

# Cardioembolism as the unsuspected missing link between migraine and ischemic stroke

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First identified in 1975, the relationship between migraine and stroke has received considerable attention.<sup>1</sup> Forty years later, solid evidence indicates that those with migraine have a 1.5-fold to 2.5-fold increased risk of stroke.<sup>2–4</sup> However, the strength of this relationship varies based on the subtypes of migraine (with vs without aura) and stroke (hemorrhagic vs ischemic). While the majority of data support an increased risk of ischemic stroke in those with migraine, the association between migraine without aura and ischemic stroke seems weaker and more controversial, possibly due to methodologic heterogeneity across studies.<sup>2,3</sup>

In this issue of *Neurology*®, in a collaboration based on the cohort from the Atherosclerosis Risk in Communities (ARIC) study, Androulakis et al.<sup>5</sup> report findings regarding potential mechanisms implicated in the increased risk of ischemic stroke in migraineurs, opening a new and exciting door to future research in the field. This prospective, longitudinal, community-based cohort study comprised 12,758 participants without a stroke history, who were followed prospectively between 1993–1995 and December 2012. The main outcome was incident ischemic stroke occurring during the 20-year follow-up period.

Overall, the study has 2 thought-provoking findings. First, the authors substantiated an increased risk of ischemic stroke in this cohort of predominantly older migraineurs with aura. Second, and most interestingly, migraine with visual aura was associated with cardioembolic ischemic stroke but not with ischemic stroke caused by other mechanisms.

The study showed an increased adjusted risk of ischemic stroke in a cohort of patients with migraine with visual aura after adjustment for a large number of relevant covariates in Cox proportional hazards models (hazard ratio 1.7). No association with ischemic stroke risk was found for migraine without aura. Although a substantial proportion of patients continue to have migraine with advancing age, the prevalence for migraine peaks between the ages of 18 and 49 years.<sup>6</sup> As acknowledged by the authors, all

participants were older than 44 years at enrollment, and the mean age of the study cohort was 59 years. Thus these findings are not generalizable to those with migraine in general, but more specific to older migraineurs. Rather than being a limitation, this distinctive quality of the study cohort serves to illuminate the relationship between migraine and stroke in older segments of the population, where uncertainty exists and stroke risk is greatest.<sup>7,8</sup>

In addition, this study demonstrated that migraine with visual aura was associated with increased risk of cardioembolic ischemic stroke (hazard ratio 3.7) but not with other types of ischemic stroke. The authors suggest that this association could hypothetically be explained, at least in part, by paradoxical embolization through undiagnosed patent foramen ovale (PFO). While possible, this seems less likely, given that PFO was not considered as a definite cardioembolic source in this study. Indeed, cardioembolic sources were predefined as valvular heart disease, atrial fibrillation or flutter, acute or recent (within 4 weeks) myocardial infarction, cardiac procedures, intracardiac thrombus, or bacterial endocarditis. As a result, the association between migraine with visual aura and cardioembolic ischemic stroke is likely best explained by the latter sources of cardioembolism rather than by PFO itself. Notably, if the authors had considered PFO as a potential cardioembolic source in this study, the association between cardioembolic stroke and migraine with visual aura could have been regarded as spurious. PFO is common in migraine patients<sup>9</sup> (possibly a bystander), and its role as a cause of ischemic stroke in patients older than 55 years is exceedingly controversial.<sup>7,10</sup> Thus, excluding PFO from the list of prespecified cardioembolic sources was judicious and constitutes a strength of this study.

In contrast to the ARIC study, no association was found between migraine and cardioembolic stroke in the Oxford Vascular Study (OVS).<sup>7</sup> Furthermore, migraine was twice as frequent in cryptogenic strokes compared to cardioembolic events. Disparities between results from both studies may be due to

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methodologic differences. While in the ARIC study there were only 3 mechanisms of ischemic stroke,<sup>5</sup> the OVS encompassed 6 subtypes: cardioembolic, large artery disease, small vessel disease, multiple causes, other causes, and cryptogenic.<sup>7</sup> In addition, the population demographics (e.g., mean age: ARIC 59 years, OVS 73 years) and the considered covariates differed across these studies.

While intriguing, the results of this study need further confirmation, and debate will likely focus on which specific cardioembolic mechanisms are related to migraine. As a detailed systematic collection of data regarding cardioembolic sources was lacking, the relative frequency of each cardioembolic source in this study remains unknown. However, as mentioned by the authors, atrial fibrillation emerges as a foreseeable stroke mechanism associated with migraine. Migraine and atrial fibrillation share pathophysiologic pathways, including autonomic dysfunction. Accordingly, migraine could possibly trigger paroxysms of atrial fibrillation, or vice versa, ultimately leading to increased risk of ischemic stroke.<sup>11,12</sup> Should this be the case, ischemic stroke patients with migraine may warrant a more thorough screening for atrial fibrillation.

Despite the questions remaining, the current findings provide exciting evidence that cardioembolic events may play an important role in the association between migraine with aura and ischemic stroke, and provides important insight and direction for future research.

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