

# Migraine, cerebrovascular disease and the metabolic syndrome

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## Abstract

Evidence is emerging that migraine is not solely a headache disorder. Observations that ischemic stroke could occur in the setting of a migraine attack, and that migraine headaches could be precipitated by cerebral ischemia, initially highlighted a possibly association between migraine and cerebrovascular disease. More recently, large population-based studies that have demonstrated that migraineurs are at increased risk of stroke outside the setting of a migraine attack have prompted the concept that migraine and cerebrovascular disease are comorbid conditions. Explanations for this association are numerous and widely debated, particularly as the comorbid association does not appear to be confined to the cerebral circulation as cardiovascular and peripheral vascular disease also appear to be comorbid with migraine. A growing body of evidence has also suggested that migraineurs are more likely to be obese, hypertensive, hyperlipidemic and have impaired insulin sensitivity, all features of the metabolic syndrome. The comorbid association between migraine and cerebrovascular disease may consequently be explained by migraineurs having the metabolic syndrome and consequently being at increased risk of cerebrovascular disease. This review will summarise the salient evidence suggesting a comorbid association between migraine, cerebrovascular disease and the metabolic syndrome.

## Key Words

Comorbidities, metabolic syndrome, migraine, obesity, stroke

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## Introduction

Migraine was traditionally regarded as a disabling headache disorder with no long-term morbidity or mortality. However, growing evidence suggests that in many individuals migraine is a chronic condition associated with significant comorbidities, including cerebrovascular disease. The relationship between migraine and stroke is complex. Ischemic stroke can occur during a migraine attack but, conversely, cerebral ischemia can itself induce a migraine-like headache.<sup>[1]</sup> Additionally, migraine is a risk factor for ischemic stroke occurring outside the setting of a migraine attack.<sup>[2]</sup> Migraine also appears to increase the likelihood of developing clinically silent infarcts, noted as

hyperintense lesions on magnetic resonance imaging (MRI) scans. Both migraine and stroke manifest in individuals with conditions such as cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy and mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes, potentially implicating a common pathogenesis. The comorbid relationship between stroke and migraine may relate to observations that migraineurs have increased adiposity, reduced insulin sensitivity, an unfavourable lipid profile and hypertension, all features of the metabolic syndrome, a known risk factor for cerebrovascular disease. This review will explore the relationship between migraine, stroke and the metabolic syndrome.

## Migraine and Stroke

Migraine is increasingly being recognised as an independent risk factor for ischemic stroke occurrence outside the setting of the migraine episode.<sup>[3]</sup> A recent metaanalysis identified that all types of migraine headache were associated with an increased risk of stroke (pooled relative risk 1.73; 95% confidence interval [CI]: 1.31–2.29), but this risk was double among migraine with aura patients (2.16; 95% CI: 1.53–3.03) and was further increased

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in women less than 45 years of age, smokers and in those taking the oral contraceptive pill.<sup>[4]</sup> In keeping with this study, others have noted that the increased risk of stroke in women was most pronounced in younger patients (45–54 years).<sup>[5]</sup> Men with migraine are, however, also at increased risk of cerebrovascular disease.<sup>[6]</sup> Aura in migraineurs appears to not only increase the relative risk of a cerebrovascular event<sup>[3,4]</sup> but to also amplify the mortality rates, following a cerebrovascular event.<sup>[7]</sup> The significant association of aura with cerebrovascular disease raises the possibility that aura may be linked to the pathogenesis of stroke in migraine patients.

Migraine is a risk factor for other forms of vascular disease. Migraineurs have been noted to be at increased risk of cardiovascular comorbidities (angina and myocardial infarction).<sup>[7]</sup> In women, the risk of myocardial infarction and cardiovascular deaths is approximately doubled.<sup>[8]</sup> In the Physician's Health study, men with migraine were found to have a significantly increased risk of major cerebrovascular disease (nonfatal ischemic stroke, nonfatal myocardial infarction or death from ischemic cerebrovascular disease) (hazard ratio of 1.24; 95% CI: 1.06–1.46).<sup>[6]</sup> Migraine additionally increases the risk of peripheral vascular disease (claudication) and retinal microvascular disease.<sup>[9,10]</sup> Aligned to these findings for migraine and stroke, there is a magnified association between migraineurs with aura, compared with those without aura, and extracranial vascular disease comorbidity.<sup>[7]</sup> This diminishes the potential for aura to be pathogenic in stroke comorbidity, as it is unlikely that aura would have effects on the extracranial circulation. Therefore, it is more probable that patients with aura represent a subgroup of migraineurs in whom the underlying pathogenesis increases their probability of developing both aura and vascular disease.

### Neuroimaging Studies in Migraine

Imaging studies have highlighted that migraine is associated with increased prevalence of subclinical infarcts, noted as focal hyperintense lesions (typically white matter lesions) on MRI, independent of other cardiovascular disease risk factors.<sup>[11,12]</sup> The presence of aura in migraineurs further increases the risk of developing white matter hyperintensities on MRI and impacts on the lesion load.<sup>[11–13]</sup> The study by Kurth and colleagues demonstrated that migraine with aura is the only headache type associated with evidence of distinct brain infarction on MRI.<sup>[13]</sup> The association of migraine and white matter lesions is also significantly increased among female patients with migraine (Odds ratio [OR] 2.0; 95% CI: 1.0–4.2).<sup>[11,12]</sup> The frequency of migraine attacks (greater than one per month) further increases the risk of developing focal hyperintense lesions on MRI scan (OR 2.6; 95% CI: 1.2–6.00).<sup>[11,14]</sup> More recently, both the migraine disease duration (14 vs. 20 years,  $P=0.004$ ) and the migraine frequency (4 vs. 6 attacks per month,  $P=0.017$ ) have been found to significantly affect the load of hyperintense lesions on MRI.<sup>[15]</sup> Interestingly, hyperintense MRI lesions have been noted to have a predilection for the posterior circulation, particularly the cerebellum (8% of patients with migraine with aura had evidence of silent cerebellar infarction [OR 13.7; 95% CI: 1.7–112] compared with controls).<sup>[12,14,16]</sup>

The pathogenesis of the MRI focal hyperintense lesions, observed in migraineurs, has not been fully elucidated. A report detailing the disappearance of lesions thought to represent cerebellar infarction in a migraineur rescanned after an interval of 16 days further questions the etiology of the lesions.<sup>[17]</sup> Findings of decreased grey matter density in migraineurs, particularly in the frontal, parietal and temporal lobes, measured by voxel-based morphometry add evidence that migraine is a progressive disorder that alters brain morphology.<sup>[18–20]</sup> This is further supported by evidence of a correlation between migraine load (duration and frequency of attacks) with the extent of grey matter volume loss.<sup>[18–20]</sup>

### Why are Migraine and Stroke Comorbid Conditions?

A number of theories have been proposed to explain the comorbidity between cerebrovascular disease and migraine. Cortical spreading depression (CSD) describes the wave of neuronal and glial depolarization that occurs during the aura of a migraine attack. CSD results in altered vascular permeability, driven in part by activation of matrix metalloproteinases<sup>[21]</sup> and hypoperfusion of small penetrating arteries (possibly by 50%),<sup>[22]</sup> which could lead to hypoxic brain injury, manifesting as white matter lesions on MRI. CSD-induced cerebral ischemia could explain why aura exaggerates the cardiovascular disease risk, and load of subclinical lesions on MRI, in migraineurs.<sup>[22,23]</sup> Neurogenic inflammation, resulting from either CSD or exogenous activation of the trigeminovascular system, causes the release of neuropeptides (e.g., calcitonin gene-related peptide, substance P and neurokinin A), extravasation of plasma proteins (bradykinin and prostanoids) and inflammatory cytokines.<sup>[24]</sup> This could drive cerebral ischemia via effects on cerebral blood flow.<sup>[25]</sup> These concepts do not, however, explain the increase in systemic vascular disease, noted in migraine patients.

Genetic associations have been proposed to link migraine and cerebrovascular disease. Interestingly, migraine has been noted in association with methylenetetrahydrofolate reductase (MTHFR) C677T homozygosity, a genotype variant associated with hyperhomocysteinemia, a risk factor for stroke.<sup>[26]</sup> In keeping with this, elevated homocysteine levels have been demonstrated in the cerebrospinal fluid and serum of patients with migraine (with and without aura).<sup>[27,28]</sup> Impaired endothelial repair capacity may be important in predisposing migraineurs to stroke. Reduced function and numbers of endothelial progenitor cells (angioblasts are key to driving collateral vessel growth into ischemic tissues and repairing damaged endothelium to prevent atherosclerotic plaque formation) has been shown in migraineurs with and without aura.<sup>[29,30]</sup>

Migraine treatment may influence the risk of cerebrovascular events. Several of the migraine abortive therapies, particularly triptans and ergot alkaloids, have vasoconstrictive effects that may predispose individuals to ischemic events.<sup>[31]</sup> However, large population studies have not found an increased risk of adverse vascular events among migraineurs using triptan therapy.<sup>[32,33]</sup> Medication overuse, however, may be more problematic. Overuse of ergot-derived medications (greater

than 90 days in a year) has been shown to increase the risk of ischemic events (coronary, peripheral or cerebral vascular).<sup>[34]</sup> Additionally, it is not clear whether the use of triptan or ergot derivatives amplify the risk of cerebrovascular disease in individuals with an adverse cardiovascular disease risk profile. The proischemic effect of migraine medication does not explain why migraine with aura carries an increased cerebrovascular disease risk compared with migraine without aura, as the treatments for these two subtypes of migraine are similar. Prothrombotic states among migraine patients have also been suggested as a factor predisposing patients to cerebrovascular disease. However, studies to date have not identified a causal thrombophilia.<sup>[35]</sup>

Patent foramen ovale (PFO) occur at higher prevalence among migraineurs; in the general population, PFO prevalence is 27%, with 4.9% having large shunts, while among migraineurs, 60% have shunts of which 38% are large PFOs.<sup>[36,37]</sup> Speculation exists whether the PFO contributes to the pathogenesis of migraine and if closure of the PFO is clinically beneficial.<sup>[37-39]</sup> Independent of the potential causality by PFOs in migraine, the existence of a right-to-left shunt may predispose migraine patients to paradoxical embolism and stroke.<sup>[40]</sup> This may relate to the ability of paradoxical emboli to trigger cortical spreading depression and aura in migraineurs.<sup>[41]</sup> In support of the importance of PFOs in the comorbidity of migraine and stroke, right-to-left shunts in migraineurs are associated with MRI white matter lesions (OR=3.24; 95% CI: 1.56–6.72;  $P<0.01$ ) with lesions occurring in 6.23% of migraineurs compared with 4.05% of those with tension-type headache.<sup>[42]</sup>

In summary, debate continues as to whether migraine itself increases the risk of stroke. Alternatively, migraine and stroke may be comorbid due to a shared underlying pathogenesis, potentially the metabolic syndrome. The metabolic syndrome encompasses a collection of features, chiefly a state of impaired insulin sensitivity predisposing to type 2 diabetes mellitus, abnormal concentrations of triglycerides and high-density lipoprotein cholesterol, hypertension and obesity.<sup>[43,44]</sup> The metabolic syndrome is an established risk factor for cerebrovascular disease.<sup>[45]</sup>

## The Metabolic Syndrome

### Obesity

Initial investigations of obesity in headache found that patients with episodic headache were more likely to progress to chronic daily headache in the presence of comorbid obesity.<sup>[46]</sup> Subsequently, in a large population study of episodic migraineurs, obesity was not found to increase the prevalence of migraine but did affect the frequency and severity of episodic migraine.<sup>[47]</sup> In this study, frequent migraines (10–14 headache days per month) were noted in 4% of normal weight migraineurs (body mass index [BMI] 18.5–24.9), 6% of overweight migraineurs (BMI 25–29.9), 14% of obese migraineurs (BMI 30–4.9) and 21% of morbidly obese migraineurs (BMI>35).<sup>[47]</sup> Other studies have demonstrated a change in the prevalence of migraine as a function of BMI (prevalence of 0.9% in normal weight, 1.2% in overweight, 1.6% in obese and 2.5% in morbidly obese migraineurs).<sup>[48]</sup> Centrally

distributed adiposity is a key feature of the metabolic syndrome and, interestingly, migraine prevalence has been noted to be increased in individuals with abdominally distributed obesity (a reflection of the waist circumference).<sup>[49]</sup>

### Insulin resistance

Evidence of insulin resistance has been demonstrated in migraineurs following fasting analysis of glucose and insulin<sup>[50]</sup> and following glycemic challenge with a glucose load (impaired in 65% of migraineurs compared with 19% of controls).<sup>[51,52]</sup> Findings of elevated insulin and Homeostasis Model Assessment (HOMA) scores among normal weight migraine populations suggests that insulin resistance is not solely a manifestation of obesity in these patients.<sup>[53]</sup> This relationship also appears to be specific to migraine as other headache syndromes have not been associated with insulin resistance.<sup>[51]</sup> Interestingly, studies characterising the relationship between migraine and frank diabetes are conflicting, with one population-based study even finding an inverse relationship.<sup>[54]</sup> Of note, differences in insulin resistance have not been investigated between migraineurs with or without aura.

### Hyperlipidemia

Migraine has been associated with hyperlipidemia. This relationship appears to relate particularly to migraineurs with aura as suggested by findings of adverse lipid profile, characterised by reduced high-density lipoprotein (<1.1 mmol/L) among migraineurs, which was more pronounced in those with aura (migraine with aura OR 1.77; CI 1.35–2.32; migraine without aura OR 1.32, CI: 1.15–1.51).<sup>[55]</sup> These findings are backed up by a large population-based study in the Netherlands, which found that, compared with controls, migraineurs with aura were more likely to have elevated total cholesterol (>6.2 mmol/L, OR 1.43; CI: 0.97–2.1) and a poor total cholesterol: High-density lipoprotein ratio (>5.0, OR 1.64; CI: 1.1–2.4).<sup>[56]</sup> This relationship was less pronounced in the Women's Health Study (total cholesterol >6.2 mmol/L, OR 1.09; CI: 1.01–1.22); however, this study was methodologically limited due to self-reporting and consequently potential recall bias of migraine diagnosis, aura and hypercholesterolemia.<sup>[5]</sup> Heightened risk of hyperlipidemia among migraineurs has also been reported to be independent of weight.<sup>[57]</sup>

### Hypertension

Hypertension has also been found to be comorbid with migraine, although the limited studies in the area are conflicting. In the Population-Based Genetic Epidemiology of Migraine study (GEM), a history of hypertension was more prevalent in patients with migraine compared with nonheadache controls, and this was greatest in those with aura compared with those without (OR 1.73; CI 1.2–2.2 and OR 1.64; CI: 1.3–2.0, respectively).<sup>[56]</sup> Actual systolic and diastolic blood pressure readings did not show a similar significant elevation in migraineurs, possibly reflecting effective treatment with antihypertensive agents.<sup>[56]</sup> In the HUNT study (Nord-Trøndelag Health Study), diastolic but not systolic blood pressure was noted to be elevated among migraineurs, with no significant difference between those patients with aura and those without.<sup>[55]</sup> This study also demonstrated that the Framingham cardiovascular disease risk score was elevated for all headache patients compared with controls. However, after lifestyle-modifying covariates



(smoking, BMI and exercise) had been taken into account, the score was only significantly elevated among patients with migraine with aura.<sup>[55]</sup> Collectively, these studies support a comorbid association between migraine and hypertension, and the differences in study results likely reflect the differing methodologies between studies. Interestingly, obesity, diabetes, high cholesterol and hypertension have all been reported to occur more frequently in patients with chronic compared with those with episodic migraine.<sup>[58]</sup>

## Discussion

The relationships between migraine, stroke and the metabolic syndrome are complex. It is not clear from the literature whether migraine predisposes to stroke and, consequently, whether aggressive treatment to reduce migraine attack frequency, particularly aura frequency, would reduce the risk of cerebrovascular disease. However, migraine is associated with cardiovascular and peripheral vascular disease, which potentially implicates a more systemic underlying pathogenic link. This article has outlined the relationship between migraine and obesity, impaired insulin sensitivity, hyperlipidemia and hypertension. Taken together, these features of the metabolic syndrome may explain why migraineurs appear to be at higher risk of cerebrovascular and cardiovascular disease. As migraine appears to be comorbid with the metabolic syndrome, one could speculate that treatment of the underlying metabolic syndrome would ameliorate both migraine as well as the vascular disease risk. Of interest, a recent study demonstrated that morbidly obese migraine patients (mean BMI 47 kg/m<sup>2</sup>) who underwent weight-reducing bariatric surgery (mean percentage excess weight loss of 49%) experienced a significant reduction in headache frequency, severity and disability.<sup>[59]</sup> Although this study was uncontrolled, it does raise the possibility that weight loss strategies could represent a therapeutic avenue for migraine patients. This therapeutic approach may also modify the cardiovascular disease risk in migraine patients.

Further longitudinal studies are needed to disentangle the relationship between stroke, the metabolic syndrome and migraine, and to establish causality. The growing evidence detailed in this review suggests that migraine is not just characterised by headache but may represent a condition associated with multiple other comorbidities, including the metabolic syndrome, stroke and ischemic heart disease. Currently, there are no evidence-based guidelines detailing how physicians should address migraine comorbidities. From the literature, it would seem reasonable to adopt the following approach: (1) patients with lifestyle factors such as obesity and smoking should be counselled to modify these risks, (2) female migraineurs, particularly those with aura, wanting to use the combined oral contraceptive pill should be warned of the associated increased risk of cerebrovascular disease and an alternative, safer contraceptive preparation should be suggested (progestogen-only pill, levonorgestrel implant, contraceptive injections or an intrauterine device), (3) Triptan and ergot-derived drugs remain some of the most effective abortive treatments available to patients, but should be prescribed cautiously in patients with significant other cardiovascular disease risk factors. Newer preparations in the drug pipeline, such as calcitonin gene-related peptide

antagonists, would be useful in these situations as they are not vasoactive, (4) the assessment, and if necessary treatment, of diabetes, hyperlipidemia and hypertension may help mitigate the long-term cardiovascular risk in migraine patients. Calculations of the Framingham Heart Score may be helpful to risk stratify the patients and (5) the use of long-term antiplatelet agents for vascular prophylaxis has not been robustly studied in migraineurs and consequently cannot be commented on.

In summary, heightened awareness of the importance of treating not just the headache in migraine sufferers but also cerebrovascular disease and associated risk factors is likely to lead to improved long-term morbidity and mortality in these patients. However, evidence-based management strategies are awaited.

## Competing Interests

There are no competing interests. AS has no disclosures. MSM serves on the advisory board for Allergan and St. Jude Medical, and has received payment for the development of educational presentations from Allergan, Merck Sharp and Dohme Ltd. and Medtronic.

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