Patent foramen ovale and migraine: no reason to intervene

A Statement of European Headache Federation

Cardiac embolism is the most frequent cause of ischemic stroke in hospital-based and population-based registers. Patent foramen ovale (PFO) with and without atrial septal aneurysm (ASA) has been recognized as a potential risk factor for ischemic stroke. Besides paradoxical embolism from small thrombi that arise in the venous system and cardiac thrombus formation secondary to PFO/ASA-related cardiac arrhythmia, another likely ischemic stroke cause is thrombus formation in the PFO.

Several studies have investigated a possible link between PFO and migraine. Del Sette *et al.* compared 44 patients with migraine with aura, 73 patients less than 50 years of age with focal cerebral ischemia, with 50 control individuals without cerebrovascular disease nor migraine using transcranial Doppler.(1) The prevalence of right-to-left shunt was significantly higher in patients with migraine with aura (41%) and cerebral ischemia (35%) than in controls (8%). Anzola and colleagues performed a case-control study of 113 consecutive patients with migraine with aura, 53 patients with migraine without aura and 25 age-matched nonmigraine individuals; the prevalence of PFO was significantly higher in patients with migraine with aura (48%) compared with patients with migraine without aura (23%) and controls (20%) (2).

A coincidence of two conditions, however, does not necessarily imply a causal relationship. Moreover, it is difficult to imagine how PFO should lead to a migraine

attack with aura—a neural event in the occipital cortex caused by spreading depression. Even if small emboli arise from a PFO, these would travel preferentially into the anterior circulation rather than into the posterior cerebral artery. A recent family study indicated that migraine with aura and cardiac right-left shunts are inherited in a dominant pattern(3).

Should PFOs be closed? Even if we assume there is a causal relationship between PFO and migraine, closure of PFO should then result in migraine improvement. To date, one randomized controlled prospective trial has been performed (MIST) and failed its primary outcome measure. The trial compared transcutaneous PFO closure in patients with migraine with aura compared to a sham procedure. In a retrospective study, 215 stroke patients with PFO were examined and underwent closure of PFO as a secondary prevention measure (4). A year later, patients were asked about their migraine frequency before and after PFO closure to determine whether this intervention affected migraine attacks. Patients with a PFO and a history of stroke had higher migraine prevalence (22%) than the general population (10%). In patients with migraine with aura, percutaneous PFO closure reduced the frequency of migraine attacks by 54% and in patients with migraine without aura by 62%. PFO closure did not have a statistically significant effect on headache frequency in patients with nonmigraine headaches. Several other retrospective studies found a similar relationship between PFO closure and migraine improvement. However, all these studies had major limitations. First, despite migraine improving spontaneously with age, no study had a control group. Second, the high placebo response can reduce the frequency of migraine by up to 70%. Third, after PFO closure, most patients received aspirin or clopidogrel both of which have a modest migraine prophylactic activity, at least in men.(5-7) Fourth, retrospective collection of headache data is highly unreliable; recall bias has a major influence on

the results. Furthermore, the most recent study observed that as many patients improve from migraine as develop new onset migraine after PFO closure (8). In addition it has to be considered that PFO closure has a small but relevant incidence of serious adverse events including stroke, pericardial tamponade, atrial fibrillation or death.

Thus, to date there is insufficient evidence on the hypothesis that migraine frequency is improved by PFO closure. Properly conducted, prospective studies in migraine patients including control groups with other or no headaches are needed. Until then PFO closure should not be used for the prophylaxis of migraine outside of randomized controlled trials.

References

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