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Patent Foramen Ovale and Migraine

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Introduction

There are now multiple studies which have identified an association between patent foramen ovale (PFO) and migraine. Migraine with aura is more prevalent in subjects with PFO and PFO is more prevalent in subjects who have migraine with aura. However, it is unclear if there is a causal relationship or simply a co-existence of these two conditions.

In utero, the foramen ovale connects the right and left atrium of the heart. After birth when left atrial pressures exceed those in the right atrium, the foramen ovale usually closes via fusion of the septum primum and septum secundum. In approximately 25% of the general population, the foramen ovale is covered but fusion does not occur, resulting in a PFO. The PFO tunnel serves as a persistent connection that may allow for passage of blood from the right atrium to the left atrium, thus bypassing the lungs, either with each beat of the heart or only with further increases in right atrial pressure such as during Valsalva.

PFO in Migraine

PFO is more common in migraineurs with aura than in the general population. PFO is found in approximately 40% to 60% of people who have migraine with aura as compared to 20% to 30% of people in the general population. [1-5] Although migraine without aura has been studied less extensively, it does not seem to be associated with an increase in the prevalence of PFO. [2] A recent meta-analysis suggests that migraineurs with aura are more than 4x more likely to have a PFO [odds ratio 4.45] than the general population. [6]

Migraine with PFO

Migraine with aura is more prevalent in subjects who have a PFO as compared to those without PFO. It is present in about 13% to 50% of people with PFO as compared to approximately 4% of the general population. [7-13] The risk of migraine with aura may be higher among those with larger PFO and with right-to-left shunting at rest. Meta-analysis suggests that the odds ratio of migraine in subjects with PFO is 5.19. [6] Available evidence to date suggests that PFO is not a risk factor for migraine without aura. [7-13]

Proposed Association
It is unclear at this time if there is a causal or comorbid association between migraine with aura and PFO. A non-causal relationship is supported by the finding of autosomal dominant inheritance of large PFOs in some families. [14] It is hypothesized that PFO and migraine could be co-inherited due to common development of endocardium, endothelium, and platelets. However, PFO may be causally related to migraine. It can be hypothesized that passage of blood directly from the right to left atrium, bypassing the normal filtering activity of the lungs, allows for paradoxical emboli and/or higher concentrations of serotonin, nitric oxide, kinins or other migraine precipitating chemicals to reach the brain and trigger migraine attacks. Supporting this hypothesis, a single study found that among patients with PFO and cryptogenic stroke, those with migraine with aura had a higher frequency of underlying thrombophilic conditions which would predispose them to paradoxical emboli. [15] Further supporting a causal relationship, a significant increase in migraine aura attacks and development of de novo attacks has been documented in patients following PFO closure. The frequency of such attacks, likely due to thrombus formation on the closure device or platelet degranulation, is reduced after the administration of clopidogrel and aspirin. [16]

PFO Closure
It has been suggested that PFO closure may be an effective treatment for migraine. Combining results of several retrospective studies, each with significant methodological flaws, following PFO closure about 55% of migraine sufferers had resolution of headaches, an additional 25% had improvement, and 20% had no change. [17] Results were similar among migraineurs with and without aura. Although conclusions cannot be drawn from these studies, they provide justification, especially in light of the inevitable off-label use of PFO closure devices in migraineurs, for the prospective, randomized, sham-controlled trials of PFO closure in migraineurs that are currently in progress.

Unpublished results from the first such study, MIST-I, are now available. [4] One-hundred and forty-seven migraineurs with aura who had large PFOs were randomized to PFO closure or sham closure. All subjects received anti-platelet therapy with aspirin and clopidogrel for 3 months following closure. MIST-I failed to meet its primary end-point of complete migraine resolution in 40% of the treated group at 6 months post-closure. Only 3 subjects from the treatment group (as well as 3 subjects in the sham closure group) had migraine resolution at 6 months. Adverse events in the treatment group included 1 subject with cardiac tamponade, 1 with pericardial effusion, 1 with bleeding at the puncture site, 1 with atrial fibrillation, and 1 with atypical chest pain. Adverse events among the sham group included 2 subjects with bleeding secondary to antiplatelets (nosebleed, menstrual), 1 with bleeding at the puncture site, and 1 with stroke occurring 4 months after randomization.

The safety and efficacy of PFO closure for the treatment of migraine is unknown. There are currently several prospective trials of PFO closure in subjects with migraine actively enrolling in North America. These trials are using more feasible primary outcomes than used in the MIST-I trial.

Conclusion
At this time, migraine should not be considered an indication for PFO screening. Patients with migraine should not undergo PFO closure for the treatment of migraine unless enrolled in a clinical trial. The possible role of PFO closure for the treatment of migraine will be further elucidated as results from additional prospective trials become available.

Key Points:

- Migraine with aura is more prevalent in the presence of PFO.
- PFO is more prevalent in migraineurs with aura.
- At this time, PFO closure is not recommended for the treatment of migraine since the safety and efficacy of closure in migraineurs has yet to be established.

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