Migraine is a primary chronic-intermittent headache disorder that affects ~12% of the population, with women being 3 to 4 times more likely to have migraine than men at any given age.1 Migraine typically starts before age 40, and its 1-year prevalence peaks in midlife. The pain character is moderate to severe and of pulsating quality, and headache attacks are accompanied by various combinations of gastrointestinal, autonomic nervous system dysfunction, as well as sensitivity to light and sound. In some patients, transient neurological symptoms occur that mostly involve the visual field and include flickering light, light spots or lines, or partial vision loss but can also involve the sensory or motor system. These symptoms, known as migraine aura, usually last for <30 minutes and affect as many as one third of migraine patients. The pathophysiology of migraine has been explored in detail, and it is known that a dysfunction of brain cells and brain arteries is a major component of this disorder.2

In recent decades, migraine, and specifically migraine with aura, has been consistently associated with increased risk of ischemic stroke, particularly among young women.3–6 Despite several hypotheses, the mechanisms explaining this association are not fully understood.7 Because patent foramen ovale (PFO) can be a cause of ischemic stroke among young individuals, it has been suggested that this congenital heart defect may be involved in the association between migraine with aura and ischemic stroke.

PFO is an often-asymptomatic condition that is present in ~25% of the general population, and at first glance migraine and PFO have little in common. In recent years, however, several clinic-based case-control studies have suggested that PFO is more common among individuals with migraine with aura and that migraine with aura is more common among individuals with PFO.8–12 This suggestion has led to speculations that PFO might be linked causally with migraine with aura. Specifically, it has been suggested that the right-to-left shunt may serve as a conduit for the passage of particulate or humoral factors from the venous to arterial circulation, which then, in a predisposed individual with migraine, could serve to trigger an attack. It can be envisioned that such a mechanism either induces cortical spreading depression, a neuronal depolarization wave that is likely the cause of the migraine aura,2 or another mechanism leading to migraine with aura.7,11

The potential association between migraine with aura and PFO has stimulated immense interest, and several observational studies, as well as randomized clinical trials, have been initiated investigating whether PFO closure leads to reduced migraine attack frequency and migraine burden. Indeed, several observational studies have reported beneficial associations with reduction in the number of attacks or complete disappearance of migraine in 70 to 80% of patients.11 On the basis of these results, hope was high that the Migraine Intervention with STARFlex Technology (MIST) trial would confirm these potential benefits from observational studies. In this trial, 147 patients were either randomized to transcutaneous PFO closure with the STARFlex device or a sham procedure and then followed up for six months. The results, however, which have been published recently in Circulation, were negative and showed no benefit for the primary outcome, cessation of migraine headache.13 In exploratory secondary analyses, the implant group had a greater reduction in total headache days (difference of 1.3 days over the 6-month period), but the implant group also experienced more procedural serious adverse events. Several methodological and design-related issues relative to the MIST trial have been previously discussed in detail in Circulation.14 Differences in applied analytic methods could also explain the apparent difference in the results of the observational studies compared with those of MIST. The evaluation of intervention or treatment effects in observational research is challenging. In particular, selection of patients who receive or who do not receive treatment or use of analytic methods that implicitly or explicitly focus on specific target populations must be carefully considered.15 In addition, the role of a placebo effect is difficult to address, an effect that seems particularly high in treatment studies among patients with migraine.16

In the current issue of Circulation, Rundek and colleagues provide the first population-based data on the association between migraine and PFO.17 They use data from the Northern Manhattan Study (NOMAS), an ongoing cohort of individuals living in northern Manhattan. A total of 1101 stroke-free individuals were evaluated by transthoracic echocardiography with provocative maneuvers for the presence of PFO, and migraine was ascertained by standardized questionnaires that were adapted using Second International Head-
ache Society criteria.18 The prevalence of PFO did not differ according to migraine status (14.6% among individuals with migraine and 15.0% among those without; adjusted odds ratio 1.01, 95% confidence interval, 0.63 to 1.61), and the conditions coexisted in only 2% of individuals. Although the prevalence of PFO among individuals with migraine with aura was somewhat higher than among those with migraine without aura (19% versus 11%), the difference was not statistically significant (P = 0.42). The lack of association between migraine and PFO was not modified by age or gender in the study population.

How can this finding be interpreted when contrasted with the evidence from many case-control studies that have suggested an association between migraine with aura and PFO? Several reasons for the contrast should be considered, including differences in study design, potential modifying effects of specific factors, and remaining issues in studying comorbidities of migraine with aura. In case-control studies of the association between migraine and PFO, individuals are selected on the basis of having or not having migraine followed by an evaluation of PFO (or vice versa). In this context, it is specifically problematic to select an appropriate control population, which should provide an estimate of the baseline prevalence of PFO or migraine. Often, control populations are considerably healthier or have conditions associated with PFO or migraine, which can lead to potential selection, recall, or measurement bias. Only population-based studies like NOMAS, in which individuals have not been selected on the basis of migraine or PFO status, can avoid most of these biases. Thus, population-based studies are considered the best evidence in observational research to establish an association of interest. In that regard, the results of NOMAS can be seen as the strongest evidence against an association between migraine or migraine with aura and PFO.

The difference in the results from NOMAS and those from previous studies could, however, also be an indication that the association between migraine with aura and PFO is limited to subgroups of individuals with migraine with aura. For example, the age distribution of participants in NOMAS was older (mean age 69) compared with the age distribution of the previously published case-control studies. Thus, one could speculate that a potential association between PFO and migraine with aura may be limited to younger individuals. Interestingly, effect modification by age has been described for the association between migraine with aura and ischemic stroke, indicating increased risk specifically for younger age groups.5 It has further been shown that the association between migraine with aura and ischemic stroke is particularly strong for women who smoke and/or use oral contraceptives.4,6,19 Recent evidence further suggests that this association is limited to individuals with a lower vascular risk profile6,20 and to individuals who carry a specific genotype.21,22 Thus, it may be plausible that the association between migraine with aura and PFO may also be limited to specific subgroups.

Migraine and migraine with aura are very heterogeneous disease entities, a fact that is important to consider when studying associations with comorbid conditions or treatment effects among these patients. Specifically, primary migraine with aura should be distinguished from symptomatic or secondary forms of migraine with aura. Secondary forms of migraine with aura are less common than the primary form and can be caused by other chronic disorders, such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) or mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). Further, an attack of migraine with aura can be induced by a cerebral ischemic event.7 It can thus be envisioned that in some patients migraine with aura is secondary to PFO.

So, where do we stand? First, results from clinic-based case-control studies linking migraine with PFO have a low grade of available evidence23 and are in contrast to the lack of association from population-based data in NOMAS.17 Second, we are lacking evidence that patients with migraine with aura who have PFO are at particular increased risk of ischemic stroke; recent data do not support a significant association.6 Third, low-grade evidence from observational studies23 and the negative results of MIST do not support PFO closure as an effective treatment of migraine. Thus, detection of PFO or PFO closure should not be recommended to patients who only have migraine. It is, however, plausible that PFO may affect specific subgroups of patients with migraine, and future studies identifying and targeting such subgroups are warranted; many such studies are currently under way. Although interesting potential associations exist between migraine with aura and the heart, migraine remains primarily a matter of the brain.

Disclosures

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