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Patent foramen ovale and migraine

Migraine is a complex disorder in which many psychological, environmental, biochemical, neurophysiologic, and genetic factors may play a role to trigger attacks.[1,2] Although its course is usually benign and it tends to abate with age, migraine has long been suspected as a risk factor for stroke. A number of case-control studies and a recent meta-analysis have demonstrated that the relative risk of stroke is as follows in the following groups of migraineurs compared with nonmigraineurs:[3–6]

- 1.83 in people with migraine without aura
- 2.27 in people with migraine with aura
- 8.27 in female migraineurs who smoke and take oral contraceptives.

Furthermore, migraineurs are more likely to exhibit silent ischemic lesions on magnetic resonance imaging.[7]

STROKE RISK AND THE PFO-MIGRAINE ASSOCIATION

The mechanisms by which migraine conveys an increased risk of stroke had been an object of speculation[6] until the discoveries that the prevalence of patent foramen ovale (PFO) is the same in patients with migraine with aura as in patients with cryptogenic stroke[8–10] and that the frequency of migraine in PFO-associated cryptogenic stroke is twice what would otherwise be expected.[11,12] These findings have prompted a twofold hypothesis:[13,14]

(1) That the association with PFO accounts for the increased stroke risk in patients with migraine through the mechanism of paradoxical brain embolism

(2) That the presence of a right-to-left shunt 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 hyperexcitable neurons.

The latter point would imply that, to a certain extent, PFO may cause migraine attacks. However, PFO and migraine are common conditions and their co-occurrence in a single patient might be coincidental; alternately, PFO and migraine both could derive from a common underlying disorder (eg, a dysfunction in the endothelium) without necessarily being linked in a causal relationship.[14]

Nevertheless, a number of recent findings tend to support an etiologic link.

We recently assessed the extent of right-to-left shunt with contrast-enhanced transcranial Doppler imaging in 420 consecutive patients.[15] Patients with prior stroke had larger shunts than patients without prior stroke (mean bubble count of 91 vs 58, respectively, on transcranial Doppler). Migraineurs with and without aura both had significantly larger shunts than nonmigraineurs (bubble counts of 104, 74, and 46, respectively). As detailed in **Table 1**, patients with both migraine and prior stroke had larger shunts than migraineurs without prior stroke, than nonmigraineurs with prior stroke, and than patients without migraine or prior stroke.

Possible effect of shunt size

These findings suggest that shunt size may have a dose effect in terms of the risk of having migraine and stroke. The plausible hypothesis is that, via the atrial septal defect, a venous-to-arterial passage of activated platelets or chemical substances may trigger headache by overwhelming the filtering capacity of the lung.[16]

Larger shunt might also increase the likelihood of paradoxical embolization to the brain and hence explain the statistically significant increase in stroke risk that is associated with migraine. The presence of a right-to-left shunt may be the most potent trigger of attacks in migraine with aura as well as migraine without aura and may be the main determinant of aura.

Specificity to migraine with aura

However, any interpretation of a causal link between PFO and migraine needs to take into account the fact that although PFO is found in nearly half of patients who have migraine with aura, its frequency in migraine without aura is the same as in nonmigraineurs.[9,10]

For migraine with aura, a common inheritable trait linking migraine with atrial septal abnormalities has

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been suggested by Wilmshurst et al, who studied 71 relatives of 20 probands with a significantly sized atrial shunt.[17] When the proband had migraine with aura and an atrial shunt, 15 of 21 (71.4%) first-degree relatives with a significant right-to-left shunt also had migraine with aura compared with 3 of 14 (21.4%) first-degree relatives without a significant shunt ($P < .02$), which suggests that migraine trait may be inherited in association with atrial shunts, at least in some kinships, and that the occurrence of atrial shunts is consistent with autosomal dominant inheritance.

CAN PFO CLOSURE IMPROVE MIGRAINE?

Further along the migraine-PFO connection are the effects of PFO closure on migraine severity. When Wilmshurst et al observed serendipitously that PFO closure to prevent decompression sickness in a cohort of scuba divers resulted in a dramatic decrease of migraine severity,[18] this finding raised considerable interest on the possible curative effect of atrial septal repair on migraine. A number of subsequent publications reported a consistent benefit on migraine following PFO closure in patients who had suffered a stroke.[19–24] The cumulative results of such studies are presented in **Table 2**. Although the validity of these results is limited by major methodologic flaws (retrospective design, lack of a control group, subjective rating of migraine severity, short follow-up, presence of previous stroke in all patients), recent findings from a prospective case-control study[25] have substantially confirmed the favorable effect of PFO closure on migraine, although to a somewhat less dramatic extent (see **Table 2**).

MIST trial raises questions

However, in partial contrast with these results are the recently reported findings of the Migraine Intervention with STARFlex Technology (MIST) trial,[26] the first prospective, multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy of PFO closure with the STARFlex® septal repair implant (NMT Medical, Inc., Boston, MA) to prevent refractory migraine headaches. The MIST trial enrolled patients with migraine with aura and moderate to large PFO as assessed by contrast-enhanced transthoracic echocardiography (TTE); patients had to have at least 5 days of migraine in the month preceding enrollment and their migraines had to be refractory to at least two different prophylactic medications. The primary outcome measure was the proportion of patients without headache at 6 months. Of 432 screened patients, 163 were found suitable for randomization and 147 were actually randomized to the interventional (n = 74) or sham (n = 73) arms. At 6-month follow-up, three patients in each arm were migraine-free, which corresponds to a 4% response rate in each arm and a clearly nonsignificant difference between the groups. A secondary post hoc outcome measure, the proportion of patients with a 50% reduction in the number of headache days, showed a statistically significant difference favoring the interventional arm (42% vs 23%, $P = .038$).

The results of the MIST trial generate more questions than answers in that they are presently published solely on the Web and in slide format, and a substantial amount of information is lacking; for instance, the proportion of residual shunts is unknown, as is the proportion of patients who experienced a worsening of their migraines, which has been reported to occur in the initial postoperative period.[16,27] Furthermore, the use of transthoracic echocardiography as the only tool to quantify the amount of shunt and to discriminate between true PFO and atrial septal defect is questionable. Finally, the inclusion criterion of high frequency of migraine attacks, far exceeding the expected frequency of pure migraine with aura, may have allowed the enrollment of patients with mixed forms of headache, including episodic tension-type headache, which has proved unresponsive to PFO closure.[20]

TABLE 1
Age and shunt according to cerebrovascular history and migraine status*

	No migraine		Migraine	
	No prior stroke	Prior stroke	No prior stroke	Prior stroke
No. patients	100	85	139	96
Sex (M/F)	40/60	38/47	21/118	18/78
Age, yr (mean ± SD)†	48 ± 17	55 ± 14	36 ± 14	42 ± 11
Mean bubble count (SE)‡	38 (5)	55 (8)	72 (8)	123 (24)

* In a series of 420 consecutive patients undergoing transcranial Doppler imaging.[15] See text for details.

† Age significantly different in all comparisons (P between < .0001 and .023).

‡ Mean bubble count in migraine patients with prior stroke was significantly higher than in any other group (P between < .0001 and .038).

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TABLE 2
Summary of results of nonrandomized trials on the effects of patent foramen ovale closure on migraine*

Author	Year	Type of study	No. of pts	Mean follow-up (months)	Patients with resolution (%)	Patients with improvement (%)
Wilmshurst et al[18]	2000	Retrospective	21	17	48	38
Morandi et al[19]	2003	Prospective	17	12	29	59
Schwerzmann et al[20]	2004	Retrospective	47	24	Not reported	83
Post et al[21]	2004	Retrospective	26	6	84	Not reported
Azarbal et al[22]	2005	Retrospective	37	3	60	40
Reisman et al[23]	2005	Retrospective	50	12	56	14
Giardini et al[24]	2006	Retrospective	35	20	83	8
Overall results of retrospective trials			**233**	**13**	**60**	**40**
Anzola et al[25]	2006	Prospective case-control	50	12	38	48

* The only case-control study (reference 25) is contrasted with earlier reports.

PINPOINTING WHO MIGHT BENEFIT FROM PFO CLOSURE

Taken at face value, however, the MIST trial results put the therapeutic efficacy of atrial septal repair in a more realistic perspective. The hypothesis that PFO closure improves migraine needs further refinement and has to be stated in different terms, such as with the qualification that a proportion of patients with PFO-associated migraine might, in principle, benefit from PFO closure. Preliminarily, we need to identify which clinical features are most likely to be related to the presence of a right-to-left shunt. In other words, we need to identify the shunt-associated migraine syndrome.

From preliminary results of an ongoing Italian study,[28] it seems that some features help to differentiate patients in whom the right-to-left shunt may exert a pathophysiologic effect: being a female with a positive family history of migraine with aura and a higher frequency of migraine attacks with aura vs without aura appears to represent the core specificity of shunt-associated migraine (Anzola et al, unpublished data).

Future randomized controlled trials comparing PFO closure with medical treatments will have to incorporate the knowledge of which features are pathophysiologically related to PFO in migraine sufferers in order to enroll only those patients in whom investigating PFO closure in a randomized trial is worthwhile.

Finally, it is worth recalling that, even if transcatheter 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.[29,30]

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