Migraine and cardiovascular disease

Possible mechanisms of interaction

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ABSTRACT

Migraine, especially migraine with aura (MA), is an established risk factor for ischemic lesions of the brain. Recent evidence has also linked migraine to a broader range of ischemic vascular disorders including angina, myocardial infarction, coronary revascularization, claudication, and cardiovascular mortality. The mechanisms which link migraine to ischemic vascular disease remain uncertain and are likely to be complex. Cortical spreading depression, the presumed substrate of aura, may directly predispose to brain lesions and that would explain why MA is consistently demonstrated as a risk factor for cerebral ischemia, while for migraine without aura (MO), the evidence is less consistent. Additionally, individuals with migraine have a higher prevalence of risk factors known to be associated with cardiovascular disease (CVD), including hypertension, diabetes, and hyperlipidemia. The increased prevalence of CVD risk factors is also higher for MA than for MO. Since the evidence linking migraine and CVD is getting robust, neurologists should be aware of this association. Individuals with MO seem to be at little increased risk of CVD. MA is associated with an increased risk of ischemic stroke and likely also for other ischemic CVD events. Accordingly, heightened vigilance is recommended for modifiable cardiovascular risk factors in migraineurs, especially with MA. Ultimately, it will be important to determine whether MA is a modifiable risk factor for CVD and if preventive medications for migraine or antiplatelet therapy might reduce the risk of CVD in patients with MA. *Neurology*® 2009;72:1864-1871

GLOSSARY

BMI = body mass index; **CDH** = chronic daily headache; **CI** = confidence interval; **CSD** = cortical spreading depression; **CVD** = cardiovascular disease; **EPC** = endothelial progenitor cells; **HR** = hazard ratio; **MA** = migraine with aura; **MMP** = matrix metalloproteinase; **MO** = migraine without aura; **MTHFR** = methyltetrahydrofolate reductase; **RR** = relative risk.

The association between migraine and ischemic vascular events has been studied for many years.^{1,2} Although the link between migraine without aura (MO) and cardiovascular events may be disputed, since the evidence is not consistent,³ migraine with aura (MA) is an established risk factor for subclinical ischemic lesions of the brain,⁴ as well as for ischemic stroke, particularly among women of younger age.^{5,6} The association has also been shown in men.⁷

Recent evidence has also linked migraine, mostly MA, to a broader range of ischemic vascular disorders including coronary disease.⁸⁻¹⁰ Studies of subclinical markers of vascular disease show that migraine is associated with retinopathy and with small vessels arteriolar intima thickening.¹⁰

The mechanisms that link migraine, especially MA, to ischemic vascular disease remain uncertain and are likely to be complex (figure 1). Cortical spreading depression (CSD), the presumed substrate of aura, may predispose to brain lesions by reducing cerebral blood flow and by activating a cascade of inflammatory events.¹¹ It is more difficult to implicate CSD in vascular events outside the brain (i.e., ischemic heart disease), and other mechanisms may be of importance. It has also been suggested that persons with MA have a higher prevalence of risk

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Figure 1 Conceptual mechanisms of the relationship between migraine with aura and cardiovascular disease

factors known to be associated with cardiovascular disease (CVD), including hypertension, diabetes, and hyperlipidemia,¹² and there is an ongoing discussion about whether migraine overall, or specific migraine subtypes (e.g., MA), associates with specific genotypes that have been linked with increased risk of CVD.¹³

A better comprehension of the relationship between migraine and CVD is therefore important for many reasons. First, identifying the subpopulations of migraine sufferers at a higher risk for CVD (e.g., individuals with MA, or women at younger ages) may enable treatment to be targeted at those most likely to benefit, while avoiding unnecessary fears in individuals not at risk for CVD. Second, once the subgroups at higher risk are clearly identified, the association implies a need for diagnostic vigilance. Third, because certain analgesics

may be associated with ischemic vascular events,¹⁴ the relationship impacts treatment choices. Finally, some studies have suggested that, at least in individuals with MA, risk of cerebral lesions increases with the frequency of headache attacks,¹⁵ which may indicate that preventive strategies to reduce migraine frequency are a potential target to decrease the risk of ischemic stroke in these individuals.

In this article, we review the associations between migraine and CVD. We start by briefly reviewing the pathophysiology of migraine, in order to provide a background for data interpretation. We then highlight the evidence suggesting that migraine and CVD are associated. We follow by providing a framework for understanding the linkages, and use this framework to discuss the data. We close by discussing clinical implications of these findings.

MIGRAINE PATHOPHYSIOLOGY Migraine is best understood as a primary disorder of the brain, with peripheral consequences.^{16,17} There is abundant evidence that migraine is a familial disorder with genetic foundation.¹⁸ The first neurologic event of migraine is a point of controversy and two non-mutually exclusive hypotheses exist.^{19,20} 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, and has also been shown to control trigeminocervical nociceptive inputs.²¹ According to this view, the pain is understood as a combination of altered perception (due to peripheral or central sensitization) of stimuli, as well as the activation of a feed-forward neurovascular dilator mechanism in the first division of the trigeminal nerve.²² The brainstem activation would induce a pro-nociceptive state and also lead to deficits in the autonomic vascular control.²⁰

An alternative theory proposes that spreading depression of cortical activity (CSD) is the first neurologic event happening in migraine.²³ CSD would explain the migraine aura and would cause further activation of trigeminovascular afferents ultimately associated with inflammation at the level of the extracerebral blood vessels.²⁴

Regardless of the exact site of initiation of migraine, neurologic events that are fairly specific to migraine (CSD and activation of the trigeminal nucleus caudalis), nonspecific dysregulation in pain processing pathways, and vascular consequences seem to be of importance in migraine pathophysiology.

Table Putative mechanisms of the relationship between migraine and cardiovascular disease (CVD)		
Mechanisms of association	Putative mechanisms	Comments
Causal association (migraine causes CVD)	Repetitive episodes of cortical spreading depression may predispose to ischemia, perfusion changes, and chronic inflammation	Justifies migraine with aura as a stronger risk factor; justifies the relationship with stroke but not with coronary problems
Shared predisposition (environmental or biological factors predispose to both migraine and CVD)	Migraineurs with aura are more likely to have poor cholesterol profile, elevated Framingham risk score for coronary heart disease, hypertension, and history of heart attack in the family; a polymorphism of the C677T gene was seen in one study and codes high levels of homocysteine (not confirmed by a second study)	Accordingly, migraineurs with aura are more likely to present one or multiple risk factors for CVD
Common comorbidities	Obesity is associated with increased headache frequency in migraine with and without aura; limited evidence also suggests that metabolic syndrome predisposed to increased headache frequency; clinic-based studies suggest that patent foramen ovale and other congenital heart problems are more common in migraine with aura	Likely magnifies the relationship between migraine with aura and cardiovascular disease, since frequency of attacks is associated with number of deep brain lesions; however, in some studies, adjustments for body mass index were conducted

POSSIBLE LINKS OF MIGRAINE AND CVD Possible reasons for the association between migraine and CVD are summarized in figure 1 and in the table. We will use this framework to build the discussion that follows.

Spurious interaction. It could be that migraine and CVD appeared to be related as a consequence of biased ascertainment. For example, individuals with TIA may be erroneously classified as having aura, and TIAs, not aura, would be associated with future stroke.^{25,26} Alternatively, medications used to treat migraine could increase the chance of CVD.^{14,27} Nonetheless, since the association between migraine and CVD is supported by large studies conducted with different methods,^{5,28} spurious interaction seems to be unlikely, although certainly not impossible.

Unidirectional causal relationships. Herein, one disease would lead to the other. For example, migraine could lead to clinical or subclinical lesions in the brain as a consequence of repetitive episodes of CSD.²⁴ Since only MA is consistently associated with stroke and deep brain lesions, in the following section we build on this hypothesis to specifically discuss this relationship.

Shared environmental and genetic risk factors and shared comorbidities. A common genetic or environmental underpinning would explain both migraine and CVD, or common comorbidities would be at least partially responsible for the association. For example, specific genes could predispose to both migraine and CVD.¹³ More likely, it has been suggested that migraineurs have a “poor cardiovascular profile.” Accordingly, if migraine is associated with higher levels of cholesterol, the increased chances of CVD seen in migraineurs is a consequence of shared co-

morbidty, not of migraine per se.¹² Nonetheless, doctors should be aware of the relationship and be extra vigilant.

UNIDIRECTIONAL RELATIONSHIP: AURA, STROKE, AND SUBCLINICAL BRAIN LESIONS

Migraine and stroke: The evidence. The association between migraine and ischemic stroke has been demonstrated in case-control and cross-sectional studies, in patients selected from specialty care settings, registries, and from the general population.²⁸⁻³⁰ A meta-analysis of 11 case-control studies and three cohort studies published before 2004 showed that, relative to individuals without migraine, the risk of stroke was increased in migraineurs (pooled relative risk [RR], 2.16; 95% confidence interval [CI], 1.9–2.5). This risk was higher for MA (RR, 2.27; 95% CI, 1.61–3.19), but was also apparent in patients with MO (RR, 1.83; 95% CI, 1.06–3.15).²⁸

More recently, two large longitudinal studies added to the evidence linking migraine and ischemic stroke. As a part of the Women’s Health Study, data were prospectively gathered over more than 10 years.⁵ Compared with controls, participants who reported MA (but not MO) had increased adjusted hazard ratios (HRs) of 1.53 (95% CI, 1.02–2.31) for total stroke and 1.71 (95% CI, 1.11–2.66) for ischemic stroke but no increased risk for hemorrhagic stroke. The increased risk for ischemic stroke was further magnified (HR 2.25; 95% CI, 1.30–3.91) for the youngest age group in this cohort (45–54 years). The associations remained significant after adjusting for cardiovascular risk factors and was not apparent for nonmigraine headache.⁵

The second prospective study used data from the Atherosclerosis Risk in Communities Study and in-

cluded over 12,000 men and women aged 55 and older.³¹ Compared to participants without headaches, migraineurs (of both subtypes) had a 1.8-fold increased risk of ischemic stroke (RR, 1.84; 95% CI, 0.89–3.82). The fact that the risk estimates did not reach statistical significance may be due to migraine classification, since the category of “other headache with aura” showed a significant increased risk of ischemic stroke (RR, 2.91; 95% CI, 1.39–6.11). Similarly, in a stroke prevention study in young women, those with MA had 1.5 greater odds of ischemic stroke, as compared to individuals without migraine (95% CI, 1.1–2.0).⁶

Migraine and subclinical brain lesions. Incidental deep brain lesions have long been reported as happening more frequently in migraineurs,³² although most studies lacked a contemporaneous control group. In a well-designed population-based study from the Netherlands, Kruit and colleagues^{4,15} randomly selected approximately 150 individuals from each of three groups for neuroimaging (MA, MO and nonmigraine controls). They excluded individuals with a history of stroke, TIA, or with abnormal neurologic examination. This study included blinded evaluation of MRI by a neuroradiologist and aura classification was performed under the supervision of expert headache diagnosticians without knowledge of the MRI results. Overall, there were no differences in the prevalence of clinically relevant infarcts between migraineurs and controls. This may be explained by the exclusion of prior history of TIA and stroke (which would also exclude those with clinically relevant infarcts). However, those with MA had significant increase of subclinical infarcts in the cerebellar region of the posterior circulation. Risk was highest in MA with more than one headache attack per month (OR = 15.8; 95% CI, 1.8–140). In addition, women with migraine were about twice as likely to have deep white matter lesions as the nonmigraineurs (OR = 2.1; 95% CI, 1.0–4.1). Consistent with the earlier studies on clinical stroke and white matter abnormalities, these findings were independent of the presence of some traditional cardiovascular risk factors.

Potential mechanisms to explain the association. In most studies, the association of CVD is either limited to MA or it is stronger in this group. The physiologic substrate of aura is CSD, a self-propagating wave of neuronal and glial depolarization.^{33,34} Cascading depolarization marching across the cortical mantle initiates a series of cellular and molecular events, resulting in transient loss of membrane ionic gradients, as well as massive surges of extracellular potassium, neurotransmitters, and intracellular calcium.

CSD may mediate its effects in part by altering the permeability of the blood–brain barrier via activation of matrix metalloproteinases (MMPs), a family of neutral metalloproteases.³⁵

During CSD, oxygen free radicals, nitric oxide, and proteases—factors that have been implicated in MMP activation—are dramatically increased. The CSD-related MMP activation may underlie changes in vascular permeability in the CNS and thus contribute to the generation of migraine symptoms.³⁶ Recent human studies using neuroimaging have demonstrated thickness abnormalities in an area (V3A) suggested as a source in spreading changes involved in visual aura.³⁷

Although a direct relationship between CSD and intracerebral lesions may be speculated, a direct relationship to heart disease is more difficult to explain. In theory, the stress of migraine attacks could unmask coronary artery disease acutely or could contribute to the development of vasculopathy over the course of multiple headache attacks. If that were true, an association also would be expected with migraine without aura, not just MA.³⁸ This hypothesis is, therefore, inconsistent with the data. Similarly, an environmental exposure that would account for the association would have to have differential effects in migraine with and without aura. For example, medications that constrict coronary arteries, such as the triptans and compounds containing ergotamine, could increase the risk of CVD in treated migraine patients. Since migraine with and without aura are similarly treated, this hypothesis is unlikely. Accordingly, we hypothesize that shared risk factors and comorbidities explain the relationship between migraine and coronary disorder, a topic we explore in the next section.

SHARED RISK FACTORS AND SHARED COMORBIDITIES: MIGRAINE AND CORONARY DISEASE

Migraine and coronary heart disease: The evidence. Due to the association between migraine (mostly MA) and ischemic stroke, it is of interest whether migraine is similarly associated with coronary heart disease as well. Although some studies yielded negative or conflicting results for overall migraine,³⁹ case reports⁴⁰ and large-scale cohort studies⁹ found an association between migraine and chest pain. In some cases, migraine was associated with ischemic electrocardiographic changes.⁴¹

Three population studies supported the relationship between migraine, especially MA, and coronary disease. In the Atherosclerosis Risk in Communities study,⁹ patients with headache were roughly twice as likely to have a history of angina as compared to controls, with the risk most elevated in the headache group with aura.

Figure 2 Cumulative incidences of major cardiovascular disease events according to migraine status in the Women's Health Study

(A) Ischemic stroke, (B) myocardial infarction, (C) coronary revascularization, (D) angina. Reprinted with permission from JAMA 2006;296:283-291.⁸ Copyright © 2006 American Medical Association. All rights reserved.

In the Women's Health Study, MA but not MO approximately doubled the relative risk of major CVD (ischemic stroke, myocardial infarction, coronary revascularization procedures, angina, as well as death related to ischemic cardiovascular events).^{5,8} These associations remained significant after adjusting for many cardiovascular risk factors (figure 2).

Finally, as part of the Physician's Health Study, men with migraine (with or without aura) were at increased risk for major CVD (HR = 1.24; 95% CI, 1.06–1.46), a finding which was driven by a 42% increased risk of myocardial infarction (figure 3).⁷

Migraine and markers of subclinical vascular disease: The evidence. Subclinical markers of vascular disease have also been suggested to be altered in patients

with migraine. As a part of the Atherosclerosis Risk in Communities study, retinal microvascular signs were assessed among middle-aged individuals.¹⁰ After controlling for age, gender, race, and cardiovascular risk factors, migraine was associated with retinopathy (OR = 1.38; 95% CI, 0.96–1.99 for MA; OR = 1.49; 95% CI, 1.05–2.12 for MO). Associations were stronger among the subset of migraineurs without a history of diabetes or hypertension (OR = 1.79; 95% CI, 1.09–2.95 for MA; and OR = 1.74; 95% CI, 1.11–2.71 for MO). Migraineurs had smaller mean arteriolar and venular calibers. The changes were restricted to small vessels and were not apparent for the carotid artery.⁴²

Possible mechanisms to explain the association. Specific disorders have been linked to migraine and CVD and may partially account for the relationships among them, although many studies adjusted for these covariates. In this section, we consider some of these potential links, including obesity and metabolic syndrome.

Obesity. Obesity is a well-established risk factor for CVD. In migraineurs, obesity has been associated with more frequent and severe headache attacks and with new onset of chronic migraine⁴³⁻⁴⁵ but it is unrelated to migraine aura.⁴⁶ In a longitudinal study, the relative odds of chronic daily headaches were five times higher in individuals with a body mass index (BMI) >30 than in individuals with normal weight.⁴³ Overweight indi-

Figure 3 Cumulative incidence of major cardiovascular disease in men according to migraine status in the Physician's Health Study

viduals had a threefold increased risk of developing chronic daily headache (CDH), suggesting a dose-response relationship between BMI and CDH.

Large cross-sectional studies confirm the longitudinal data. BMI was a risk factor for high frequency episodic migraine (OR = 2.9; 95% CI, 1.9–4.4 for obese; OR = 5.7; 95% CI, 3.6–8.8 for severe obese).⁴⁵ Additionally, the prevalence of chronic migraine ranged from 0.9% of normal weighted subjects (reference group) to 1.2% of overweight subjects (OR = 1.4; 95% CI, 1.1–1.8), 1.6% of obese subjects (OR = 1.7; 95% CI, 1.2–2.4), and 2.5% of severely obese subjects (OR = 2.2; 95% CI, 1.5–3.2).⁴⁵

Metabolic syndrome and its components. Among the putative mechanisms to explain the obesity/CVD relationship, metabolic syndrome (or the syndrome of insulin resistance) has been suggested.⁴⁷ Metabolic syndrome has been associated with chronic pain overall. Women with fibromyalgia are five times more likely than healthy controls to have metabolic syndrome.⁴⁸ Total and low-density lipoprotein cholesterol have also been significantly associated with fibromyalgia among women.⁴⁸

A recent study measured insulin and glucose levels in individuals with migraine, individuals with other headaches, and controls.⁴⁹ Tests were conducted at fasting and after an oral glucose tolerance test. Compared to controls, migraineurs had significantly higher levels of glucose and of insulin, at fasting and after glucose loading. After glucose loading, 65% of the migraineurs had an insulin resistance pattern (19% in the control group).

Dyslipidemia, another component of the metabolic syndrome, has also been associated with migraine. In the Genetic Epidemiology of Migraine study, compared to controls, migraineurs with aura were more likely to have an unfavorable cholesterol profile.¹² Risk for elevated Framingham score for coronary heart disease, as well as reduced high-density lipoprotein levels, were doubled for MA. This is of importance, since HDL cholesterol has anti-inflammatory properties that may diminish neurodegenerative processes and the perception of pain.⁵⁰ Nonetheless, findings of the Women's Health Study showed that migraine was only weakly associated with elevated total cholesterol (OR = 1.09; 95% CI, 1.01–1.18).⁵¹

Finally, a proinflammatory state has also been suggested in migraine. In the Women's Health Study, migraine was weakly associated with elevated levels of C-reactive protein (OR = 1.13; 95% CI, 1.05–1.22), although the magnitude of the effect is insufficient to support a strong biological link.⁵¹ However, in a clinic-based sample, higher magnitudes of elevation were seen, suggesting that the levels of C-reactive protein are a function of severity of illness.⁵²

OTHER SHARED BIOLOGICAL FACTORS THAT MAY BE OF IMPORTANCE

Endothelium progenitor cells. The number of circulating endothelial progenitor cells (EPC) is considered to be a surrogate biological marker of vascular function and diminished EPC counts are associated with higher cardiovascular risk.⁵³ EPCs replace injured endothelium cells, and therefore prevent the formation of atherosclerotic plaques. A recent study investigated whether abnormalities in EPC levels and functions are present in migraine patients.⁵⁴ The mean numbers of EPC colony-forming units were significantly reduced in MA, compared to other headaches. In addition, EPCs from migraine patients showed reduced migratory capacity and increased cellular senescence compared with EPCs from individuals with tension-type headache or without headaches.

SHARED BIOLOGICAL PREDISPOSITION Individuals with migraine without apparent CVD are more likely to report a parental history of early myocardial infarction, suggesting the possibility of genetic factors that predispose toward both heart disease and migraine. In the pediatric population, it has been reported that parents and grandparents of children with migraine were more likely to have a history of vascular events (OR = 1.8; 95% CI, 1.0–3.5).¹²

MA has been associated with polymorphism in the methyltetrahydrofolate reductase (MTHFR) gene C677T, which also codes moderately increased homocysteine levels.¹³ However, several small studies and recent findings from the Women's Health Study do not support such a link.⁵⁵ Accordingly, the importance of MTHFR in explaining the link between migraine and CVD remains uncertain.

CLINICAL IMPORTANCE The clinical importance of the potential relationship between migraine with aura and CVD is immense. Herein we highlight a few issues of immediate importance.

Epidemiology. Longitudinal studies assessing the predictors of the relationship between migraine and CVD should be conducted. The ultimate goal should be to elucidate the association, and to target the identification of groups at particular risk of CVD. Until now, most studies focused on migraine as a risk factor for CVD. Future studies should assess the importance of headache frequency and severity, as well as frequency of auras. If headache frequency is a risk factor for CVD, effective prophylactic treatment of migraine may reduce the risk of CVD and further studies directly evaluating this question are needed.

Furthermore, studies profiling cardiovascular health in migraineurs are crucial, since some medica-

tions for migraine are contraindicated in cardiovascular diseases (e.g., triptans and ergotamine),⁵⁶ while other analgesics may increase cardiovascular risk.¹⁴ Accordingly, it is essential to understand the risk of CVD in subpopulations of migraine sufferers to provide an appropriate context for viewing CVD rates associated with migraine treatment.

Clinical practice. Most migraine patients have migraine without aura and are at no or little increased risk of CVD. Accordingly, most patients with migraine should be reassured instead of being frightened.

Nonetheless, it seems that studies have convincingly shown that MA is associated with an increased risk of ischemic stroke and likely also for other ischemic CVD events. Based on the findings, clinicians should have heightened vigilance for modifiable cardiovascular risk factors in migraineurs, such as hypertension, hyperlipidemia, and particularly smoking, which has been associated with magnifying risk for ischemic stroke among patients with MA. In particular, women with MA who take oral contraceptives should strictly avoid smoking and alternative contraceptive methods should be considered on an individual basis. Ultimately, as described above, it will be important to determine whether MA is itself a modifiable risk factor for CVD. Additionally, studies should investigate the possibility that preventive medications for migraine or antiplatelet therapy might reduce the risk of CVD in patients with overall migraine or MA.⁵⁷

Finally, migraine, per se, is currently seen as a disorder that is progressive in some individuals, and it has been recommended that modifiable risk factors for migraine progression should be assessed in clinical practice.^{58,59} While we await clinical trials regarding the benefits of intervention in the prevention of migraine progression, several interventions are justifiable based on their other established benefits. Among them, monitoring BMI and encouraging maintenance of normal body weight is good practice in patients with and without migraine that would also impact the cardiovascular risk. For some interventions, the possibility of preventing migraine progression and decreasing cardiovascular risk may motivate clinicians to offer good care, and patients to engage in the treatment plan. Nonetheless, it is important to emphasize that many of the suggested associations are so rare that they may not have an impact on migraine management in clinical practice.

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