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PEDIATRIC AND CONGENITAL HEART DISEASE

Interventional Rounds

Incidence of Patent Foramen Ovale and Migraine Headache in Adults with Congenital Heart Disease with No Known Cardiac Shunts

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The purpose of this study was to understand why patients with adult congenital heart disease (CHD) but no obvious shunt have an increased frequency of migraine headaches (MH). CHD patients with no known cardiac shunts (CHD-NKS), based on their echocardiographic or angiographic procedures, were tested for a right-to-left shunt using agitated saline contrast transcranial Doppler (TCD). Medical records of 2,920 patients from the UCLA Adult CHD Center were screened to participate in a study to evaluate the prevalence of MH in adults with CHD; 182 patients (6.23%) had CHD-NKS; of these, 60 (30%) underwent a TCD; 23 (38%) tested positive and 37 (62%) tested negative for a right-to-left shunt ($P = 0.01$ compared with controls). The frequency of MH was 43% in CHD-NKS compared with 11% in controls ($P < 0.0001$). TCD demonstrated right-to-left shunting in approximately 2/3 of patients with pulmonary stenosis, the Marfan syndrome and congenitally corrected transposition of great vessels, 1/4 of patients with bicuspid aortic valve, 1/5 of patients with mitral valve prolapse and all patients with Ebstein's anomaly. Approximately half of these experienced MH. Patients who had MH did not show a higher frequency of right-to-left shunt when compared with patients without MH ($P = 0.57$). In conclusion, CHD patients with conditions usually not associated with a shunt have a higher than expected prevalence of PFO which permits intermittent right-to-left shunting undetected by standard non-contrast TTE and TEE; the increased prevalence of right-to-left shunting may partially explain the higher than expected frequency of migraines. © 2012 Wiley Periodicals, Inc.

Key words: congenital heart disease; migraine; patent foramen ovale; right-to-left shunt

BACKGROUND

There is an association between right-to-left shunting, usually through a patent foramen ovale (PFO) or pulmonary arterio-venous fistula, and migraine head-

ache with aura [1–3]. Migraine headache, a chronic disabling condition, affects 12% of the general population (18% women and 6% men) [4]. Studies indicate a strong correlation between migraine associated with aura and the presence of PFO; the frequency of PFO is

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TABLE I. Congenital Heart Diseases Not Known to Be Associated with a Cardiac Shunt

| Condition | Abbreviation |
|--|--------------|
| Bicuspid aortic valve | BAV |
| Coarctation of the aorta | COA |
| Pulmonic stenosis | PS |
| Dilated aortic root | DAR |
| Congenitally corrected Transposition of the Great Arteries | ccTGA |
| Ebstein's anomaly | Ebstein |
| Marfan syndrome | Marfan |
| Aortic Stenosis | AS |
| Mitral valve prolapse | MVP |
| Redundant tricuspid valve | – |
| William's Syndrome | – |
| Congenital anomalous coronary artery | – |

3.5 times higher in patients with migraine with aura than in people without migraine headaches [5–9]. It is hypothesized that an intermittent right-to-left shunt through the PFO provides a conduit for bioactive substances to bypass the pulmonary circulation, where they would otherwise be metabolized, enter the cerebral circulation, and trigger receptors in the brain of susceptible individuals to induce a migraine headache [10]. If this concept is valid, then patients who have persistent or intermittent right-to-left shunts should have a higher frequency of migraine. This hypothesis was assessed by reviewing the history of 800 adult patients with a history of congenital heart disease (CHD) [11]. Patients with a congenital defect that produced a right-to-left shunt had the highest incidence of migraine headache (55%) while those with left-to-right shunts (which can intermittently shift right-to-left with straining) had a migraine incidence of 44%. Surprisingly, adults with CHD lesions not known to be associated with a shunt, such as bicuspid aortic valve, the Marfan syndrome, pulmonary stenosis, or aortic coarctation, also had a higher incidence of migraine (32%) as compared with 12% in a control population ($P < 0.0001$). The present study investigated the possible mechanisms behind the higher than expected rate of migraine headaches in this subset of CHD patients who usually do not exhibit evidence of a shunt by the standard echocardiographic or angiographic examination, or CHD patients with no known cardiac shunt (CHD-NKS).

METHODS

From April 2006 to December 2010, records of 2,920 patients from the Ahmanson UCLA Adult Congenital Heart Disease Center were screened to evaluate the prevalence of migraines in adults with CHD. Of these, 182 patients (6.23%) had a condition not known

TABLE II. Assessment of Patent Foramen Ovale Related Co-morbidities in the Patient Population

| PFO Related Conditions |
|---|
| Migraine Headache with or without aura |
| Stroke (cryptogenic/other) |
| High Altitude Sickness |
| Hereditary Hemorrhagic Telangiectasia/Epistaxis |
| Raynaud's Phenomenon |
| Mitral Valve Prolapse |
| Family History of Early Stroke/Heart Attack |
| Decompression Sickness |
| Sleep Apnea |
| Migraine Aura without Headache |
| Embolus (fat/air/pulmonary/none) |
| Hypercoagulability ^a |

^aHypercoagulability states include use of oral contraceptive pill/hormone replacement therapy, pregnancy, factor V Leiden, prothrombin G20210A mutation, antiphospholipid antibodies, homocysteinemia, protein S deficiency, protein C deficiency, elevated lipoprotein A, antithrombin III deficiency, antidiolipin AB, increased factor VIII levels, B2-glycoprotein-1 AB, and thrombocytosis.

to be associated with an intracardiac shunt, were living, and consented to being contacted. The congenital heart disease conditions not known to be associated with a shunt are listed in Table I.

Medical records including patient history, surgical reports, imaging, and echocardiographic data were reviewed to determine the underlying lesions comprising the diagnosis of CHD. This diagnosis was then confirmed with the patient.

Patients were invited to be screened for the presence of a right-to-left shunt by performing a transcranial Doppler (TCD) study with agitated saline using a power M-mode Terumo 150 PMD machine (Spencer Technologies, Seattle, Washington). The agitated saline consisted of a mixture of 8 cc normal saline, 0.5 cc of air, and 1 cc of blood agitated between two syringes connected by a three-way stopcock. This mixture was injected into the brachial vein and embolic tracks were counted over the middle cerebral arteries. The degree of right-to-left shunt was evaluated by TCD at rest and with the Valsalva maneuver at 40 mm Hg, as measured by a manometer [12]. The Spencer logarithmic scale was used to grade the results—grade 3 and higher (≥ 31 embolic tracks/60 sec) was considered to be positive for a significant shunt [13].

During the setup of the procedure, patients were briefly asked about whether they had experienced conditions that have been known to be associated with a right-to-left shunt (Table II). The assessment of the frequency of migraine headaches during a 90-day period was performed using the Migraine Disability Assessment (MIDAS) questionnaire.

The control group consisted of 252 patients without CHD who underwent cardiac catheterization at the

TABLE III. Comparison of Demographic Descriptors in the Study Group and the Control Population

| Variable | Study group (n = 60) | Controls (n = 252) | P value |
|---------------|-------------------------|-----------------------|---------|
| Mean age | 43.6 ± 14.7 | 64.1 ± 13 | 0.0001 |
| Female gender | 24 (40%) | 126 (50%) | ns |
| Diagnosis | | | |
| | AS 3 (5%) | — | — |
| | BAV 20 (33.3) | — | — |
| | COA 5 (8.3%) | — | — |
| | PS 6 (10%) | — | — |
| | MVP 5 (8.3%) | — | — |
| | Marfan 7 (11.7%) | — | — |
| | Ebstein 3 (5%) | — | — |
| | ccTGA 3 (5%) | — | — |
| | Combined 5 (8.3%) | — | — |
| | Other 3 (5%) | — | — |

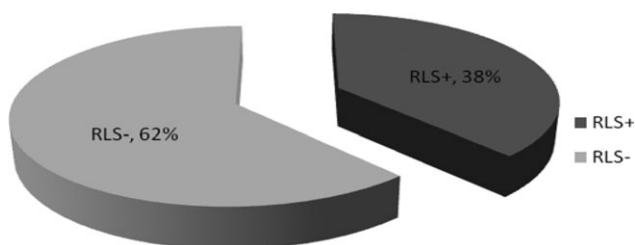


Fig. 1. Incidence of a right-to-left shunt by transcranial doppler in congenital heart disease patients with no known cardiac shunt.

UCLA Adult Cardiac Catheterization Laboratory from October 2005 to January 2006. This population included patients with coronary artery disease, acquired valvular heart disease, and patients who were being evaluated for heart transplantation due to cardiomyopathy. Patients with CHD were excluded from the control group.

Continuous data are presented as mean ± SD. The two-tailed Student's *t*-test was used to determine the equivalence of means for continuous variables. The chi-square test was used to analyze the equivalence for ordinal variables. The analysis was conducted using SPSS version 11.5 (SPSS, Inc., Chicago, Illinois). A *P* value of < 0.05 was considered statistically.

RESULTS

Of the 182 patients with CHD without a known shunt, 60 people (30%) agreed to have a TCD examination. The mean age in the patient cohort was 43.6 ± 14.7, and 40% were female (Table III).

Of the 60 patients with CHD-NKS prior who were tested with TCD, 23 (38%) tested positive and 37 (62%) tested negative for a right-to-left shunt (Fig. 1). This is significantly higher than the prevalence of right-to-left shunt in the control population (18%, *P* = 0.01).

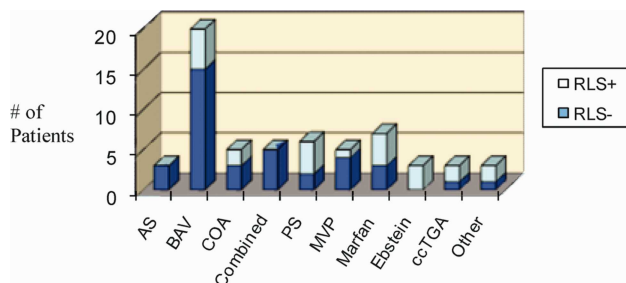


Fig. 2. Prevalence of a right-to-left shunt by transcranial doppler in congenital heart disease patients with no known cardiac shunt, categorized by anatomic abnormality. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

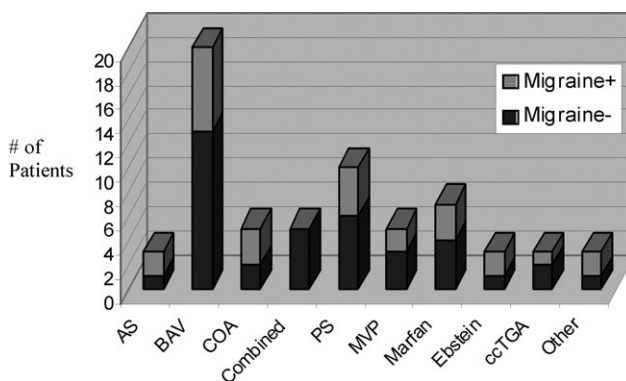


Fig. 3. Frequency of migraine headache, categorized by anatomic abnormality.

When the patients with CHD-NKS were categorized by anatomic abnormality (Fig. 2), 25% of BAV, 67% of PS, 40% of COA, 20% of MVP, 100% of Ebstein's, 57% of Marfan's, 67% of ccTGA, and 67% of other types of CHD-NKS had a right-to-left shunt when tested with agitated saline contrast TCD.

The frequency of migraine headaches in patients with CHD-NKS (Fig. 3) was 43% compared with 11% in controls (*P* < 0.0001); 50% of these patients experienced aura associated with the headache. The prevalence of migraine headache in this patient population, separated by cardiac abnormality, was 67% in BAV, 60% in COA, 40% in PS, 40% in MVP, 67% in Ebstein's, 43% in Marfan's, 33% in ccTGA, and 67% in patients with other types of CHD-NKS. The frequency of the migraine attacks in the study cohort varied widely, from one in a 30-day period to almost daily headache experienced by some of the patients. The mean number of migraine days per month was 8.2 ± 17.5. The majority of the patients (80%) were taking preventive medications and blood thinners in conjunction with episodic regimens used to abort migraine attacks. Very often these were originally prescribed for the management of the cardiac condition. The most frequent drug combination was that of beta-

TABLE IV. Distribution of Migraine Headache in Patients with and without a Positive Transcranial Doppler

| | Migraine+ | | Migraine- | | Total |
|-------|-----------|---------|-----------|---------|-------|
| | Aura | No Aura | Aura | No Aura | |
| TCD+ | 7 | 4 | 4 | 8 | 21 |
| TCD- | 6 | 9 | 4 | 18 | 37 |
| Total | 26 | | 34 | | |

$P = 0.57$ when comparing patients with migraines, who have a right-to-left shunt with those that do not.

blockers and angiotensin-converting enzyme inhibitors. Only one patient in our study completely abstained from medication use, including that of aspirin and over-the-counter anti-inflammatory regimens.

Roughly half of the female patient population in the study was prescribed estrogen-containing birth control or hormone replacement therapy. The effect of the hormonal preparations on the frequency of migraine attacks in these patients is unclear.

Of the 23 patients with CHD-NKS by echocardiography who were diagnosed with a right-to-left shunt by TCD, 11 (48%) had migraine headache. Patients who had migraine headaches did not show a significantly higher frequency of right-to-left shunt when compared with patients with no migraines ($P = 0.57$; Table IV).

Of the 11 patients who had migraine headache and also tested positive for a right-to-left shunt, two patients with Marfan syndrome subsequently had their PFO closed. PFO closure was indicated in these patients due to co-existing cryptogenic stroke. Transcatheter closure resulted in resolution of migraine symptoms in both patients.

DISCUSSION

Migraine headache is a chronic disabling condition that affects 12% of the general population (18% women and 6% men) [4]. Studies indicate a strong correlation between migraines with aura and the presence of a right-to-left shunt. The most common form of right-to-left shunt is due to a PFO, which occurs in approximately 20% of the population. The prevalence of PFO is 3.5 times higher in patients with migraine headache with aura (MHA) as compared to individuals without migraines [5–9].

Similar to PFO in its physiological aspects, pulmonary arterio-venous fistula, either isolated or associated with hereditary hemorrhagic telangiectasia, is the etiology of the shunt in about 1–2% of people with a right-to-left shunt; these people also have a high incidence of migraine [14].

It is hypothesized that a continuous or intermittent right-to-left shunt through a PFO or a pulmonary arterio-venous fistula provides a conduit for bioactive substances to bypass the pulmonary filter, enter the cerebral circulation, and induce a migraine headache in susceptible individuals [10]. This hypothesis is currently being tested in a multicenter prospective randomized trial, the PREMIUM Trial [15]. The natural closure of a PFO following birth is presumed to be mediated through genetic factors since PFOs tend to occur in families. In addition, at least one gene defect is associated with a high frequency of PFO, as seen with the Notch3 gene in the CADASIL syndrome [16,17]. Therefore it is not surprising that some congenital heart defects have a higher association with the presence of PFO and migraine.

In a previous study conducted by our group, the frequency of migraine headache was determined in adult patients with congenital heart disease with and without apparent shunting by echocardiography. The results of this analysis revealed [11]:

1. A control population had a migraine frequency of 11% (36% with aura).
2. In patients with right-to-left shunts, the frequency of migraines was 52% (80% with aura) ($P < 0.001$ compared with controls).
3. In patients with left-to-right shunts, the frequency of migraines was 44% (76% with aura) ($P < 0.001$ compared with controls).
4. In patients with a diagnosis of CHD-NKS the frequency of migraines was 38% (83% with aura), which was still significantly higher than in the control population ($P < 0.001$).

The objective of the present study was to understand why patients with congenital heart disease but no obvious shunt on standard non-contrast transthoracic or transesophageal echocardiography studies have a higher frequency of migraine headache than a control population. The hypothesis was that a number of these patients actually have a PFO but had never been screened specifically for it with agitated saline contrast studies, despite the vigorous testing they have undergone throughout the course of their disease. TCD was chosen because it is a sensitive noninvasive method of assessing patients for a right-to-left shunt. The vast majority of people with a positive TCD for right-to-left shunt (\geq grade 3) will have a PFO, although a pulmonary shunt cannot be ruled out. This study shows that despite previous vigorous testing, 38% of patients with CHD-NKS were found to have a right-to-left shunt as demonstrated by an agitated saline bubble study on a TCD. This is most likely mediated through a PFO that remains undiagnosed by traditional

echocardiographic tests, which do not specifically look for a PFO using a contrast solution such as agitated saline. These patients also had a high prevalence of migraine with aura which is more closely associated with right to left shunting than is migraine without aura. One limitation of this study is its small sample size. However, this data was generated from one of the largest available populations of adults with CHD.

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