidence from the epidemiological studies linking PFO and migraine are less supportive. Among 1,100 elderly stroke-free subjects from the NOMAS, PFO evaluated by transthoracic echocardiography was not significantly associated with IS (HR 1.64, 95% CI, 0.87 to 3.09) after adjustment for demographics and risk factors. The same trend was observed in all age, gender, and race-ethnic subgroups (36). Moreover, using the same study population in NOMAS, there was no significant association between PFO and migraine (with or without aura), and a lack of the association was not modified by vascular risk factors such as diabetes, hypertension, cigarette smoking, or dyslipidemia (45).

Based on these findings the causal relationship between PFO, stroke and migraine remains uncertain, and the role of PFO closure among unselected patients with migraine remains questionable.

Genetic Association between Migraine and Stroke

There is sufficient evidence that migraine is a familial disorder with genetic inheritance (46). A relevant genetic effect has also been demonstrated in IS, stroke related risk factors, and subclinical stroke precursors (47). Some genetic syndromes including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial myopathy, encephalopathy, lactacidosis, and stroke (MELAS), and autosomal dominant vascular retinopathy, migraine, and Raynaud's syndrome may present with both migraine and stroke (48). Common genetic susceptibility, increased susceptibility to CSD and vascular endothelial dysfunction are among the possible explanations for the association between migraine and stroke in these syndromes.

Migraine and stroke are determined by the interplay of environmental and genetic factors. Specific genes determining these diseases are not well established. However, several candidate genes for migraine are also possible candidates for IS. In the GenomEUtwin project which included 29,717 twin pairs from six countries, the heritability for phenotypic variation of migraine ranged

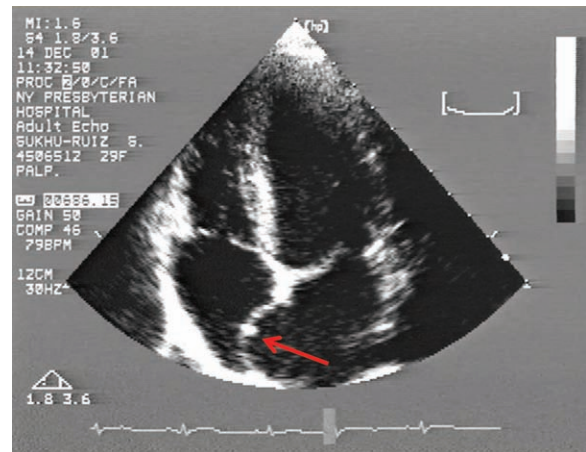


Figure 2. Transesophageal Echocardiography Image of Patent Foramen Ovale and Atrial Septal Aneurysm (courtesy of Dr. Marco R. Di Tullio, Division of Cardiology, Columbia University Medical Center, NY.)

from 34% to 57% (49). Recently, a genome-wide association study (GWAS) conducted on 2,326 clinic-based German and Dutch individuals with Mw/oA and 4,580 population-matched controls identified association between Mw/oA and loci on chromosome 1q22 in the myocyte enhancer factor 2D (*MEF2D*), a gene associated with cell cycle and neurodegenerative disease such as Parkinson disease, and at chromosome 3p24 near to transforming growth factor, beta receptor II (*TGFBR2*), a gene encoding a transmembrane protein with a protein kinase domain, which has been previously associated with Marfan Syndrome, Loeys-Deitz Aortic Aneurysm Syndrome, and the development of various types of tumors (50). In another study among 5,122 women with migraine, single nucleotide polymorphisms (SNPs) on rs7698623 in matrix extracellular phosphoglycoprotein (*MEPE*) gene, that encodes for a protein associated with cellular differentiations, and rs4975709 in iroquois homeobox 4 (*IRX4*) gene, previously related with congenital heart disease, was associated with IS. Moreover, rs2143678 located close to antigen identified by monoclonal antibody A-3A4 (*MDF1*), a gene with not identified function, with major CVD, and the intergenic rs1406961 with CVD death (51).

However, the only relevant genetic variant found for both migraine and CVD is the 677C > T polymorphism of the methylenetetrahydrofolate reductase (*MTHFR*) gene. Among 25,001 women from the Women's Health Study, coexistence of MwA and the TT genotype of the *MTHFR* raised this risk of CVD (RR 3.7; 95% CI, 1.7–7.9) and IS (RR 4.2; 95% CI, 1.9–12.7). This suggests an important predictive role of the *MTHFR* for IS among patients with MwA who are also carriers of *MTHFR* 677TT (52). In contrast, using the same population study, there was no significant association between D/I polymorphisms of the angiotensin-converting enzyme (*ACE*) gene with migraine, migraine with aura or CVD (53).

The development of new genetic techniques including the whole exome and genome sequencing will allow

for in-depth investigations of the genetic impact to complex diseases such as migraine and stroke and hold promise for future personalized medicine.

Conclusions and Future Perspectives

Factors linking migraine to IS are yet to be clearly understood. However, based on the current evidence the several recommendations can be made for patients with migraine to help preventing stroke, including identification and treatment of modifiable vascular risk factors, such as smoking, hypertension, diabetes, and hypercholesterolemia; limitation of wide spread use of medications such as triptans and use of oral contraceptives among woman with the presence of vascular risk factors. No direct linking evidence has been found for PFO, migraine and stroke. Therefore, the PFO closure in unselected migraine patients cannot be recommended for migraine and stroke prevention at this time. Further studies are imperative to identify the exact link between migraine and IS, which will lead to targeted and effective preventive strategy for these patients. Genetics may be the new frontier to fill this knowledge gap.

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