Migraine in patients with Patent Foramen Ovale: is there a link?

Background: PFO is a hole between right and left atrium, that is normally present in human fetus, but that sometimes persists in adulthood. Migraine is a neurological disorder frequent in adult patients having Patent Foramen Ovale (PFO).

Methods and Results: A variety of clinical manifestations, such as migraine (with or without aura), TIA or cryptogenetic stroke can be present in adult patients with PFO persistence. Echographic findings for diagnosis and percutaneous closure with an Amplazer or other devices for migraine improvement were described. Nevertheless, while some studies report a significant improvement of migraine after PFO closure, other trials refer uncertain or negative results on migraine symptoms after the placement of Amplazer or other devices inducing PFO closure.

Conclusion: These uncertain results indicate the relationship between PFO and migraine not is clear and the evidences obtained till now testify both for causal or casual account between two events.

Keywords: Migraine • Patent Foramen Ovale (PFO) • Right-to-left shunt • Contrast medium • Microbubbles • Amplazer or other devices

Introduction

Migraine is a neurological disorder, frequently marked by recurrent headache with throbbing pain interesting one side of the head that may extend to both sides. That usually lasts from four hours to three days. It is often accompanied by nausea, vomiting and sensitivity to light or sound, and is sometimes preceded by aura and followed by fatigue [1]. Some migraneurs will have many or all the symptoms of migraine with “aura”. Aura consists of one or more focal neurological symptoms, such as visual sensory or speech disturbances. This occurs in about 15-30% of migraneurs and happens shortly before a migraine attack. They range from seeing sparks, bright dots, and zig-zags to tingling on one side of the body or on inability to speak clearly and usually last 20-60 minutes [2]. Migraine is three-times more common in women than in men and its prevalence peaks at 40 years of age [3]. Possible causes and some triggers for migraine are reported in Table 1 [4,5].

Patent Foramen Ovale

Apart the risk factors for migraine reported in Table 1. Patent Foramen Ovale (PFO) were indicated as an important cause of migraine headaches. PFO is present more than two-fold in patients with migraine with aura in comparison to those without aura [6].

PFO is a congenital heart defect defined such as an opening in the mild portion of the interatrial septum, at the junction of the septum premium to septum secundum [7,8]. PFO is seen from subcostal view (Figure 1). Mostly, spontaneous closure occurs before the birth or in the first two months of life. However, approximately 20-25% of healthy adults in the general population has a PFO and is asymptomatic. But, when the right atrial pressure increases more than the pressure in the left atrium, temporarily (Valsalva
maneuver, cough) or persistently (abdominal compression), the blood flow inverted and runs from right to left atrium through PFO. This leads the venous blood flow towards cerebral circulation. The paradoxical (reversed) circulation can cause several cerebral accidents, such as migraine TIA, or cryptogenetic stroke [9-11].

**Table 1.** Some causes and triggers for migraine.

<table>
<thead>
<tr>
<th>Possible causes of migraine and their most common triggers</th>
<th>Triggers</th>
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<tbody>
<tr>
<td>Genetic predisposition</td>
<td>Physical or mental stress</td>
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<tr>
<td>Disorders of CNS</td>
<td>Some foods (cheese, alcohol, etc.)</td>
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<tr>
<td>Irregularity in brain’s vascular system</td>
<td>Several stimuli (cigarette smoke, perfume, hormones, etc.)</td>
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<tr>
<td>Abnormalities of brain chemicals</td>
<td>Others</td>
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</tbody>
</table>

Noninvasive diagnosis of PFO is done by the ultrasound method, using trans-thoracic echocardiography (TTE), trans-esophageal echocardiography (TEE) or trans-cranial doppler echography (TCDE). TTE is performed side by side with agitation saline injection in a brachial vein of a contrast medium during the Valsalva maneuver or cough. PFO is evidenced through the demonstration of microbubbles in LV coming from right-to-left atrium (Figure 2) [12]. But, the gold standard echo-technique for to point the paradoxical blood-passing is TEE. PFO is seen in Figure 3 [13]. TCDE is the technique suitable to visualize the passage of microbubbles in the brain arteries in the presence of right-to-left shunt. The evidence of microbubbles in the middle cerebral artery before and after injection of contrast medium suggests the presence of intracardiac shunt, such as in Figure 4 is seen [14].

In this review, we illustrate the relationship between PFO and migraine. Concerning this, it must be added that PFO was found in about 40% to 60% of people suffering migraine in comparison to 20% 30% of population without PFO.

**PFO and migraine**

An increased pressure in the right atrium in the presence of PFO favors the blood-passing from pre-pulmonary to systemic circulation. That induces a right-to-left shunt (paradoxical passage) of platelets with their Serotonin content and other vasoactive amines from venous to arterial circulation. Serotonin (present in the platelets) is removed by pulmonary monoamine oxidase enzyme when the blood flow normally reaches the pulmonary circulation. For right-to-left shunt, Serotonin (jointed at the brain arterial circulation) may irritate the trigeminal nerve, triggering migraine. Concerning the connection of the monamine...
neurotransmitter and migraine, it must be added that Serotonin antagonizes Triptans that abort migraine attacks, favoring these [15]. Concordantly, a small study has demonstrated that aspirin, an antiplatelet drug that reduces the formation of platelet-fibrin complexes, improves migraine [16]. Finally, Mazal and Rachmilewitz evidenced that an anti serotonin agent, Pirotifen, reduces platelet’s aggregability in migraine patients and improves this neurological disorder [17]. The nociceptive effect of Serotonin on meningeal covering of trigeminal nerve was recently still reported [18]. Conclusively, the relation between PFO and migraine is explained by the effect of some vasoactive substances (such as 5HT), normally removed in the pulmonary circulation that, in the presence of right-to-left shunt, can bypass lungs filter and enter in cerebral circulation, inducing migraine attack [19]. Another mechanism related to the relationship of PFO with migraine is that transient hypoxemia due to the paradoxical shunt of blood through the PFO causes microinfarcts in the brain, leading to brain-irritation [15]. It was also added that some data suggest the prevalence of migraine with aura in PFO-patients, depends on the size of right-to-left shunt. This resulted in the hypothesis that substances that circumvent the pulmonary filter, can cross the shunt and cause arterial vasoconstriction, precipitating migraine with aura [19]. With regard to aura in PFO-patients, it must also add that the prevalence of PFO in patients with aura ranges between 41% and 89%, whereas it is between 7% and 34% in migraineurs without aura [20].

On the grounds of all considerations before reported, the PFO closure has been proposed as non-medical, therapeutical procedure to avoid or reduce migraine-attacks. But, whereas some studies found an improvement of migraine after PFO closure, other trials did not find significant differences in migraine attacks between before and after PFO closure. In accordance with the first statement, a case-control study refers on a causal relation between migraine (especially with aura) and PFO and reports a migraine improvement after the PFO closure using the AMPLAZER device [21]. Concordantly, other reports underline also a significant reduction of migraine attacks in patients with PFO submitted to its closure [22,23]. On the contrary, other reports, such as the MIST study pointed out that the risk of recurrent stroke was significantly lower in group treated with PFO closure plus antiplatelet therapy than in patients receiving antiplatelets alone [24]. Another interesting phenomenon, that further confirms the disagreement between PFO closure and migraine improvement, is the observation of an exacerbation of pre-existing migraine with aura after PFO closure. This paradoxical phenomenon would report to the chemical composition of Amplazer, which is made by Ninitol, an alloy of Nickel and Titanium. Specifically, Nickel allergy p induces excessive inflammation, platelet’s activation and release of Serotonin, with migraine and aura [30].

Finally, referring to the low effectiveness of percutaneous closure only and to the greater validity of medical therapy, MIST study pointed out that the risk of recurrent stroke was significantly lower in group treated with PFO closure plus antiplatelet therapy than in patients receiving antiplatelets alone [24]. Another interesting phenomenon, that further confirms the disagreement between PFO closure and migraine improvement, is the observation of an exacerbation of pre-existing migraine with aura after PFO closure. This paradoxical phenomenon would report to the chemical composition of Amplazer, which is made by Ninitol, an alloy of Nickel and Titanium. Specifically, Nickel allergy p induces excessive inflammation, platelet’s activation and release of Serotonin, with migraine and aura [30].

**Conclusion**

In accordance with Reisman and Fuller [31], we conclude that certain PFO-patients have a dramatic response to closure of PFO with an Amplazer device, with significant reduction or complete elimination of migraine headache.
On the contrary, in others the PFO closure has uncertain, aggravating or paradoxal results. At moment, the causes of these diverse behaviours are unknown. Future studies performed in wide range of PFO-populations are requested to elucidate if the relationship between migraine and PFO is causal or simply casual.

**Conflict of interest**

There is no conflict of interest

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**References**