

Prevalence of patent foramen ovale in patients with migraine

Aslı Demirtaş Tatlıdede*, Buket Oflazoğlu*,
Seden Erten Çelik**, Ülker Anadolu*, Hulki Forta*

ÖZET

Migrenli hastalarda patent foramen ovale sıklığı

Patent foremen ovale (PFO), normal kişilerin % 20-30'unda görülebilen fetal rezidual sirkülasyondur. Bu kişilerde sağ atrial basınç artarak sağ-sol şant meydana gelmektedir. PFO'nun migrenli hastalarda görülme sıklığının arttığına dair çalışmalar vardır. Bu artış özellikle auralı migrende daha belirgindir. Biz 53 migrenli hastada intra-atrial sağ-sol şant varlığını araştırdık ve 27 kişilik kontrol grubu ile karşılaştırdık. Transtorasik ekokardiyografi ile, IV kontrast madde vererek istirahatde ve valsalva manevrasından sonra sağ-sol şant varlığı bakıldı. Patent foramen ovale migrenli grupta daha fazla görülmekte idi ($p<.01$). Auralı migrenli grupta % 66.7, aurasız migrenli grupta % 47.4, kontrol grubunda ise % 22.2 oranında idi. Sonuçlarımız PFO sıklığının özellikle auralı migrenli grupta arttığını desteklemekte idi.

Anahtar kelimeler: Migren, Ekokardiyografi, Patent foramen ovale

SUMMARY

Recent evidence supports that the prevalence of patent foramen ovale is higher in patients with migraine with aura. We conducted a case-control study and searched for intra-atrial right to left shunt in 53 patients with migraine. PFO was detected by means of transthoracic echocardiography with administration of contrast medium during valsalva maneuver and the results were compared with age and sex matched 27 healthy controls. Patent foramen ovale was more frequent in the migraine group ($p<.01$). The percentages of PFO in migraine patients with aura, without aura and the control group were 66.7%, 47.4% and 22.2%, respectively. Our results are supportive of an association between PFO and migraine, especially with aura.

Key words: Migraine, Echocardiography, Patent foremen ovale

(*) Şişli Etfal Hastanesi, Nöroloji Kliniği

(**) Şiyami Ersek Kalp ve Damar Cerrahisi Hastanesi, Kardiyoloji Kliniği

Başvuru adresi:

Uzm. Dr. Buket Oflazoğlu, Caferağa mah. Sokollu sok. Çakıroğlu apt. No:30 Daire:7 Kadıköy, İstanbul
Tel: (0 216) 449 31 52 e-posta: g.b.oflazoglu@superonline.com

(*) Şişli Etfal Training and Research Hospital, Neurology Clinic

(**) Şiyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Cardiology Clinic

Correspondence to:

Buket Oflazoğlu, MD, Caferağa mahallesi, Sokollu sokak, Çakıroğlu apt. No: 30 Daire: 7 Kadıköy, İstanbul, TURKEY
Tel: (+90 216) 449 31 52 e-mail: g.b.oflazoglu@superonline.com

Introduction

Migraine is a common neurological disorder that affects up to 18% of the general population (Launer et al. 1999) and exerts a considerable impact on quality of life primarily by personal grief, decreased productivity and significant health care expenses. The disease aetiology is complex, and involves multiple interacting genetic and environmental determinants.

Recent studies indicated that the prevalence of patent foramen ovale, atrial septal aneurysm and mitral valve prolapse are higher in patients with migraine. Even if such cardiac anomalies are not detected, migraine itself is a significant factor for stroke. The relationship between migraine and stroke is stronger in patients suffering from migraine with aura compared to those with migraine without aura (Giardini et al. 2006, Carol-Artal et al. 2006, Ferrarini et al. 2005, Schwerzmann et al. 2005, Boogousslavsky et al. 1988).

PFO is a residual foetal circulation that can be detected in 20-30% of normal adults. In these subjects, when the right atrial pressure exceeds the left atrial pressure, a right-to-left shunt occurs (Ferrarini et al. 2005). PFO is a well-known risk factor for ischemic stroke in young patients, while its role as an independent factor in migraine is still pondered (Carol-Artal et al. 2006). Right-to-left shunt by way of the PFO might allow trigger substances of migraine in the venous circulation to bypass the pulmonary filter and reach the systemic circulation in amounts large enough to induce a migraine attack (Wilmshurst et al. 2001).

There is evidence that the rate of PFO is especially higher in migraine patients with aura (Schwerzmann et al. 2005). A diagnosis of PFO can be demonstrated via transthoracic echocardiography (TTE), transcranial doppler ultrasound (TCD) or with transoesophageal echocardiography (TEE); following an i.v. injection of contrast medium detection of a right to left shunt, at rest or during Valsalva maneuver, defines the presence of PFO.

The aim of this study is to evaluate the prevalence of PFO in migraine patients with or without aura and compare the results with the healthy age-matched control group using transthoracic echocardiography with concomitant injection of contrast medium.

Methods

Participants: A total of 53 patients who were evaluated by the headache outpatient clinic of Sisli Etfal Hospital between 2004 and 2006 were included in the study. International Headache Society (ICHD-II) criteria (Int. H. Soc 2004) were used to make the diagnosis of migraine with aura (MA) or without aura (MO) and patients with any history of cardiac or cerebrovascular disease were excluded. The control group consisted of 27 non-migrainous healthy individuals of similar age and sex distribution.

Both patients and controls underwent a full neurological examination and were interviewed for information on current cigarette smoking and the use of oral contraceptives. In migraine patients severity, duration and the average frequency of headache attacks were recorded. visual, sensory, or motor aura-related symptoms were questioned in detail. Patients with MA, MO and the control group were investigated for signs of right to left shunt by an echocardiographic examination.

Echocardiographic examination: Transthoracic echocardiography recordings were obtained from parasternal, apical, and subcostal windows by using GE-Vingmed System V and Vivid 7 ultrasound systems equipped with 1.5-3.7 MHz broadband electronic transducers. Conventional M-mode, two-dimensional, pulsed wave and colour Doppler images were acquired with simultaneous ECG tracings. Left ventricular systolic and diastolic dimensions and wall thickness were measured from the M-mode traces according to the recommendations of the American Society of Echocardiography (Schiller et al. 1989). Left ventricular mass was calculated by Devereux formula and Teichholz formula was used to calculate left ventricular ejection fraction (Devereux et al. 1977). Transmitral inflow velocities were recorded at the level of mitral leaflet tips. The early-(E) and late-diastolic velocities(A), deceleration time of E were also measured with previously described methods (Oh et al. 1997). The off-line analysis of all echocardiographic variables was made by using the Echopac program (ver.6.2) within the echocardiography equipment. Presence of PFO was defined by a right to left shunt at rest or after a Valsalva procedure after a i.v. injection of contrast medium, solution of mixed saline 9 ml plus air 1 ml. PFO size was classified into 2 groups: 1.Small or medium sized, according to single or confluent spikes recorded after Valsalva strain and 2. Large, if bubbles could be detected during nor-

Table 1: Echocardiography results in the two groups.

Group	Values	ECHOCARDIOGRAPHY		Total	X ²	Sd	P
		PFO+	PFO -				
Patient	N	28	25	53	6,857	1	.009
	% Within the Group	52.8	47.2	100.0			
Control	N	6	21	27			
	% Within the Group	22.2	77.8	100,0			

mal breathing. This grading is roughly related to PFO size, reflecting a progressively larger amount of shunted blood (Anzola et al. 1999). To avoid any possible bias toward a positive finding, the Doppler operator was blinded to the diagnosis.

Statistical analysis: We compared the data using Mann Whitney-U two-sample statistics. Univariate statistical analyses were performed with Pearson X2 test. A value of $p < 0.05$ was considered to be statistically significant.

Results

Fifty-three patients and 27 healthy control subjects were included in the study. Female gender was predominant in both groups, patient and control group were comprised of 46 (%86.8) and 22 female subjects (%81.5), respectively. The age range varied between 16-70 (35.5 ± 11.3) for the patients and 19-70 (42.3 ± 15.8) for the control groups. There was no statistical difference between the two groups with respect to age distribution ($z = -1.583$; $p > .05$).

At the time of first admission, the duration of migraine ranged from 1.5 months and 45 years whereas the frequency of migraine attacks varied between everyday to 1-2 times a month. The rates for tobacco and oral contraceptive use were 21.1% and 24.2% respectively. Fifteen patients reported an aura preceding the migraine attack

while in the remaining 38 patients migraine was not accompanied by an aura.

A right to left shunt was detected in 28 patients (52.8%). PFO was small or medium sized in 26 patients and in the remaining two, large and permanent PFO was demonstrated. In the control group, PFO was identified in only 6 of the 27 individuals (22.2%) and none of them was considered large. The prevalence of PFO in the overall patient group was significantly higher than in the control group ($z = 6.857$; $p < .01$) (Table 1). While PFO was identified in 10 of the 15 patients with MA (66.7%), it was present in 18 out of 38 subjects with MO (47.4%). Both groups revealed considerably higher percentage of PFO compared to the control group and even though the percentage of PFO was higher in MA group, the difference between the MA and MO groups was not proven to be statistically significant ($p > 0.5$) (Table 2). No association was found between the presence of a PFO and smoking or oral contraceptive use in MA patients.

Discussion

Recent studies indicate that the rate of PFO is higher in people with migraine, especially in migraine patients with aura. In these studies over the last decade, transcranial doppler ultrasound (TCD), transthoracic echocardiography (TTE) and transoesophageal echocardiography (TEE) have all

Table 2: Comparison of patients with and without aura (WITH: with aura, WITHOUT: without aura).

Groups	Values	AURA		Total	X ²	Sd	P
		WITH	WITHOUT				
ECHO PFO PRESENT	N	10	18	28	1.607	1	.205
	% Within A	66.7	47.4	52.8			

been used to detect PFO (Schwedt et al. 2006). Del Sette and colleagues conducted a TCD study in 44 migraine patients with aura and 41 % of the patients were shown to have a right to left shunt (Del Sette et al. 1998). In another TCD study by Anzola et al., this rate was found to be 48 % in the same group of patients (Anzola et al. 1999). On the other hand, Schwerzmann et al. reported the rate of PFO as 47 % in migraine patients with aura using TTE and the shunt diameter was distinguished to be larger in the migraine group than in the control group (Schwerzmann et al. 2005).

For the opposite, prevalence of migraine has also been searched in subjects with PFO. Wilmshurst and colleagues retrospectively assessed patients with decompression sickness who underwent TEE and concluded that the prevalence of migraine with aura was higher in patients with right to left shunt, especially in those with a large diameter (Wilmshurst et al. 2001).

Furthermore, setting out from this probable causal relationship, effects of PFO closure on migraine has been widely investigated by independent investigators (Schwedt et al. 2006). Significant reduction of migraine attacks after PFO closure has led to theories about the pathogenesis of migraine. Paradoxal microemboli to the basovertebral arteries, vasoactive substances (like atrial natriuretic peptide), platelet factors and amines' bypassing of the pulmonary filter via the intracardiac shunt have all been suspected to trigger migraine (Beda et al. 2005, Bousser 2006).

Our results support the assumption of an association between PFO and migraine. We demonstrated the PFO rate to be significantly higher in the migraine patients compared with healthy controls. Although this rate was far higher in migraine patients with aura, its comparison with the common migraine group was not of statistical significance. This result may be due to our inadequate number of patients with aura. A relationship between PFO and migraine, especially MA, seems to exist and prospective randomized controlled studies targeting larger populations are required.

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