Abstract

Introduction: Migraine is one of the most common headaches, and is one of the most common disabling medical conditions worldwide. Migraine has two types, with aura and without aura. Nearly 15% of migraines are with aura, and the most common aura is visual. Patent Foramen Ovale (PFO) is the most common defect in atrial septum of heart, and prevalence rate population is 25%. Lately PFO has been recognized to be a risk factor for migraine with aura.

Methods and materials: This study is cross sectional and has been done on 50 patients of migraine with aura, and 25 normal people (without migraine) as control group. We used saline agitated test by Doppler sonograph for recognizing PFO.

Results: The rate of PFO in patients’ group was 44% and in control group was 20%. The rate of PFO is more in patients with rate of headaches more than 3 times in a month.

Conclusion: migraine with aura has relation with PFO, especially for patients with frequent attacks more than 3 times per months. The closure of PFO in these patients need to be studied more, especially that there are feasible procedures available now.

Keywords: migraine, migraine with aura, PFO, patent foramen oval, saline agitated test.
Introduction
Of all the painful states that afflict humans, headache is undoubtedly the most frequent and rivals backache as the most common reason for seeking medical help.\(^{(1)}\)
The lifetime prevalence for any type of headache as estimated from population-based studies is more than 90% for male and 95% for female. Migraine is one of the most common headaches. Prevalence rate for migraine in USA is 6.5% for male and 18.2% for female, and can begin at any age, but most common in adolescence. Migraine is one of the most common disabling medical conditions worldwide. Migraine is classified into two general groups (by International Headache Society) with aura and without aura, and other types or subtypes that are not frequent. Nearly 15% of migraines are with aura, and the most common aura is visual.\(^{(2)}\)

In a study done in Iran, the prevalence rate is 7% for male, and 14.2% for female.\(^{(3)}\)
Patent foramen ovale (PFO) is the most common defect in atrial septum of heart, and prevalence rate population is 25%.\(^{(2)}\) This defect often has no clinical signs or symptoms, and remains undiagnosed. But it is recognized as a factor of right to left shunt in heart.\(^{(4)}\)

Lately PFO has been shown to be a factor for producing migraine with aura and stroke in young adults, it’s considered, probably with non-ischemic mechanisms of migraine.\(^{(5)}\)
However, there is currently insufficient evidence to support a causal link between PFO and migraine.\(^{(6)}\) PFO can be diagnosed by transesophageal echocardiogram which is an invasive procedure. Another method that can be use for PFO diagnosis is agitated saline test which is an easy and non invasive procedure. This method is easily tolerated by patients and needs Doppler ultrasonography to detect echogenous bubble of air. This test has 94% sensitivity and 97% specificity.\(^{(7)}\) In an evaluation done, the rate of PFO in migraine without aura is the same as normal population, but in migraine with aura is 62%.\(^{(8)}\) We didn’t find any study about frequency of headaches and duration of disease. In this study we evaluated frequency of PFO in migraine with aura, control group (without migraine) and additionally, relation of frequency of PFO to frequency of attack of headaches per month and duration of disease.

Methods and materials
This study was cross sectional and has been done on 50 patients of migraine with aura, and 25 normal people (without migraine) as control group. Patients were selected from admitted migraine patients to Shafa medical center. The goal and method of exam was described for the patients. For every patient a form including sex, age, age of onset of headaches, type of headache, unilateral, bilateral, duration of attacks, familial history of migraine, precipitating factors like specific foods, stress, menstrual periods, frequency of attacks in a months, and signs or symptoms associated with headaches,
nausea, vomiting, photophobia, phonophobia was filled. The control group consisted of normal population without history of migraine headache and cardiovascular disorders. Inclusion criteria are:

1- migraine with aura (IHS criteria) diagnosed by neurologist.\(^9\)
2- Normal physical examination, specially cardiopulmonary diseases has been ruled out.
3- Signed form of information by the patient.

The test has been done by a Doppler sonograph Pulse Wave (PW) instrument made in Germany and a software box (DWL2.5X2) to detect blood flow with 2 mega hertz’e probe with gain 50, deep 450-55 mm fixed on right Middle Cerebral Artery (MCA) from temporal window.

Saline agitated test: The patient lay on the bed, and an angio-catheter No 20 use to put in brachial vein and then joint with special connector. 9 ml of saline normal solution, 0.5 ml air and 0.5 ml blood of patient shake well to produce a homogenize solution. This solution inject with 1 ml/second speed in every phase, but may repeat to three phases. In first phase without Valsalva maneuver, if bubble of micro emboli was detected in MCA by PW when homogenize solution is injected, test is complete. If bubble of micro emboli has not been detected, second phase should be done. This phase is the same as first phase but the patients has deep inspiration and after that sever expiration (equivalent of Valsalva maneuver), this maneuver increase right to left shunt of heart, and as a result the micro emboli of air passes from shunt and enter to MCA, and then can be detected by PW instrument.\(^{10}\) If micro emboli was not detected, the third phase will be done. Third phase is the same as other phases, but 5 minutes after expiration ending has been done. On monitor of PW instrument the waves were evaluated and findings were detected on form.

**Results**

50 patients with migraine with aura were evaluated (78% female and 22% male) with mean age of 37.54 years. 25 normal people were studied.

Table 1 shows the rate of frequency of PFO in patients and control groups (male and female). Mean age of control group was 35.77 years old (without significant difference with patients' group).

Table 2 shows the frequency of headaches per month in patients and the rate of PFO.

The average duration of disease is 8.43 years without significant sex difference and also between PFO positive and PFO negative. Headache frequency is not significantly different in sex groups. Other variables, like foods, age, onset-age of headaches, type of headache, unilateral, bilateral, duration of attacks, familial history of migraine, precipitating factors such as special foods, stress, menstrual periods, and signs or symptoms associated with headaches, nausea, vomiting, photophobia, phonophobia were not statistically different.
Discussion

Studies linking migraine with aura and a hole in one’s heart have been big news in recent years. The hole is present in fetuses to allow blood to pass from one side of heart to another. In most people, the gap will be closed at or after birth. For an estimated 25% of the US population, it doesn’t close completely and PFO forms. But in other studies the rate of PFO is different. A 10% prevalence rate in ultrasound evaluation, and 27% in autopsy was reported, but this rate is equal in men and women.\(^{(11)}\) In a study PFO was found in 9.2% of all patients and also seen in all age groups. Incidence in patients with ages of 40-49 years was greater than aged 70-79 years (12.86% vs 6.15%).\(^{(12)}\) In a study, the rate of PFO in migraine with aura was reported to be 41%.\(^{(13)}\) In another study, this rate was 48% in migraine with aura and 23% in migraine without aura.\(^{(8)}\) In a study which has been done in Iran, this rate for migraine with aura was 38.5% and for migraine without aura was 26.7%.\(^{(14)}\) In a study which has been done by transesophageal echocardiography, the rate of PFO was 47%,\(^{(15)}\) and another study the rate of PFO is twice in migraine with aura.\(^{(16)}\) About relation of migraine with aura and PFO, there is not definite mechanism, may be genetically association between migraine with aura and PFO.\(^{(17)}\) In patients with paradoxical cerebral embolism, migraine headaches are more frequent than in the general population, and transcatheter closure of PFO, results in complete resolution or marked reduction in frequency of migraine headaches.\(^{(18-19)}\) In a study, rate of PFO in migraine with aura is 62%.\(^{(20)}\) In our study the rate of PFO in migraine with aura is 44%, and 20% in control group (P=0.005), but without significant sex difference, for the patients that have PFO, the transesophageal echocardiogram has been done, and results for all patients was positive. In our study those patients who had more frequent headaches, the PFO frequencies is also more. That’s important, because PFO may be one of the causes of strokes in young. The frequency of PFO in stroke patients is higher than among the general population, particularly in individuals with stroke of unknown etiology (cryptogenic stroke) and in younger patients.\(^{(21)}\) Wildly speculated that people have PFO, die earlier than those who don’t have.\(^{(22)}\) Accordingly individuals with a history of migraine with aura should be screened for the presence of a large shunt before they dive or exposed to subatmospheric decompression.\(^{(23)}\) Migraine may be associated with other disorders, for example depression.\(^{(24)}\) Our study proved other studies about association of migraine with aura and PFO. The PFO has association with stroke, thus we must consider these patients, because several secondary stroke prevention strategies have been developed: antiplatelet agents, oral anticoagulants, percutaneous closure, surgical repair,\(^{(6-25)}\) and thermal PFO closure is feasible, safe, effective and
may be possible in future.\textsuperscript{(26)}

**Conclusion:**
Migraine with aura has relation with PFO, especially in patients with frequent attacks more than 4 times per months. The closure of PFO in these patients need to be studied more, especially that, there are feasible procedures available now.
References
3-Hamzeimoghadam A; Bahrampoor B; Mobasher M. the evaluation of migraine prevalence and associated demographic factors among government employee of Kerman City. Journal Kerman University of Medical Sciences 1998;5(2):84-91.
4-Valentine Fuster R; Wayne Alexander; Robert A.O Rurke. Hurst’s the heart 10th Mc-Grav Hill 2005.
5-Dinia L; Roccatagliata L; Benano L; Fnochci C; Del Sette M. Diffusion MRI during migraine with aura attach associated with diagnostic microbubbles injection in subjects with large PFO. Headache 2007; 47(10): 1455-6.
10-Dirk W. Droste, MD; Stefan Lakemeier; Thomas Wichter, MD; Jörg Stypmann, MD; Ralf Dittrich, MD; Martin Ritter; Martin Moeller, MD; Michael Freund, MD E. Bernd Ringelstein, MD. Optimizing the Technique of Contrast Transcranial Doppler Ultrasound in the Detection of Right-to-Left Shunts Stroke. 2002;33:2211.)
13-Del Sette M; Angel S; Leandri M; Ferriero G; Bruzzon G; Fnochci C; Gandolof C. Migraine with aura and right-to-left shunt on transcranial Doppler. Cerebrovasc Dis 1998;8:327-30.
15-Schewezman M; Nedeltchev K; Lagger F;ol, Mattle HP, Windecker S; Meier B; Seiler C. Preva17-Anzola GP; Del Sette M; Rozzini L; Zavarise P; Morandi E; Grandolfo C; Angeli S; Finocch C. The migraine-PFO connection is independent of sex. Cerebrovasc Dis 2002;10:163-163.
16-Schewerzman M; Nedeltchev K; Lagger F; Mattle HP; Windecker S; Meier B; Seiler C. Prevalence and size of directly detected patent foramen oval in migraine with aura. Neurology 2005;55:1415-8.
19- Kimmelstiel C; Gange C; Thaler D. Pediatric and congenital heart disease Is patent foramen ovale closure effective in reducing migraine symptoms? Catheterization and Cardiovascular Intervention Volume 69; issue 5 Feb 2007 Pages 740-746

20-Della Volta G; Guindani M; Zavarise P; Griffin S; Pezzini A; Padovani A. Pravalence of patent foramen ovale in a large sries of patients with migraine with aura, migraine without aura and cluster headache, and relationship with clinical phenotype. J of Headache Pain 2005 Sep; 6(4):328-30.


22-Seiler C. How should we assess PFO ?. Heart 2004; 90:1245-1247.


24-Hamzeimoghadam A; Ghafari Nejad AR; Bahrampoor B. Evaluation of the frequency of migraine and depression and the relationship between them among medical students of Kerman University of medical sciences 1997; 4(2):85-90.

25-Morandi E; Anzola G.P; Angleis S; Melzi G; Onorato E. transcatheter closure of patent foramen ovale. J interventional Cardiology 2003 Feb; 16.

26-Hideheke Hara; Thomas K Jones; Elena R Ladich; Reno Virmani; david C Aoth; Joseph E Eichinger; Robert J Sommer; Robert A Vantassel; Robert S Schwartz. Circulation 2007; 116:648-653.

Figure 2: Frequency of headaches and rate of PFO in migraine with aura

Figure 1: Patients and control groups
چکیده
سابقه و هدف: سر درد میگرندی یکی از شایع ترین سر دردهای است، و یکی از شایع ترین عوامل ناوان کننده پزشکی در دنیا است. سر درد میگرندی بر دو نوع است: با اوراء و بدون اوراء. تقیباً 15% سر دردهای میگرندی با اوراء هستند و شایع ترین اوراء بینانی است.

باز بودن سوراخ بیضی شایع ترین نقص بین دیوارهای دهلیزی قلب است و 25% افراد جامعه سوراخ بیضی باز دارند. سوراخ بیضی باز اخیراً بعنوان یکی از عوامل ایجاد کننده سر درد میگرندی با اورaea شناخته شده است.

روش بررسی: این مطالعه مقطعی روی 50 بیمار با 50 سر درد میگرندی با اوراء و 200 فرد سالم بدون سر درد میگرندی انجام گردید. با استفاده از تست سالین آزمون آزمون دوطرفه سونوگرافی دیالر تشخیص انجام شد.

یافته‌ها: میزان فراوانی سوراخ بیضی باز در گروه بیماران سردرد میگرندی با اوراء 42% و در گروه سالم 22% بود. بیمارانی که به یک سال سردرد میگرندی در یک ماه داشتند میزان شیوع سوراخ بیضی باز بیشتری داشتند.

نتیجه‌گیری: سر درد میگرندی با اوراء با سر درد میگرندی باز ارتباط دارد، و بخصوص در بیمارانی که به یک سال سردرد میگرندی در یک ماه داشته‌اند. بیمارانی با اوراء سر درد میگرندی به به دسترس بودن امکانات این مورد توجه بیشتر قرار دارند.

واژگان کلیدی: سر درد میگرندی، سر درد میگرندی با اوراء، سوراخ بیضی باز و تست سالین آزمون.