Title

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Journal

Neuroimaging Clinics of North America, 29(2)

ISSN

1052-5149

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Publication Date

2019-05-01

DOI

10.1016/j.nic.2019.01.006

The Connection Between Patent Foramen Ovale and Migraine

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KEYWORDS

• Migraine headache • Patent foramen ovale • Right-to-left shunt

KEY POINTS

- Although observational studies have shown that migraineurs with aura respond well to patent foramen ovale (PFO) closure, randomized trials have not confirmed this.
- Until a randomized double-blinded study clearly demonstrates a significant benefit of PFO closure to reduce migraines, medical therapy will remain the treatment of choice for migraines.
- One challenge in conducting such a study is adequate patient recruitment in a timely fashion given strict inclusion criteria.

BACKGROUND

A patent foramen ovale (PFO) is a remnant of the fetal circulation that permits oxygenated blood from the placenta to pass from the inferior vena cava across the atrial septum into the arterial circulation (**Fig. 1**). This mechanism of bypassing the nonfunctional fetal lungs and directing oxygenated blood to the fetal brain is critical for fetal development and is preserved by evolution in all mammals. After birth, the lungs are aerated and serve to oxygenate the blood; the pressure in the left atrium exceeds that in the right atrium and the septum primum closes over the foramen ovale and fuses with the septum secundum. By genetically determined mechanisms,[1] the foramen ovale remains patent in 20% to 30% of the general adult population. Thus, PFO is by far the most common congenital heart defect. Although most people with a PFO remain asymptomatic, in people who have migraine with aura, the presence of a PFO is about 50%.[2] One hypothesis for this 2-fold higher frequency of PFO is that a genetic influence might predispose some patients to a higher risk of developing both migraine and atrial septal abnormalities. Another hypothesis is that migraine, especially migraine with aura, may be triggered by vasoactive substances (eg, serotonin) that are ordinarily metabolized during passage through the lungs, and the presence of a right-to-left shunt such as a PFO or a pulmonary arteriovenous malformation allows these chemicals to bypass metabolic alteration in the lungs and gain entry to the arterial circulation in a higher concentration so that on reaching the brain, they stimulate receptors in susceptible individuals, which produces the cerebral migraine phenomena. The latter hypothesis was derived after the observation that PFO closure often resulted in relief of migraine headaches (**Figs. 2–5**).

OBSERVATIONAL STUDIES SUGGESTING AN ASSOCIATION BETWEEN MIGRAINE AND PATENT FORAMEN OVALE

In 1998, Del Sette and colleagues at the University of Genova, Italy, described the first association between right-to-left shunting, stroke, and migraine with aura. Del Sette and colleagues

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Neuroimag Clin N Am 29 (2019) 261–270
https://doi.org/10.1016/j.nic.2019.01.006

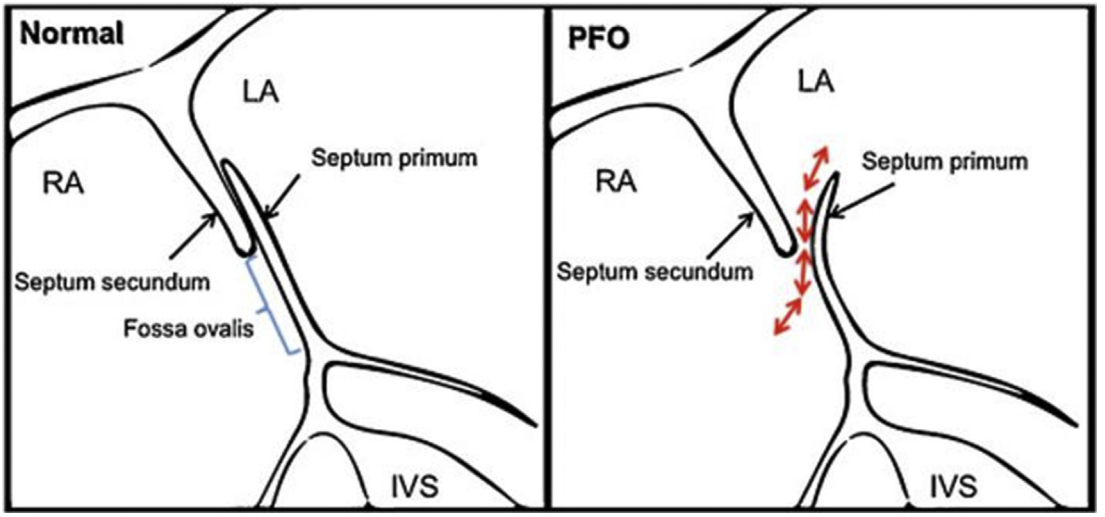

Fig. 1. PFO anatomy. IVS, interventricular septum; LA, left atrium; RA, right atrium. (*From* Yasunaga D, Hamon M. MDCT of interatrial septum. Diagn Interv Imaging 2015;96:893; with permission.)

carried out a case-control study in which 44 patients suffering from migraine with aura, 73 patients younger than 50 year with a history of cryptogenic focal cerebral ischemia, and 50 controls asymptomatic for cerebrovascular disease and without a history of migraine underwent bilateral transcranial Doppler (TCD) with injection of contrast medium during normal ventilation and during Valsalva maneuver. The prevalence of a right to left shunt was 41% (18/44) in patients with migraine with aura and 35% (26/73) in patients with cryptogenic stroke, compared with 16% (8/50) in normal controls ($P<.005$).[3]

Schwedt and colleagues[4] conducted a systematic review of case-control studies published up to 2008 looking at PFO and migraines and concluded that there is a bidirectional association. Migraine with aura (but not without aura) is more common in patients with PFO than in the general population, and PFO is more prevalent in patients who have migraine with aura than in the general population. Anzola and colleagues[5] compared the frequency of right-to-left shunt using TCD in 113 patients who had migraine with aura, 53 patients who had migraine without aura, and 25 age-matched controls. PFO was present in 48% of subjects who had migraine with aura, but was not different in migraineurs without aura (23%), compared with the control group without migraine (20%) ($P = .002$).

Wilmshurst and colleagues[6] were the first to report the benefits of PFO closure on migraine headache. Of 37 patients who underwent PFO closure, 21 (57%) had a history of migraines, with 16 having a history of migraine with aura and 5

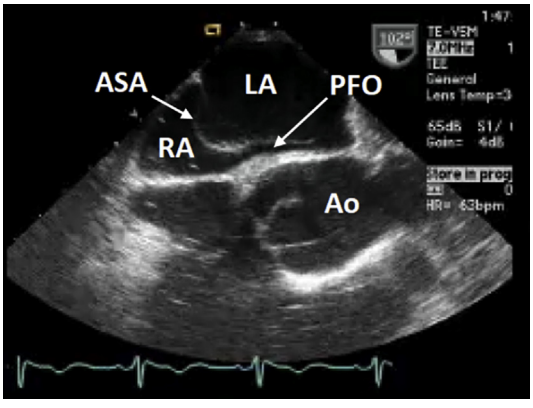

Fig. 2. Transesophageal echocardiography showing a long-tunnel PFO with an atrial septal aneurysm (ASA). Ao, aorta; LA, left atrium; RA, right atrium.

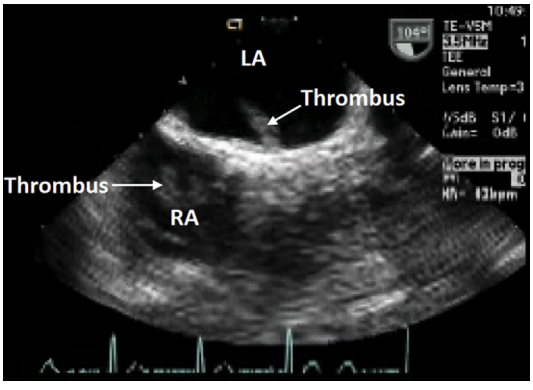

Fig. 3. A thrombus caught straddling the PFO between the right and left atrium. LA, left atrium; RA, right atrium.

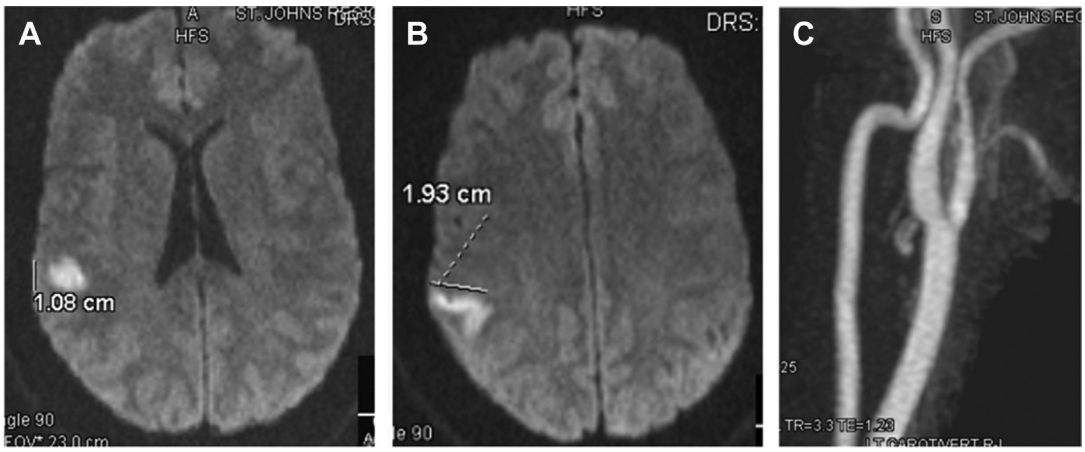

Fig. 4. (*A*, *B*) Axial diffusion-weighted images showing a 1.08 × 1.93 cm cortical infarct. (*C*) MR angiogram of the neck showing patent carotid arteries.

having a history of migraine without aura. Following PFO closure, 7 out of 16 (44%) migraineurs with aura had complete resolution of migraines and 8 of the remaining 9 had an improvement in both frequency and severity of migraines, whereas 3 out of 5 (60%) migraineurs without aura had complete resolution of migraines.

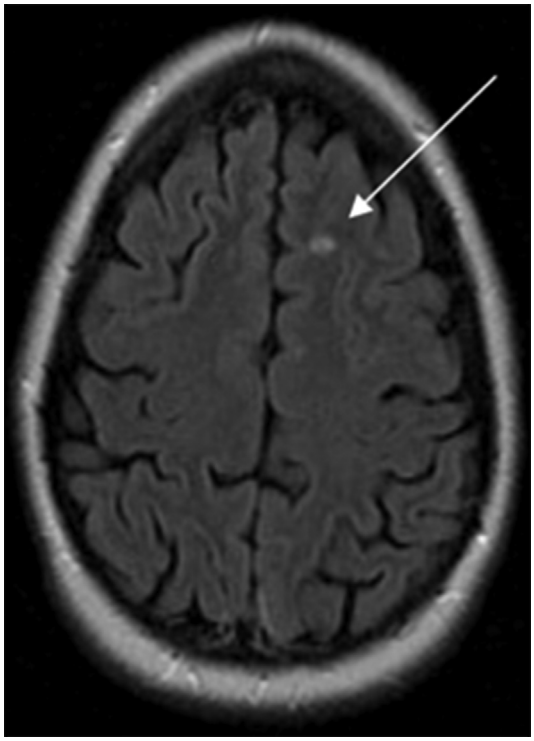

Fig. 5. Brain MR imaging of a patient with frequent migraines who had white matter lesions. *Arrow* identifies white matter lesion visible on FLAIR axial image.

Khessali and colleagues[7] assessed the prevalence of right-to-left shunt in patients with visual aura and evaluated the effect of shunt closure on resolution of aura. The investigators divided the study population into 2 groups, one group with visual aura (n = 225) and the other group as the control (n = 200). The visual aura group was further subdivided into 3 subgroups. Group A (n = 175) consisted of patients who had a history of visual aura that was followed by a migraine headache immediately or within 60 mins. Group B (n = 29) consisted of patients with a history of visual aura and migraine headache that were temporally unrelated (ie, not occurring within 60 mins of each other). Group C (n = 21) consisted of patients with a history of visual aura without a history of headache. In the 3 groups, 168 (96%, $P<.0001$), 21 (72%, $P<.0001$), and 14 (67%, $P<.0001$) patients were positive for right-to-left shunt, respectively. PFO closure was performed in 67 (40%), 8 (38%), and 5 (36%) patients within each group, respectively; and 52% (35/67), 75% (6/8), and 80% (4/5) had complete resolution of visual aura at the 12-month follow-up. The similar distribution of right-to-left shunt in all 3 patient groups and the correlation between PFO closure and improvement of aura suggests a similar pathophysiology between the presence of PFO and the visual aura phenomenon, regardless of whether headache is present in the symptom complex.

In contrast to the findings of the above mentioned studies, Rundek and colleagues[8] conducted a population-based study in which 1101 patients with a history of migraines were evaluated for PFO using transthoracic echocardiography (TTE) with saline contrast and provocative maneuvers and the investigators did not find a significant difference in the prevalence of PFO among

subjects who had migraine compared with those who did not have migraine (14.6% vs 15%). It is important to understand that the frequency of finding a right-to-left shunt highly depends on the type of testing that is performed. TTE has a 40% false-negative rate, TEE has a 10% false-negative rate, and TCD is the most sensitive noninvasive test with a 3% false-negative rate when all 3 studies are compared with a diagnostic right heart catheterization and probing the atrial septum with a guidewire.[9]

The aforementioned studies are summarized in **Table 1**.

RANDOMIZED CLINICAL TRIALS SUGGESTING AN ASSOCIATION BETWEEN MIGRAINE AND PATENT FORAMEN OVALE

The previous studies were all observational and subject to recognized bias of nonrandomized data. The MIST (Migraine Intervention with STARFlex Technology) trial was the first to investigate the effects of PFO closure for migraine in a prospective, randomized, double-blind, sham-controlled clinical trial. Patients who suffered from migraine with aura, experienced frequent migraine attacks, had more than or equal to 2 previously failed classes of prophylactic treatments, and had a moderate or large right-to-left shunt consistent with the presence of a PFO were randomized to transcatheter PFO closure with the STARFlex implant or to a sham procedure. One hundred forty-seven patients were randomized and followed for 6 months. The primary efficacy end point was complete cessation of migraine headache 91 to 180 days after the procedure. No significant difference was observed in the primary end point of migraine headache cessation between implant and sham groups (3/74 vs 3/73, respectively; $P = .51$). The secondary efficacy end point was the frequency of migraine headache days. The reduction in migraine days was not statistically significant. Two hypotheses were developed to explain why the MIST trial did not achieve the expected success and dramatic reduction in frequency of migraine headaches that was described in the observational studies. The first hypothesis stated that the patient population was somehow fundamentally different on a mechanistic or physiologic basis than the patient populations that were treated in the observational studies. The second hypothesis stated that the right to left shunt in the study population was not effectively closed by the particular device used.[10]

The PREMIUM (Prospective, Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Using the AMPLATZER PFO Occluder to Medical Management) trial was a double-blind study investigating migraine characteristics for more than 1 year in subjects randomized to medical therapy and PFO closure with the Amplatzer PFO Occluder device (Abbott Vascular, Chicago) versus medical therapy and a sham procedure (right heart catheterization). Subjects had to have 6 to 14 days of migraine per month, had failed at least 3 migraine

Table 1
Observational studies of the prevalence of migraine in patients referred for PFO closure and the effect of the procedure on migraine

Study	Prevalence of Migraine in Patients Referred for PFO Closure	% Migraine Improved/ Cured Following PFO Closure	Length of Follow-up (mo)
Wilmshurst et al,[32] 2000	21/37 (57%)	86	30
Morandi et al,[33] 2003	17/62 (27%)	88	6
Schwerzmann et al,[34] 2004	48/215 (22%)	81	12
Post et al,[35] 2004	26/66 (39%)	65	6
Reisman et al,[36] 2005	57/162 (35%)	70	12
Azarbal et al,[37] 2005	37/89 (42%)	76	18
Donti et al,[38] 2006	35/131 (27%)	91	20
Anzola et al,[39] 2006	50/163 (31%)	88	12
Kimmelstiel et al,[40] 2007	24/41 (59%)	83	3
Papa et al,[41] 2009	28/76 (37%)	82	12
Khessali et al,[7] 2012	204/590 (35%)	76	12
Total	547/1632 (34%)	80.5	13 ± 7.5

preventive medications, and had a significant right-to-left shunt defined by TCD grade 4 or 5. Of 1653 subjects consented, 230 were enrolled. The primary efficacy endpoint was responder rate (defined as 50% reduction in migraine attacks). The primary endpoint was achieved in 45/117 (38.5%) patients randomized to device and 33/103 (32%) patients randomized to control, failing to show statistical significance ($P = .32$). The secondary efficacy endpoint was reduction in migraine days. The study group experienced migraines less often than the control group and the difference was statistically significant (−3.4 vs −2.0 d/mo, $P = .025$). In addition, 10 of 117 patients (8.5%) who underwent PFO closure had complete migraine remission by 1 year versus 1 (1%) in the control group ($P = .01$). Although the PREMIUM trial did not demonstrate efficacy for PFO closure using the primary endpoint of responder rate, an additional subset analysis was performed that evaluated subjects who had aura as a consistent component of their migraine attacks (aura present in >50% of migraine episodes). For this subgroup analysis, there was a significant difference in the responder rate: 49% (19 of 39) versus 23% (9 of 40) for device versus control group, respectively ($P = .015$). In addition, for subjects with frequent aura, 15.4% (6 of 39) had complete cessation of their migraine attacks versus 2.5% (1 of 40) in the control group ($P = .04$). The potential benefit in a minority of migraine patients suggests a need to further investigate populations who are more likely to benefit from PFO closure than the medication refractory population.[11] It is expected that future trials will focus on PFO closure in a more select patient population of migraine with frequent aura.

The PRIMA (Percutaneous closure of patent foramen ovale in migraine with aura) trial was a multicenter, prospective, randomized, open-label international trial that evaluated if percutaneous PFO closure was effective in reducing migraine headaches in patients with migraine with aura that were refractory to medical treatment. Participants had to be diagnosed with migraine before the age of 50, had to experience more than or equal to 3 migraine attacks or more than or equal to 5 migraine headache days per month and less than 15 migraine days per month over the 3 months preceding enrollment, and had to be unresponsive to 2 commonly prescribed preventive medications. Of 705 subjects screened over a 90-day screening period involving 3 screening visits, 107 were enrolled. The enrolled patients were subsequently randomized 1:1 to either percutaneous PFO closure (n = 53) or medical management (n = 54) and then followed for 12 months. Of note, within 14 days of randomization, both groups were given acetylsalicylic acid 75 to 100 mg/d for 6 months and clopidogrel 75 mg/d for 3 months. The primary efficacy endpoint was reduction in monthly migraine days during months 9 to 12 after randomization compared with months 1 to 3 before randomization. Although the PFO closure group experienced less migraine days per month than the control group, the difference was not significant (−2.9 vs −1.7 days, respectively, $P = .17$). The secondary efficacy endpoint was average reduction in migraine attacks and although the PFO closure group experienced less migraine attacks than the control group, the difference was not significant (−2.1 attacks vs −1.3 attacks, respectively, $P = .097$). Four of forty patients (10%) in the PFO closure group were completely free of migraine attacks during months 10 to 12 compared with 0 of 41 patients (0%) in the control group but this was not significant ($P = .055$). Neither antiplatelet agent had significant influence on headache days. Although the PRIMA trial failed to show that PFO closure significantly reduced overall monthly migraine days compared with ongoing medical management in patients with refractory migraine with aura and PFO, a post hoc analysis focusing solely on migraines with aura showed that the number of migraine with aura days and migraine with aura attacks were markedly reduced in the PFO closure group compared with controls (−2.4 vs −0.6 days, respectively, [$P = .0141$] and −2.0 vs −0.5 attacks, respectively, [$P = .0003$]). In addition, 16 of 40 patients (40%) in the PFO closure group were completely free of migraine attacks with aura compared with 4 of 40 patients (10%) in the control group ($P = .004$). These latter findings support the hypothesis that PFOs play a major role in pathogenicity for migraine with aura. In stroke, the ROPE score is used to determine if a PFO is stroke related or incidental. Similarly, it is theorized that the presence or absence of aura can resolve the question of incidental versus pathogenic PFO. Limitations to the trial include lack of blinding of the PRIMA patients, premature termination of the study by the sponsor due to slow enrollment, due to slow enrollment, lack of a sham intervention, and failure to completely abolish the right-to-left shunts in 12% of the PFO closure group.[12]

ASSOCIATION OF PATENT FORAMEN OVALE, MIGRAINE, AND CRYPTOGENIC STROKE

People who have migraine headache, especially migraineurs with aura, have an increased risk of cryptogenic stroke.[13] Cryptogenic stroke, or stroke of unknown cause, is a diagnosis of

exclusion after standard causes of stroke have been ruled out by an extensive workup. This definition typically applies to people younger than 60 years, above which it is assumed that atherosclerosis is present and is the most likely cause of the stroke. The origin of the thrombus is usually not found unless a peripheral deep vein thrombosis is present. It is hypothesized that one cause of cryptogenic stroke is a venous thrombus, perhaps from peripheral or pelvic varicose veins, that bypasses the lungs via a PFO and enters the arterial circulation. Occasionally, this paradoxic embolism can be documented by echocardiography when a large thrombus trapped in a PFO (**Fig. 3**). The venous clots that produce cryptogenic stroke are usually less than 3 mm in diameter. However, once the clot passes to the brain, it is not possible to prove how it got there.

According to a meta-analysis of 6 case-control studies, the relative risk (RR) of ischemic stroke for migraine with aura and migraine without aura are 2.3 and 1.8, respectively. The RR of ischemic stroke in women with migraine using oral contraceptives is increased to 8.7, suggesting that women with migraine should not take oral contraceptives.[14] One study in the Netherlands used MR imaging to assess 134 patients who had migraine without aura, 61 patients who had migraine with aura, and 140 matched controls. Although the total percentage of patients with an ischemic infarct was not increased in migraineurs versus controls (5% vs 8.1%), when the data were analyzed by vascular supply, there was an increased incidence of posterior circulation infarcts in migraineurs with aura (8.1% vs 0.7%).[15]

In Iceland, the Age Gene/Environment Susceptibility (AGES) – Reykjavík study prospectively observed 4689 people for an average of 25 years and then performed a brain MR imaging. Migraine was present in 12.2% of the participants and 63% of this subgroup was identified as having migraine with aura. Patients who had migraine with aura had an increased risk of subsequent infarct lesions on MR imaging (OR 1.4; 95% CI 1.1–1.8). However, because the study did not assess for the presence of right-to-left shunting, we do not know the relative frequency of PFO in those migraineurs who developed stroke versus the migraineurs who did not develop a stroke.[16]

According to the initial theory of migraines and aura, it was believed that migraine was "a vascular headache" due to ischemia caused by intense arterial vasospasm. It was also thought that if the arterial constriction was prolonged and severe enough, a cerebral infarct could ensue. Over time, the understanding of the cause of migraine has changed. Several lines of evidence, including functional MR imaging, PET imaging during migraine, and gene insertion studies of familial migraine with hemiplegia in mice, demonstrate that migraine is initiated by vasodilation and then vasoconstriction (not the converse), but the severity of decreased flow is about 25%, which is not sufficient to induce an infarct. The current theory is that migraine represents neurovascular dysfunction associated with allodynia (painful response to any stimuli) involving multiple areas within the brain. The transient neurologic deficits, manifested as aura, are due to a spreading wave of depolarization over the cerebral cortex (cortical spreading depression [CSD]) that starts in the occipital area and progresses over the sensory and motor cortex at 2 to 3 mm/min. The aura sequence corresponds to the timing of the CSD and usually lasts 20 minutes. The question remains, why is there a higher prevalence of stroke in migraineurs? One possibility is that there is an association of migraine with accelerated atherosclerosis, but there has never been any evidence to demonstrate this metabolic hypothesis.

The prevalence of migraine headache in people who present with cryptogenic stroke is approximately 30% to 50%. Both migraine with aura and cryptogenic stroke are associated with a higher frequency of PFO. So, in people with migraine headaches who develop stroke, what is the frequency of right-to-left shunting? Wilmshurst and colleagues[17] demonstrated that the prevalence of a right-to-left shunt in patients with a history of migraine with aura who had a stroke (84%) was significantly greater compared with patients with a history of migraine with aura but no history of stroke (38.1%, $P<.001$), patients without a history of migraine who had a stroke (55.6%, $P<.05$), and population controls (12.2%, $P<.001$). In addition, the prevalence of right-to-left shunt in patients with a history of migraine without aura who had a stroke (75%) was also significantly greater compared with patients who had migraine with aura but no history of stroke (38.1%, $P<.05$) and population controls (12.2%, $P<.001$). This observation led to the theory that the increased frequency of stroke in migraineurs is due to the presence of a PFO for both conditions: the PFO is the pathway through which the migraine with aura is chemically triggered and also increases the likelihood of having a paradoxic embolism pass from the venous side to the brain.

This theory is also consistent with the higher risk of stroke in migraineurs who are on birth control pills or hormone replacement therapy.[18] Estrogen increases the risk of venous thrombosis. If a PFO is present, as suggested by the history of migraine with aura, it is possible that a venous thrombus,

induced by the addition of estrogen, may permit a paradoxic embolism to occur and result in a cryptogenic stroke. If this hypothesis can be confirmed, the next step would be evaluation of prophylactic closure of PFO in a randomized trial to test whether it is an effective method of treatment for prevention of stroke in migraineurs. However, this type of study would be difficult to perform as the absolute risk of stroke in migraineurs is small. Therefore, a large number of patients would need to be treated with PFO closure and followed-up over many years to show an effect.

Between January 2008 and November 2017, the UCLA Comprehensive Stroke Center identified 712 patients with ischemic stroke; 127 patients (18%) were diagnosed as having a cryptogenic stroke. Of these, 68 patients had adequate testing for PFO and a documented migraine history. Of the 34 patients with both cryptogenic stroke and migraines, 27 (79%) had a PFO. Of the 15 patients with cryptogenic stroke and migraine with frequent aura, 14 (93%) had a PFO. Of the 34 patients with cryptogenic stroke but without a history of migraines, 20 (59%) had a PFO. The difference in prevalence of PFO between patients with cryptogenic stroke with migraine, with migraine with aura, and without migraine was statistically significant ($P = .042$). When compared with a control general population of 200 people where the prevalence of PFO was 18%, patients with cryptogenic stroke with or without migraine had significantly greater prevalence of PFO ($P<.00001$ and $P<.00001$, respectively).[13] These observations suggest that the majority (60%) of cryptogenic strokes are associated with a PFO and that the strokes that occur in migraineurs with aura are almost always associated with a PFO.

ASSOCIATION OF MIGRAINE AND FLOW RATE ACROSS A PATENT FORAMEN OVALE

A retrospective study in 142 migraine subjects looked at the relationship between the degree of right-to-left shunt and visual aura. Eighty-two (58%) subjects were classified into the frequent aura (aura present in >50% of migraine attacks) group, and 60 (42%) were classified into the occasional ($\leq$50%) or no aura group. The degree of right-to-left shunt was measured by TCD using the Spencer Logarithmic Scale, which assigns a score of 0 to 5, with grade 3 or higher considered as a positive result representing a significant right-to-left shunt. TCD Spencer grade in the frequent aura group was significantly greater than that in the occasional or no aura group both at rest and post-Valsalva (3.2 ± 1.4 vs 2.1 ± 1.6, $P<.001$ for rest; 4.3 ± 1.0 vs 3.8 ± 1.3, $P = .009$ for post-Valsalva). Therefore, migraineurs who have frequent visual aura have a greater degree of right-to-left shunt than migraineurs with infrequent visual aura.[19] This observation that the degree of right-to-left shunting affects the frequency of migraine aura demonstrates that there is a dose-response effect between PFO flow and aura frequency.

MIGRAINE AND CEREBRAL WHITE MATTER LESIONS

Migraineurs have a higher frequency of white matter lesions (WML) in the brain detected by MR imaging.[20] WML are usually 2 to 5 mm hyperintense signals appearing on FLAIR or T2 sequences that are secondary to axonal degeneration, gliosis, and demyelination believed to be the result of microvascular ischemia (see **Fig. 5**). WML can be detected anywhere along the white matter tracts of the cerebrum, cerebellum, and the brainstem. WML appear similar to lesions found in multiple sclerosis, vasculitis, and lacunar strokes. It is not clear why migraineurs should have a higher incidence of WML, but the assumption has been that migraine produces vascular constriction and ischemia that could damage the axonal myelin. A second possibility is that migraine stimulates a metabolic process that is detrimental to the myelin sheath.

In one study from France, 1643 individuals older than 65 years had WML on MR imaging and were followed-up for 5 years. The risk of developing a subsequent stroke in these patients was directly correlated with the volume of the WML and was 5 times higher for the highest quartile of WML volume. However, the presence of WML did not predict other cardiovascular outcomes, suggesting that the pathophysiology of WML may be different from large vessel atherosclerosis.[21] The presence of a PFO was not assessed in this population.

Another theory for the presence of WML in migraineurs is ischemic insult associated with a right-to-left shunt due to embolic material such as platelet clumps that could bypass filtration in the lungs and enter the cerebral circulation. An Italian group headed by Carlo Vigna conducted an observational study of 82 patients, all of whom had a PFO, severe migraine, and WML on MR imaging. All 82 patients were offered PFO closure and 53 patients elected to undergo a PFO closure procedure. In the subjects who had their PFO closed, the number of migraine attacks was reduced from 32 ± 9 in the 6 months before closure to 7 ± 7 in the 6 months after closure ($P<.001$). In the 29 subjects who elected not to

undergo PFO closure, there was no significant reduction in migraines (from 36 ± 13 to 30 ± 21). This study suggests that migraineurs with WML may identify a group that is particularly sensitive to PFO closure. It also suggests that in some people, the presence of a PFO could be causally related to WML. However, it is unclear whether this is because PFO is casually related to migraine, or whether the WML are a sign of greater responsiveness to PFO closure.[22] In addition, this was an observational study and not a randomized trial.

Data supporting this hypothesis have been conflicting. Bosca and colleagues[23] imaged 44 migraineurs with and without aura; 29 patients (66%) had WML but only 7 of the 29 (24%) patients with WML had a right-to-left shunt. This suggests either that there are multiple causes for WML in migraine or that right-to-left shunting is unrelated to WML. Del Sette and colleagues[24] conducted a similar study with 80 patients and arrived at the same conclusion.

In support of the theory that migraine produces WML is the observation that migraineurs without a PFO have a high incidence of WML on MR imaging.[23,24] But WML also are present in people with PFO who do not have migraine. This is a difficult area to study, because there is an increase in WML with increasing age, so that comparison studies need to adjust for the age of the subjects. In addition, it is difficult to obtain a control population of people who are asymptomatic but have had a brain MR imaging. There are several open-access repositories of brain MR imaging in a normal population.[25] The prevalence of WML per decade was looked at in subjects with a known right-to-left shunt versus this control general population (Yasufumi Kijima, MD and Jonathan M. Tobis, MD, unpublished data, 2016). There were 397 subjects who had a documented right-to-left shunt using TCD with bubble contrast who underwent brain MR imaging. These subjects were then divided into migraineur (N = 244) and non-migraineur (N = 153) groups. Between 20 and 60 years of age, in nonmigraineurs with a right-to-left shunt, WML were more prevalent compared with age-matched controls. However, in people aged 60 to 80 years, the incidence of WML in non-migraineurs with known right-to-left shunt was no greater than that of the general elderly population. Within each 2 decade age group of migraineurs with a right-to-left shunt (group A), nonmigraineurs with a right-to-left shunt (group B), and the control subjects (group C), WML were more prevalent in migraineurs versus controls in 2 age groups: 20 to 39 years (27% vs 13% vs 10%, $P<.01$) and 40 to 59 years (58% vs 47% vs 30%, $P<.001$). However, WML were also more prevalent than controls in the group with a right-to-left shunt but without migraine in the 40 to 59 year olds. This observation suggests that both migraine without a right-to-left shunt and a right-to-left shunt without migraine may predispose to the development of WML. The results of prior studies may vary if they did not take into account the age of the subjects.

One concern regarding the presence of WML is the long-term consequences. To date, WML have been linked to strokes, cognitive impairment, and dementia but some of these links have conflicting evidence. In regard to stroke, a 2010 meta-analysis of 12 studies looking at the association of white matter hyperintensities with risk of first ever stroke demonstrated a significant association between the 2 (hazard ratio [HR] 3.3, 95% CI: 2.6–4.4, $P<.001$).[26] Furthermore, a pooled population-based analysis of the Atherosclerosis Risk in Communities Study and Cardiovascular Health Study (CHS), which followed 4872 clinically stroke-free individuals over a median of 13 years, demonstrated that greater MR imaging–defined burden of WML was a risk factor for spontaneous intraparenchymal hemorrhage ($P<.0001$).[27] In regard to cognitive impairment, a study looking at 67 American participants with normal cognition found that high baseline WML was related to the risk of progression to mild cognitive impairment (MCI) (HR 3.3; 95% CI 1.33–8.2, $P = .01$) but the Framingham Offspring Study, which observed 1694 participants for a mean duration of 6.2 years, showed that the volume of WML was associated with risk of MCI only in those aged 60 years or older (OR 1.49, 95% CI: 1.14–1.97, $P<.05$).[28,29] Lastly, other studies, showed that the burden of WML was significantly associated with an increased risk of dementia.[29,30]

THE PATHWAY FORWARD

Although observational studies have shown that migraineurs with aura respond well to PFO closure, randomized trials have not confirmed this. Until a randomized double-blinded study clearly demonstrates a significant benefit of PFO closure to reduce migraines, medical therapy will remain the treatment of choice for migraines. One challenge in conducting such a study is adequate patient recruitment in a timely fashion given strict inclusion criteria. For example, a large number of patients who were screened for MIST II were excluded because the number of headache days exceeded the upper cutoff for the trial. Another challenge is finding patients with similar clinical characteristics to those who benefitted from PFO closure in the observational studies. Often, these patients presented with migraine

and frequent aura or cryptogenic stroke. Another proposal has been to enroll patients who respond to antiplatelet therapy.[31] The authors are optimistic that a future randomized trial of PFO closure to reduce migraine will identify the correct patient subset, and PFO closure will become part of the treatment options for people who suffer from migraine.

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