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The Migraine Association with Cardiac Anomalies, Cardiovascular Disease and Stroke

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Synopsis

Migraine is positively associated with cardio- and cerebrovascular disorders and with structural heart anomalies. Migraine is more prevalent among people with right-to-left shunts via patent foramen ovale, atrial septal defects, and pulmonary arteriovenous malformations, and among those with altered cardiac anatomy such as mitral valve prolapse, atrial septal aneurysm, and congenital heart disease. Meanwhile, migraine increases the risk for cardiovascular disease and stroke. Although several hypotheses exist, explanation for these associations is lacking. This manuscript reviews data supporting the association of migraine with right-to-left shunt, structural heart anomalies, cardiovascular disease, and ischemic stroke.

Introduction

Migraine has complex relationships with disorders of the cerebrovasculature, the cardiovascular system, and the heart. It has been proposed that right-to-left shunts and structural cardiac anomalies may serve causal or triggering roles in production of migraine headaches. Conversely, migraine has been identified as a risk factor for stroke and coronary artery disease. Herein, we review the evidence in support of the relationships of migraine with right-to-left shunt, structural cardiac anomalies, cardiovascular disease, and ischemic stroke.

Migraine and Right-to-Left Shunt

Right-to-left shunts are more prevalent in patients with migraine. Migraine is more common among those with right-to-left shunt. While most of the focus has been on the relationship between patent foramen ovale and migraine, atrial septal defects and extracardiac shunts have also been associated with the occurrence of migraine.

Patent Foramen Ovale

A significant amount of attention has been recently placed on investigating the association between patent foramen ovale (PFO) and migraine. There have been multiple studies of PFO prevalence in migraineurs, studies of migraine prevalence in those with PFO, and retrospective

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reports of the effect of PFO closure on migraine patterns. The large magnitude benefit noted in these uncontrolled retrospective reports of PFO closure have created excitement in regards to a possible role for PFO closure in the treatment of intractable migraine. At this time, one prospective clinical trial of PFO closure for migraine has been completed and several others are actively enrolling.

The association between PFO and migraine has been studied bi-directionally. Several studies have examined the prevalence of PFO in subjects with migraine while others have investigated the prevalence of migraine in subjects with PFO. The odds of a patient with migraine having a PFO is 2.5 (95% confidence interval (CI) 2.01–3.08) times greater than the odds of PFO in those without migraine. [1] PFO is found in 40% to 70% of subjects with migraine with and without aura as compared to 25% of people in the general population. [2–7] The increased risk of having a PFO is attributable to migraineurs who have aura. Although migraine without aura has been studied less extensively, there is not evidence for an increased prevalence of PFO in migraineurs without aura. It is estimated that just over 50% of migraineurs with aura have a PFO. [8] When the association between PFO and migraine is studied in the other direction, examining the prevalence of migraine among subjects with PFO, the positive association persists. The odds of a person with a PFO having migraine is 5.1 times (95% CI 4.67–5.59) that of a person without PFO. [1] Migraine prevalence ranges from 20% to 65% in subjects with PFO, compared to a point prevalence of about 13% for migraine in the general population. [9–21] The increased odds of migraine in the presence of PFO is attributable to migraine with aura. The odds of migraine without aura are not clearly elevated in the presence of PFO. Migraine with aura is found in 13% to 50% of subjects with PFO, a significantly higher prevalence than the expected 4% in the general population. [9–21] The odds of having migraine with aura in the presence of PFO is 3.2 (95% CI 2.38–4.17) times the odds of migraine with aura in the absence of PFO. [1] Migraine is more prevalent among subjects with large PFO as compared to those with smaller PFO and less active right-to-left shunting. [6,12,17,19,22–23]

Multiple retrospective analyses regarding the effect of PFO closure on migraine patterns have suggested a significant benefit. [13,16,17,24–25] These retrospective, non-controlled studies serve as an important base from which prospective analyses of the effect of PFO closure on migraine patterns have been designed. The nature of the retrospective studies does not allow for conclusions to be drawn regarding the safety and efficacy of PFO closure for the treatment of migraine. Nonetheless, these studies have suggested that PFO closure results in high magnitude benefit in a large proportion of subjects with migraine. Despite the prevalence studies identifying an association between PFO and migraine with aura only, retrospective PFO closure studies have found similar benefits among migraineurs with and without aura. Following PFO closure, approximately 50% of subjects retrospectively reported complete migraine resolution, about 25% reported significant reductions in headache frequency, and 15% reported no change in their headaches. [8]

The first prospective study of PFO closure for migraine was completed in late 2006. The MIST-I (Migraine Intervention with STARflex® Technology) trial was a prospective, randomized, sham procedure controlled trial conducted in Europe. Although publication of the results is still pending, preliminary results have been presented. [26] Subjects had migraine with aura, at least 5 migraine days per month and 7 headache free days per month, and a moderate or large sized PFO. Subjects had failed standard prophylactic migraine medications from at least 2 different classes. Based upon the results of retrospective studies of PFO closure, the primary endpoint was complete migraine resolution at 4 to 6 months following PFO closure in 40% of subjects. However, among the 147 randomized subjects (randomized 1:1 to treatment or sham procedure), only 3 from the treatment arm and 3 from the sham procedure group, had migraine resolution. There has been suggestion that secondary endpoints may have been met, but until

this data is adequately presented, this is not clear. Although MIST-I was a negative study, North American trials with modestly different criteria, closure devices, and outcomes are currently enrolling.

Although there is compelling evidence for an association between PFO and migraine, the nature of the relationship is not yet clear. Well-crafted hypotheses have been offered suggesting a causal relationship, a triggering relationship, and a co-incidental association. The argument for a causal relationship has focused on two main theories. First, right-to-left shunts allow for thrombi, which could develop in the PFO tunnel or elsewhere, to pass from the venous system to the arterial system and thus reach the central nervous system. A small paradoxical embolism reaching the brain's cortical surface may trigger cortical spreading depression and migraine headache. Second, the lungs normally filter out a significant proportion of the biogenic amines from the blood prior to it reaching the arterial system. [27] Right-to-left shunts allow for higher concentrations of these amines, including serotonin, to reach the arterial system and potentially trigger migraine headaches. Supporters of a co-incidental relationship between PFO and migraine cite evidence for co-inheritance of PFO and migraine. Autosomal dominant inheritance of atrial shunts linked to inheritance of migraine with aura has been demonstrated in some families. [28]

At this time, there is significant evidence supporting a positive association between PFO and migraine with aura. However, the nature of this association and the potential role of PFO closure for the treatment of intractable migraine are unclear.

Atrial Septal Defects

There is evidence that migraine is associated with atrial septal defects (ASDs). Although ASDs are most often associated with left-to-right shunting of blood, right-to-left shunting may occur during Valsalva or other activities increasing right atrial pressures. [29] Many of the studies primarily examining the PFO and migraine relationship also included small numbers of subjects with ASDs. [20,24–25] Azarbal and colleagues reported migraine headache in 30% of their 23 subjects with ASD (4 with aura and 3 without aura). [25] Following ASD repair, 3/7 had migraine resolution, 1/7 had improvement without resolution, and 3 had no change or worsening. Mortelmans and colleagues retrospectively examined the prevalence and outcome of migraine in 75 patients who had undergone percutaneous ASD closure. [29] Prior to ASD repair, 22/75 (29.3%) had migraine, 14 with and 8 without aura. There was no difference in migraine prevalence following closure (20/75). Rather interestingly though, this lack of difference may have been due to several subjects having new onset of migraine following closure as opposed to a lack of beneficial response in those with pre-existing migraine. Twelve subjects with migraine prior to closure reported migraine resolution following ASD repair. However, 10 patients reported new onset migraine after the procedure, 7 with aura and 3 without. Similarly, new onset migraine has been reported following PFO closure and may be due to thrombi formation on the occlusion device, intra-atrial pressure imbalance, or liberation of vasoactive substances. [24,29–31]

Pulmonary Right-to-Left Shunt

If right-to-left shunt is causally associated with production of migraine headaches, it would be expected that extra-cardiac shunts would also be associated with an increased prevalence of migraine. Accordingly, there is evidence that the presence of pulmonary arteriovenous malformations (AVMs) increase the risk of migraine. Pulmonary AVMs are found in 1/3 of people with hereditary hemorrhagic telangiectasia (HHT) and HHT is the underlying disorder accounting for pulmonary AVMs in 70% of cases. [32–33] Since pulmonary AVMs result in right-to-left shunt of blood, the HHT population is an interesting group within which to examine the association between right-to-left shunt and migraine. Thenganatt and colleagues

retrospectively reviewed 124 patients with HHT who had previously been assessed for a history of migraine and pulmonary AVMs. [34] Forty-seven (38%) of them had a history of migraine, four-fifths having migraine with aura. Presence of a pulmonary AVM was associated with migraine after adjusting for age and sex (Odds ratio 2.4, 95% CI 1.1 to 5.5). Among 14 patients with pulmonary AVMs and migraine who underwent AVM embolization, 8 (57%) retrospectively reported migraine improvement and 6 (43%) reported no change or worsening. Post and colleagues retrospectively studied 84 HHT patients with pulmonary AVMs to determine the baseline prevalence of migraine and the effect of AVM embolization on migraine patterns. [35] The prevalence of migraine prior to AVM embolization was 45.2%, 73.4% of those with migraine having migraine with aura. The prevalence of migraine decreased from 45.2% prior to embolization to 34.5% after embolization, assessed at a median follow-up time of 48 months ($p = 0.01$). There was a non-significant improvement in headache frequency and severity in those subjects who continued to have migraine following embolization. Although preliminary and inconclusive, there is suggestion that pulmonary AVMs may be associated with migraine and that treatment of these AVMs may have a beneficial effect on migraine patterns. Certainly, further investigation is required to elucidate these potential interactions.

Migraine and Structural Cardiac Anomalies Unrelated to Right-to-Left Shunt

In addition to the positive association between migraine with aura and intracardiac right-to-left shunt, migraine may be associated with structural cardiac anomalies in the absence of shunt.

Mitral Valve Prolapse

Results from several observational studies have suggested an association between mitral valve prolapse (MVP) and migraine. A study of 230 MVP patients found that 27.8% had migraine, a proportion significantly larger than that expected in the general population. [36] Nearly 30% of the migraineurs had migraine with aura. Investigating the association in the converse direction, Amat and colleagues found that 25% (16 of 64) of patients with migraine had MVP as compared to 9.2% of all headache patients. [37] MVP prevalence was equal among migraineurs with and without aura. Spence and colleagues conducted a case-control study to investigate the association between MVP and migraine with aura. [38] One hundred subjects who had migraine with aura and 100 non-headache controls were compared. All subjects underwent transthoracic echocardiography which was interpreted by a cardiologist blinded to the migraine status. Definite MVP was found in 15 subjects with migraine as compared to 7 control subjects. Probable MVP was identified in 16 migraine subjects and 8 controls. The odds ratio of having MVP in the presence of migraine with aura was 2.7 (95% CI 1.17 to 6.29). The nature of the association between MVP and migraine is uncertain. Arguments for a causal association are based upon reduced platelet survival and platelet aggregation in those with MVP. Damaged platelets release serotonin which has been implicated to play a role in the generation of migraine headaches.

Atrial Septal Aneurysm

The prevalence of atrial septal aneurysm (ASA) was investigated by transthoracic echocardiogram in 35 migraine with aura subjects, 55 migraine without aura subjects, and 53 non-migraine control subjects. [39] ASA was identified in 12/90 migraine subjects (13.3%) as compared to 1/53 controls (1.9%) ($p < 0.05$). The increased frequency of ASA among migraineurs was isolated to subjects with aura. ASA was found in 28.5% of migraine with aura subjects and 3.6% of migraine without aura subjects. ASA was associated with PFO in 3/10 migraineurs with aura, 3/3 migraineurs without aura, and 1/1 non-migraine control subjects.

Congenital Heart Disease

A recent study found an increase in the prevalence of migraine among adults with congenital heart disease. [40] Patients from the UCLA Adult Congenital Heart Disease Center were asked to complete a questionnaire to determine the presence of migraine headache. Of the 85% (395/466) who returned the questionnaire, 45.3% were diagnosed with migraine. Among 252 sex-matched controls with acquired cardiovascular diseases, 11% had migraine ($p < 0.001$). Eighty percent of congenital heart disease subjects with migraine had aura as compared to 36% of migraineurs in the control group ($p < 0.001$). The frequency of migraine was highest among congenital heart disease subjects with right-to-left shunt (52%) followed by those with left-to-right shunt (44%). Of significant interest though, the prevalence of migraine was also elevated in congenital heart disease subjects without shunt as compared to control subjects (38% vs. 11%).

Summaries of the relationship between migraine prevalence and prevalence of cardiac and vascular conditions are presented in Tables 1 and 2.

Migraine and Cardiovascular Disease

Migraine has been shown to be associated with an increase in cardiovascular risk factors. This association was investigated in the Genetic Epidemiology of Migraine (GEM) study, a population based study in the Netherlands of 5,755 subjects including 620 current migraineurs. [41] Measured cardiovascular risk factors included blood pressure, cholesterol levels, smoking, oral contraceptive use, and the Framingham risk score for myocardial infarction or coronary heart disease death. As compared to non-migraine controls, migraineurs had increased odds for smoking (OR = 1.43, 95% CI 1.1–1.8), were less likely to drink alcohol (OR = 0.58, 95% CI 0.5–0.7), and were more likely to report a parental history of early myocardial infarction. Migraine subjects who had aura were more likely to have a total cholesterol to high-density lipoprotein cholesterol (HDL) ratio of greater than 5, hypertension, and a history of early onset coronary heart disease or stroke. Female migraineurs were more likely than controls to be using oral contraceptives (OR = 2.06, 95% CI 1.05–4.0). The Framingham 10-year risk of coronary heart disease or myocardial infarction was higher in migraine subjects as compared to non-migraine controls. The odds ratio of having a 1% risk was 1.51 (95% CI 1.2–2.0), a 2–9% risk was 1.72 (95% CI, 1.3–2.3), a 10–20% risk was 1.43 (95% CI 0.9–2.3), and a 21% or greater risk was 2.25 (95% CI 1.0–5.1). Although the results from this study clearly suggest that migraineurs are more likely to have cardiovascular risk factors, the direction and nature of this relationship is not clear.

Migraine has been identified as a risk factor for cardiovascular disease in men and women. A large prospective cohort study by Kurth and colleagues used participants in the Women's Health Study to investigate the association between migraine and cardiovascular disease. [42] This investigation included 27,480 American women 45 years of age or older who were free of cardiovascular disease and angina at study entry and from whom data regarding migraine and lipid measurements were available. Among these women, 5,125 (18.4%) reported a history of migraine and 3,610 (13.1%) had migraine within the prior year. Nearly 40% ($n = 1434$) of women with migraine reported migraine aura. Major cardiovascular disease occurred in 580 women during the 10 year mean follow-up. Major cardiovascular disease was defined as the first instance of nonfatal ischemic stroke, nonfatal myocardial infarction, or death due to ischemic cardiovascular disease. Investigators also analyzed data for first ischemic stroke, myocardial infarction, coronary revascularization, and angina. Migraine with aura increased the risk of such events after controlling for age, blood pressure, diabetes, body mass index, smoking, alcohol use, exercise, postmenopausal status, family history of myocardial infarction prior age 60 years, cholesterol levels, and use of antihypertensives, hormones, oral contraceptives, and cholesterol lowering medications. Adjusted hazard ratios in the presence

of active migraine with aura were 2.15 (95% CI 1.58–2.92, $p < 0.001$) for major CVD, 1.91 (95% CI 1.17–3.10, $p = 0.01$) for ischemic stroke, 2.08 (95% CI 1.30–3.31, $p = 0.002$) for myocardial infarction, 1.74 (95% CI 1.23–2.46, $p = 0.002$) for coronary revascularization, 1.71 (95% CI 1.16–2.53, $p = 0.007$) for angina, and 2.33 (95% CI 1.21–4.51, $p = 0.01$) for ischemic cardiovascular death. Migraine without aura was not associated with an increased risk of cardiovascular disease.

The association between migraine and cardiovascular disease in men was investigated using 20,084 men aged 40 years to 84 years enrolled in the Physician's Health Study. [43] Annual questionnaires assessed for the presence of migraine, cardiovascular risk factors, and the occurrence of cardiovascular endpoints of interest. Investigators used the following endpoints: first major cardiovascular event (nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic cardiovascular disease), coronary revascularization, and angina. At baseline assessment, 7.2% of the men ($n = 1449$) reported migraine. Information regarding the presence of aura symptoms was not collected. Just over 11% of the total cohort had a major cardiovascular event during the mean 15.7 years of follow-up. Hazard ratios were calculated after adjusting for age, hypertension, diabetes mellitus, smoking, exercise, body mass index, alcohol use, cholesterol levels, and parental history of myocardial infarction before 60 years of age. As compared to non-migraine controls, men with migraine were found to have an increased risk of major cardiovascular disease (hazard ratio 1.24, 95% CI 1.06–1.46, $p = 0.008$) and myocardial infarction (hazard ratio 1.42, 95% CI 1.15–1.77, $p < 0.001$). There were not significant increases in the risk of coronary revascularization, angina, or ischemic cardiovascular death. Since data regarding the presence of aura were not collected, it is unclear if there is an increased risk of major cardiovascular disease and myocardial infarction in both migraineurs with and without aura.

The explanation for an increased risk of cardiovascular disease among migraineurs is unclear. It may be that migraineurs are at increased risk due to the migraine association with cardiac risk factors. Alternatively, the association could be explained by an increased presence of prothrombotic factors (e.g. factor V Leiden, von Willebrand factor), increased inflammatory response related to neurogenic inflammation, vascular endothelial damage or dysfunction, shared underlying genetic predisposition, or use of anti-migraine medications. [44–46] Regardless of the biologic explanation, the increased risk of cardiovascular disease among migraineurs has led to the recommendation that clinicians carefully assess their migraine patients for cardiovascular risk factors and treat modifiable risk factors when present. [47]

Migraine and Stroke

Migraine is a risk factor for ischemic stroke. This increased risk is greatest among young women who have frequent migraine with aura, especially if they smoke or use oral contraceptive pills. Nonetheless, studies suggest that both men and women migraineurs, whether young or old, are at increased risk of ischemic stroke.

A meta-analysis of 14 studies examining the association between migraine and ischemic stroke included studies published prior to 2004. [48] Increased stroke risk was found for migraineurs with and without aura. Overall, migraine was associated with a relative risk for stroke of 2.16 (95% CI 1.89–2.48). Migraineurs without aura had a relative risk of 1.83 (95% CI 1.06–3.15) while those with aura had a relative risk of 2.27 (95% CI 1.61–3.19). Studies suggest that the risk of ischemic stroke in migraineurs is more than tripled in smokers and quadrupled in migraineurs using oral contraceptive pills. [45,49–50] Migraineurs should be counseled about not smoking and the risks and benefits of oral contraceptive use must be carefully discussed.

Studies published since the time of the meta-analysis further support the association between migraine and ischemic stroke. Investigation of migraineurs in the Women's Health Study found

that migraineurs with aura had a relative risk of 1.7 (95% CI 1.11–2.66) for ischemic stroke as compared to non-migraine controls. [42] The increased risk was highest among the youngest group in the cohort, 45–55 years of age (only women 45 years of age and older were included), for whom the relative risk was 2.25 (95% CI 1.30–3.91). There was not an increased risk for ischemic stroke in migraineurs without aura. A non-significant increase in the risk of ischemic stroke in migraineurs was found in the Atherosclerosis Risk in Communities Study. [51] In this study of men and women 55 years of age and older, migraineurs had a relative risk of ischemic stroke of 1.84 (95% CI 0.89–3.82). The Stroke Prevention in Young Women Study found that women aged 15–49 with probable migraine with aura had an odds ratio of 1.5 (95% CI 1.1–2.0) for ischemic stroke. [52] Migraineurs with aura who smoked cigarettes and used oral contraceptives had a 7.0-fold increased odds of stroke (95% CI 1.3–22.8) as compared to migraineurs with aura who did not smoke and use oral contraceptives. Women without aura were not at increased stroke risk.

Kruit and colleagues performed a cross-sectional population study of Dutch adults 30 to 60 years of age to investigate the prevalence of stroke and white matter lesions in subjects with migraine. [53] None of the 295 migraineurs (161 with aura) or the 140 age and sex-matched controls reported symptoms of stroke. However, brain MRI evidence for stroke was found in 8.1% of those with migraine and 5.0% of controls, a non-significant difference. However, the adjusted odds ratio for cerebellar strokes in migraineurs as compared to non-migraine controls was 7.1 (95% CI 0.9–55, $p = 0.02$). Posterior circulation strokes were found in 0.7% of controls as compared to 5.4% of migraineurs. This risk was even higher for migraineurs with aura and for those with frequent migraine attacks. Migraineurs with aura with 1 or more migraine attacks per month had an adjusted odds ratio for ischemic stroke in the posterior circulation (cerebellum) of 15.8 (95% CI 1.8–140). Just over 10% (7 out of 69) of migraineurs with aura with at least 1 attack per month had MRI evidence for a posterior circulation stroke. Over 80% of strokes found in migraineurs were located in areas of the brain perfused by the posterior circulation. [54] Ninety percent of these were located in arterial watershed (border zone) areas of the cerebellum. Strokes were small and often times multiple.

The exact cause of the increased risk for symptomatic and asymptomatic stroke in the presence of migraine is not known. Embolism and hypoperfusion are hypothesized given the location and pattern of many of these strokes (cerebellar watershed distribution). Other possibilities relate to endothelial dysfunction, an increase in vascular risk factors among migraineurs, the increased prevalence of PFO, the use of migraine-specific medications, and a genetic link between migraine and ischemic stroke. [45–46]

Summary

Migraine is associated with cardiac and pulmonary right-to-left shunts as well as structural cardiac anomalies in the absence of shunt. Furthermore, migraine presence elevates the risk of cardiovascular disease and ischemic stroke. Further investigation is required to determine the nature and mechanisms of the migraine association with these conditions.

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Table 1

Migraine Prevalence According to Cardiac or Vascular Risk Factor.

	Migraine	No Aura	Aura
General Population	13%	9%	4%
PFO	20%–65%	3%–25%	13%–50%
ASD	29.3%–30%	10.7%–13%	17.4%–18.7%
Pulmonary AVM	38%–45.2%	7.3%–11.9%	30.6%–33.3%
MVP	27.8%	19.6%	8.3%
CHD	45.3%	9.1%	36.2%

PFO = patent foramen ovale; ASD = atrial septal defect; AVM = arteriovenous malformation; MVP = mitral valve prolapse; ASA = atrial septal aneurysm; CHD = congenital heart disease (without shunt).

Table 2

Prevalence of Cardiac or Vascular Condition According to Migraine Status.

	PFO	MVP	ASA
General Population	25%	2.4%⁵⁵	3.2%⁵⁶
Migraine	40%–70%	25%	13.3%
No Aura	16%–34%	25%	3.6%
Aura	41%–72%	25%–31%	28.5%

PFO = patent foramen ovale; MVP = mitral valve prolapse; ASA = atrial septal aneurysm.