

Prevalence of Migraine Headaches in Patients With Congenital Heart Disease

Tam Truong, MD, Leo Slavin, MD, Ramin Kashani, BA, James Higgins, MD, Aarti Puri, BS, Malika Chowdhry, BS, Philip Cheung, BS, Adam Tanious, BA, John S. Child, MD, FAHA, Joseph K. Perloff, MD, and Jonathan M. Tobis, MD*

The prevalence of migraine headaches (MH) is 12% in the general population and increases to 40% in patients with patent foramen ovale. This study evaluated the prevalence of MH in patients with congenital heart disease (CHD). Of 466 patients contacted from the UCLA Adult Congenital Heart Disease Center, 395 (85%) completed a questionnaire to determine the prevalence of MH. Patients were stratified by diagnosis of right-to-left, left-to-right, or no shunt. A group of 252 sex-matched patients with acquired cardiovascular disease served as controls. The prevalence of MH was 45% in adults with CHD compared to 11% in the controls ($p < 0.001$). Of the 179 patients with MH, 143 (80%) had migraines with aura and 36 (20%) had migraines without aura versus 36% and 64% observed in the controls ($p < 0.001$). The frequency of MH was 52% in the right-to-left shunt group, 44% in the left-to-right, and 38% in the no shunt group ($p = \text{NS}$). In patients with a right-to-left shunt who underwent surgical repair, 47% had complete resolution of MH, whereas 76% experienced $>50\%$ reduction in headache days per month. In conclusion, the prevalence of MH in all groups of adults with CHD is 3 to 4 times more than a sex-matched control population, with increasing prevalence of MH in patients with no shunt, left-to-right, and right-to-left shunt. The higher than expected frequency of MH in patients with CHD without an intracardiac shunt, suggests additional mechanisms to explain the significant association with MH. © 2008 Elsevier Inc. All rights reserved. (Am J Cardiol 2008;101:396–400)

Migraine headache (MH) is a chronic, disabling condition that despite advances in medical therapy continues to be a common cause of morbidity. Migraine affects approximately 12% of the population (18% women, 6% men).¹ The economic burden, which includes the cost of labor lost due to disability approaches \$6 billion annually.² There have been several observational studies that described a relationship between MH and patent foramen ovale (PFO). Retrospective data suggest that the prevalence of MH in patients with PFO approaches 40%.^{3–7} Adults with congenital heart disease (CHD) provide an excellent model to further assess the role of paradoxical shunting in the pathogenesis of MH. If the presence of a PFO is causally related to MH due to an intermittent right-to-left shunt, then adults with CHD and an intracardiac shunt would be expected to have a higher than average prevalence of MH. This retrospective analysis describes the prevalence of MH in a large cohort of patients with CHD, and the effect of surgical repair of an intracardiac shunt on MH.

Methods

Patient population: From April 2006 to April 2007, 466 patients from the Ahmanson UCLA Adult Congenital Heart Disease Center were contacted by telephone to participate in

a study to evaluate the prevalence of MH in adults with CHD. The patients who were available by telephone represented 1/4 of the 2,000 patients who have been seen at the UCLA Adult Congenital Heart Disease Clinic during the past 15 years. Patients were unavailable because of inaccurate contact information in the database, death, or lost to follow-up with the clinic. Of the 466 patients, 395 (85%) completed the questionnaire that evaluated for the presence of migraine. Fifty-five patients declined to participate, and 18 were excluded. Exclusion criteria were a primary diagnosis of PFO, mitral valve prolapse, or hypertrophic cardiomyopathy. Medical records including history, surgical reports, imaging, and echocardiography data were reviewed to determine the underlying lesions comprising the diagnosis of CHD. This diagnosis was confirmed with the patient. The primary diagnosis was used to stratify the cohort into groups consisting of a right-to-left shunt, left-to-right shunt, or conditions where no shunt existed. Table 1 shows the diagnoses used to stratify patients to their specific group.

A group of 252 patients without CHD who underwent cardiac catheterization at UCLA Adult Cardiac Catheterization Laboratory from October 2005 to January 2006 served as the control. This population included patients with coronary artery disease, acquired valvular heart disease, and patients who underwent heart transplantation for cardiomyopathy. Patients were chosen to obtain an equal proportion of men-to-women to match the gender distribution in the patients with CHD who responded to the questionnaire. Patients with CHD were excluded from the control group.

Department of Medicine, Division of Cardiology, David Geffen School of Medicine at UCLA, Los Angeles, California. Manuscript received July 26, 2007; revised manuscript received and accepted August 9, 2007.

*Corresponding author: Tel: 310-825-7129; fax: 310-794-2116.

E-mail address: jtobis@mednet.ucla.edu (J.M. Tobis).

Table 1
Clinical characteristics of patients with congenital heart disease and controls

Variable	CHD (n = 395)	Right-to-Left Shunt (n = 147)	Left-to-Right Shunt (n = 118)	No Shunt (n = 130)	Controls (n = 252)
Mean age (yrs)	45.2 ± 14.1	42.2 ± 13.8	47.9 ± 14.9	46.2 ± 12.9	64.1 ± 13
Women	209 (52.9%)	82 (55.8%)	72 (61.5%)	55 (42%)	126 (50%)
Diagnosis		TOF, 53 (36.3%) PS*, 25 (17.1%) PA, 17 (11.6%) TA, 13 (8.9%) dTGA, 7 (4.8%) SV, 5 (3.4%) TA [†] , 4 (2.7%) Other, 22 (15%)	ASD, 66 (55.9%) VSD, 31 (28.8%) PDA, 5 (4.2%) Other, 16 (13.6%)	BAV, 50 (38.5%) COA, 5 (11.5%) PS, 12 (9.2%) DAR, 10 (7.7%) ccTGA, 9 (6.9%) Ebstein, 3 (2.3%) Other, 31 (23.8%)	

ASD = atrial septal defect; BAV = bicuspid aortic valve; ccTGA = congenitally corrected transposition of the great arteries; COA = coarctation of aorta; DAR = dilated aortic root; dTGA = dextro-looped transposition of the great arteries; PA = pulmonary atresia; PDA = patent ductus arteriosus; PS = pulmonic stenosis; PS* = pulmonic stenosis with ADS or VSD; SV = single ventricle; TA = tricuspid atresia; TA[†] = truncus arteriosus; TOF = Tetralogy of Fallot; VSD = ventricular septal defect.

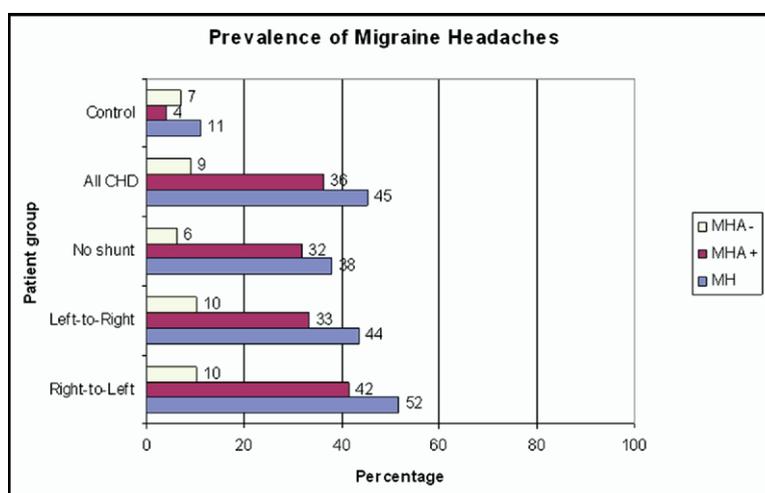


Figure 1. The prevalence of migraines divided into various patient groups. The patients with CHD are divided based on the presence and direction of intracardiac shunt. The control (n = 252) group represents patients without CHD evaluated in the adult cardiac catheterization laboratory. The frequency of the different types of migraine (MHA⁺, MHA⁻) is described as percent of the total population in that group. Values were rounded up to the nearest digit. MHA⁺ = migraine with aura; MHA⁻ = migraine without aura.

Migraine data: After informed consent was obtained, patients were asked by telephone survey regarding a history of MH using a self-report questionnaire. The questionnaire assessed for the presence of MH before and after surgical intervention. Items A and B of the previously validated Migraine Disability Assessment (MIDAS) questionnaire were included to determine the severity and frequency of migraines to assess functional limitation.⁸⁻¹¹ The history of CHD and any surgical procedure to repair or correct the lesion was also clarified. Patients who were unable to recall any medical history before surgery or simply were too young at the time of surgery to remember were excluded from the analysis on the effect of surgical repair on MH. The frequency of complete resolution of migraines or any reduction or increase in symptoms was recorded. A significant improvement in migraines was defined as >50% reduction in the number of headache days per month.⁷

Statistical analyses: Continuous data are presented as mean ± SD. The 2-tailed Student's *t* test was used to

determine the equivalence of the means for continuous variables. The chi-square test was used to analyze the equivalence for ordinal variables. Analysis was conducted using SPSS version 11.5 (SPSS, Inc., Chicago, Illinois). A *p* value <0.05 was considered significant.

Results

Patient population: Of the 466 patients contacted, 395 (85%) completed the questionnaire evaluating the presence of MH, as well as the frequency and severity of headaches. The average age of the entire cohort was 45.2 ± 14.1 years, with 209 women (53%). The cohort included 147 patients (37%) with right-to-left shunt, 118 (30%) with left-to-right shunt, and 130 (33%) with no shunt. Table 1 shows the breakdown of specific etiologies of the respective groups.

The prevalence of MH in the entire CHD cohort is shown in Figure 1. Of the 395 adults with CHD, 179 (45%) reported MH, with 143 (80%) with aura, and 36 (20%) migraines without aura. In the group with right-to-left shunt,

Table 2
The effect of surgical repair on migraine headaches in patients with intracardiac shunt

CHD with Shunt	Surgical Repair
Any improvement after surgery*	
CHD with shunt	29/44 (65.9%)
Right-to-left shunt	16/21 (76.2%)
Left-to-right shunt	13/23 (56.5%)
Complete resolution after surgery	
CHD with shunt	18/44 (40.9%)
Right-to-left shunt	10/21 (47.6%)
Left-to-right shunt	8/23 (34.8%)
Improvement, but no resolution*	
CHD with shunt	11/44 (25.0%)
Right-to-left shunt	6/21 (28.6%)
Left-to-right shunt	5/23 (21.7%)

* Improvement is defined as >50% reduction in the number of headache days in a 1-month period.

there were 76 patients (52%) that had MH, 61 (80%) had aura, and 15 (20%) denied aura. There were 51 patients (44%) who reported MH in the left-to-right group, 39 (76%) with aura and 12 (24%) without aura. In patients without an intracardiac shunt there were 49 patients (38%) with MH, 41 (83%) reporting migraines with aura, and 8 (16%) reported migraines without aura. Patients without intracardiac shunt were further divided to determine the frequency of MH in specific diseases. The prevalence of MH in patients with bicuspid aortic valve (n = 50) was 38% (84% migraines with aura, 16% migraines without aura). Four of 15 patients (27%) with coarctation of aorta, 2 of 10 (20%) with dilated aortic root, 1 of 12 (8%) with pulmonic stenosis, and 6 of 9 (67%) with congenitally corrected transposition of the great arteries reported MH. Patients in the no shunt group with diseases involving the aorta (bicuspid valve, coarctation of aorta, dilated aortic root, aortic stenosis) reported a frequency of MH of 37% (80% aura, 20% without aura). There was no significant difference in the prevalence of MH in the right-to-left, left-to-right, or no shunt groups (p = NS).

Patients evaluated at UCLA Adult Cardiac Catheterization Laboratory functioned as controls. The average age of the controls was 64.1 ± 12.9 years with 126 women (50%). Of the 252 in the control cohort, 28 (11%) had MH, with 10 (36%) reporting migraine with aura and 18 (64%) without aura (Figure 1). There was a significant increase in the prevalence of MH comparing patients with CHD (45%) versus the controls (11%) (p < 0.001).

Effect of surgical repair: A group of 44 patients consisting of either right-to-left (n = 21) or left-to-right (n = 23) shunts, who were old enough to recall a history of MH before surgery, were evaluated for the efficacy of surgical repair in the reduction of the prevalence, frequency, and severity of MH. Of the 44 patients with CHD and a history of MH, 29 (66%) demonstrated either complete resolution or significant improvement in MH (Table 2). In patients with right-to-left shunt, 16 (76%) reported complete resolution or significant improvement in their MH after surgical repair. Of the 23 patients analyzed with left-to-right shunt, 13 (56%) reported complete resolution or improvement in

MH after surgical repair. Although there was a trend toward greater benefit in patients with right-to-left shunt, it did not reach statistical significance (p = 0.2). The effect of surgical repair was not evaluated in patients without intracardiac shunt. The average number of headache days per month was significantly reduced in patients with CHD after surgical repair, from 4.6 to 2.0 (p = 0.008). There was a significant decrease in the severity of MH, from 5.9 to 3.8 (on a scale ranging from 1 to 10, p = 0.003) (Table 3). In patients with right-to-left shunt, the frequency of MH days decreased from 5.2 to 2.7 (p = 0.09) and severity from 5.2 to 3.3 (p = 0.07). Patients with left-to-right shunt showed a reduction in the frequency of headache days from 4.1 to 1.5 (p = 0.05) and a decrease in the severity from 6.5 to 4.3 (p = 0.02).

Discussion

This retrospective study evaluated 395 adults with CHD with a simple questionnaire to determine the prevalence of MH. The prevalence of MH in adults with CHD was four-fold higher than the gender-matched controls (45% vs 11%, p < 0.001). The distribution of type of MH also differed between the 2 groups. In the CHD cohort, there was a 4 times greater frequency of migraines with aura in comparison to migraines without aura. In contrast, in the control group, the rate of migraines without aura was 2 times that of migraines with aura, which matches the distribution of MH type in the general population. The increased prevalence may be partially explained by a placebo effect observed in retrospective surveys. However, the data collection were conducted in a similar manner in all groups. The data for patients with CHD are similar to that reported in the PFO literature, where the incidence of MH also approaches 40% with a similar distribution pattern of aura to migraines without aura.^{12,13}

In assessing the role of intracardiac shunt in the pathogenesis of MH in adults with CHD, patients were divided into right-to-left, left-to-right, and no shunt groups. Although the prevalence was much higher than the control population for all 3 groups, there was no significant difference in the prevalence of MH among the groups with right-to-left (52%), left-to-right (44%), and no intracardiac shunt (40%) (p = 0.12). The rates of migraines with aura were 3 to 4 times more than the rate of migraines without aura. An increased prevalence of MH in the no intracardiac shunt group may be due to an underlying PFO not previously diagnosed. Only a few patients in this group had documented transesophageal echocardiogram with bubble study.

Two recent studies from Sweden and Belgium are consistent with the findings of this study of increased prevalence of MH in patients with CHD.^{14,15} In the first study, 46 patients with Marfan's syndrome had a telephone interview by a headache specialist.¹⁴ The study reported a prevalence of MH of 63% with an equal gender ratio. Interestingly, the frequency of migraines with aura was 3 times higher than migraines without aura in men, but equivalent in women.¹⁴ The investigators hypothesized that the increased risk of MH in patients with Marfan's syndrome was associated with an increased rate of dural ectasia.¹⁴ Another study investigated the prevalence of MH with a survey conducted

Table 3
Frequency and severity of migraines in patients with shunting who underwent surgical repair

Variable	Migraine Frequency (days/month)			Migraine Severity Scale (1–10)		
	Before	After	p Value	Before	After	p Value
Any shunt	4.6 ± 7.9	2.0 ± 4.6	0.008	5.9 ± 3.1	3.8 ± 3.4	0.003
Right-to-left	5.2 ± 9.2	2.7 ± 6.7	0.09	5.2 ± 3.2	3.3 ± 3.3	0.07
Left-to-right	4.1 ± 7.0	1.5 ± 2.0	0.05	6.5 ± 3.0	4.3 ± 3.5	0.02

by a neurologist in patients with CHD, and in particular comparing patients with and without right-to-left shunt.¹⁵ Forty patients with right-to-left shunt were compared to age- and gender-matched patients with CHD without intracardiac shunt, and patients evaluated from a general practice.¹⁵ The 1-year incidence of MH in patients with right-to-left shunt was 65% (61% migraines with aura, 39% migraines without aura) and 52.5% (62% migraines with aura, 38% migraines without aura) in the CHD group, excluding right-to-left shunt.¹⁵ However, the incidence of MH in the controls from a general practice was 40% (13% migraines with aura, 87% migraines without aura), which far exceeds the prevalence of MH in the general population described in the literature. This small study is consistent with our findings of the increased prevalence of MH in patients with CHD. In addition, it supports the conclusion that the pathogenesis of MH may not solely involve intracardiac shunting.

The effect of surgical repair of intracardiac shunt and the resolution of MH was also investigated. Of the 44 patients with CHD who recalled having MH before surgical correction, 18 (41%) reported complete resolution of their migraines, and 29 (66%) reported a significant improvement, defined as a >50% reduction in the frequency of headache days per month. In patients with right-to-left shunt (n = 21), 48% described complete resolution, and 76% observed a significant improvement. Patients with left-to-right shunt (n = 23) reported 35% complete resolution, and 57% reported significant improvement. There was no significant difference in the prevalence of complete resolution or improvement between the 2 groups (p = NS). Of the patients with improvement, there was a significant decrease in the frequency of headache days and severity. There is no previous data that investigated the effect of surgical shunt repair on MH in patients with CHD. However, there are 6 published trials that evaluated the effect of percutaneous transcatheter PFO closure in patients with cryptogenic stroke and MH.^{7,16–20} A total of 215 patients with MH before PFO closure were followed for a mean of 6 to 30 months.^{7,16–20} Postprocedure, there was complete resolution of MH in 59% of patients, and an additional 20% reported a >50% reduction in the number of headache days.^{7,16–20} Of the total 215 patients, 169 (79%) reported either complete resolution or significant improvement in their symptoms.^{7,16–20} Therefore, the effect of shunt closure appears to be similar in patients with PFO compared to CHD adults with right-to-left shunt.

The increased prevalence of migraine headache in the patients with left-to-right shunt and the even greater rate of migraine headaches in patients with right-to-left shunts are consistent with the observations in patients with PFO. What

is unusual about the current study is the high prevalence of MH in adults with CHD who did not manifest any intracardiac or peripheral shunt. The improvement in MH in the adults with CHD who underwent surgical repair is also consistent with the observations of percutaneous closure of PFO. The anomaly in this observational study is the high prevalence of MH in adults with CHD who do not have any intracardiac or peripheral shunt. This appears to be predominantly associated with congenital abnormalities of the aorta.

This study was a retrospective analysis and therefore subject to recall bias. The history of MH was elicited using a telephone survey. Patients were not evaluated by a neurologist to confirm a diagnosis previously given. However, standard criteria of MH according to the International Society of Headaches were used to question the patients.²¹ The sample size of patients evaluated to determine the effect of surgical repair was significantly smaller because the majority of the patients could not recall or were too young to remember whether they suffered from MH before surgery.

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