Review Article

Migraine and Patent Foramen Ovale: Exploring the association and a possible treatment option

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Abstract

Migraine is a very common type of headache. With a prevalence of 10-12%, migraine ranks 19th among diseases causing worldwide morbidity. Number of studies have shown a high prevalence of patent foramen ovale (PFO) in patients with migraine, especially migraine with aura. The right to left shunting of blood in a PFO could serve as a conduit for chemicals that would exert a trigger effect on hyper excitable neurons leading to the development of migraine. Furthermore patients with PFO and migraine also show a marked improvement in their symptoms after percutaneous closure of the PFO. This review is a close look at this association and also explores whether subsequent closure of the shunt can be looked upon as a viable treatment option.

Migraine

Migraine is a complex disorder in which many psychological, environmental, biochemical, neurophysiologic, and genetic factors play a role to trigger attacks. The diagnosis is based on headache characteristics and associated symptoms specified by the International Headache Society.[1] The typical headache is unilateral, throbbing, and may be severe. If untreated, the migraine attacks typically last 4 to 72 hours. The attacks are usually associated with nausea, vomiting, or sensitivity to sound, light, or movement. In addition to this, migraine with aura is characterized by transient focal neurological symptoms, which are usually visual, and may precede, accompany, or follow the headache attack.[2]

With a prevalence of 10-12%, migraine ranks 19th among diseases causing worldwide morbidity.[1] Its prevalence increases with age until a peak prevalence of approximately 27% in women and 8% in men is reached in the fourth decade of life. Thereafter, it decreases with increasing age.[3]

Patent Foramen Ovale (PFO)

Foramen ovale is a slit like opening in the atrial septum. In the intrauterine life, foramen ovale has the important role of transmitting highly oxygenated inferior vena caval blood to the left atrium (LA). High right atrial (RA) pressure in foetal life keeps the valve of foramen ovale open. LA pressure rises shortly after birth and the flap is lightly pushed against the septum secundum and closes the foramen ovale functionally. Anatomic patency may occur for several months and 50% of all the infants have probe - PFO at the end of 1st year of life. However in a large proportion, anatomic closure never occurs.

A number of studies have indicated PFO to be present in around 25% to 30% of adult population, with equal incidence in the sexes.[4] It can allow only right-to-left shunt (RLS) because of the flap which covers it from the left side. TEE (Trans-esophageal echo) is better than Trans-thoracic echo in diagnosing PFO.[5]

The right-to-left shunt (RLS) may be associated with paradoxical embolization of thrombi and has been postulated as a mechanism for cryptogenic stroke in young adults.[6] PFO has also been shown to cause decompression sickness among divers.[7]

Migraine and PFO: Is it the shunt behind the headache?

Migraine has long been suspected as a risk factor for stroke. Several studies have linked migraine headache to stroke, particularly in young women.[8] However, discoveries that the prevalence of PFO is the same in patients with migraine with aura as in patients with cryptogenic stroke[9-11] and that the frequency of migraine in PFO associated cryptogenic stroke is twice what would otherwise be expected[12,13] lead to the speculation that PFO could play a role in the pathogenesis of migraine headaches.

Theoretically, the presence of a right-to-left shunt in a PFO could serve as a conduit for chemicals, that would be normally inactivated by the pulmonary filter, to reach the systemic circulation and exert a trigger effect on hyper excitable neurons leading to development of migraines. These substances may include vasoactive agents such as atrial natriuretic peptide, platelet factors, and amines, which in elevated concentrations can cause a migraine in susceptible individuals even without a PFO.[14]

Although a theoretically plausible association, PFO and migraine are common conditions and their co-occurrence in a single patient might yet be coincidental; alternately, PFO and migraine both could derive from a common underlying disorder (e.g., a dysfunction in the

endothelium) without necessarily being linked in a causal relationship.[15]

However a number of studies have supported this relationship and have validated the PFO-migraine association. While Del Sette et al[9] showed a statistically significant association between the prevalence of PFO among migraineurs versus controls; Anzola et al[10] found that the association varied with migraine subtype, as only patients with aura had a higher occurrence of PFO when compared with controls. Similar findings were reported by Schwerzmann et al[16] using trans-esophageal echocardiography, who found PFO with large shunts more often in patients with migraine with aura compared to control subjects.

Moreover, in patients with RLS, the prevalence of migraine seems to be higher when compared to those without a shunt. This finding was first reported by Wilmshurst and Nightengale[17] and later, similar findings were reported by Sztajzel et al.[13]

Finally, the strength of the relationship between the migraine and RLS due to PFO was assessed by Wammes-van der Heijden et al[18], who systematically reviewed published relevant literature, and concluded that among patients with RLS, migraine with aura was 3.5 times more prevalent than among subjects without RLS (Mantel-Haenszel odds ratio (ORMH) 3.5; 95% confidence interval (CI) 2.1, 5.8). This further elicits a clear association between RLS and migraine, especially migraine with aura.

Closing the Shunt: A possible treatment?

If PFO is the etiology behind migraine, can shunt closure be a definitive treatment? When Wilmshurst et al observed PFO closure to prevent decompression sickness in a cohort of scuba divers, results showed a dramatic decrease in migraine severity[7]; this finding raised considerable interest on the possible curative effect of shunt closure on migraine. A number of subsequent publications reported a consistent benefit on migraine following PFO closure in patients who had suffered a stroke.[14,19-23] However, none of these studies had a control group. Recently Kimmelstiel et al[24] in a controlled study showed PFO closure decrease the frequency of migraine by 83% compared to 0% decrease in frequency in open PFO and 10% decrease in the control group (no PFO). Furthermore, preliminary results of another recent case-control study have shown PFO closure to be far more effective in reducing frequency, duration and intensity of migraine attacks when compared to medical treatment.[25]

There is evidence of a strong association between the presence of a RLS and the occurrence of migraine. In addition we have also seen that shunt closure is related to a decrease in the prevalence of migraine, especially in migraine with aura. Yet at this moment shunt closure cannot be seen as a new treatment for PFO related migraines.

Most of the studies favouring PFO closure were nonrandomized, lacked a control group and investigated a relatively small number of patients with migraine. Before percutaneous shunt closure can become a new treatment in patients with migraine, especially migraine with aura, large prospective randomized trials will be necessary. Finally, it is worth recalling that, even if percutaneous closure of PFO is a safe, effective, and minimally invasive procedure, a number of complications have been reported. Among these, special emphasis should be placed on major arrhythmias, including supraventricular paroxysmal tachycardia and atrial fibrillation, which have been documented in up to 8% of patients within 1 month of the procedure.[26,27]

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