Migraine With Aura and Ischemic Stroke
Which Additional Factors Matter?

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See related article, pages 2438–2445.

Migraine with aura has been consistently associated with increased risk of ischemic stroke. Most studies suggest that this association is particularly strong for younger women. Although several potential biological mechanisms have been proposed to explain the migraine-stroke association, the precise mechanisms remain unknown. Because migraine is particularly prevalent in an age group in which ischemic stroke, even among migraineurs with aura, is very rare, it seems likely that factors in addition to migraine with aura must be present to lead to an increased risk of stroke.

In this issue of Stroke, MacClellan and colleagues evaluate several additional features that may help to identify patients with migraine with aura who are at particular increased risk of ischemic stroke. In this population-based case-control study of 386 women aged 15 to 49 with a first-ever ischemic stroke event and 614 age and ethnicity-matched controls, migraine and visual aura symptoms were ascertained using a standardized headache questionnaire. Participants could be classified into patients with probable migraine with visual aura (PMVA), probable migraine without visual aura, and patients without migraine. Compared with nonmigraineurs, women with PMVA had increased risk of ischemic stroke (odds ratio 1.5; 95% CI, 1.1 to 2.0). This association attenuated slightly when adjusting for potential stroke risk factors. Consistent with many other studies, migraineurs without aura were not at increased risk of ischemic stroke.

Before discussing additional factors that may increase this observed risk, some methodological considerations should be taken into account when interpreting the results of this study. Most importantly, the prevalence of PMVA among the controls is high (29%). This may be explained by the method used to assess migraine and visual aura and/or by a higher likelihood of migraine patients to participating as control subject in the study. These potential nondifferential biases would likely result in an underestimation of effect, which indicates the need for appropriate caution in the interpretation of null findings and may explain the somewhat diminished association between migraine with aura and stroke compared with other studies. Furthermore, one has to keep in mind that information about migraine was ascertained after a stroke event. This is noteworthy because, besides the possibility of recall bias, migraine attacks can be induced by cerebral ischemia or ischemic strokes can present with migraine attacks.

MacClellan and colleagues evaluated whether migraine severity, frequency, and length of migraine duration further increase the risk of ischemic stroke among women with PMVA. More severe PMVA attacks were not associated with increased risk of ischemic stroke. However, women who reported PMVA >12 times per year had increased risk of ischemic stroke. Moreover, a lifetime duration of <1 year (before the stroke event) was associated with further increased risk.

For more than 3 decades, there has been a debate over whether oral contraceptive use and/or smoking among migraineurs further increases the risk of ischemic stroke. The data by MacClellan and colleagues suggest that neither oral contraceptive use nor smoking alone substantially increased the odds ratio of ischemic stroke among women with PMVA. However, the combination of both resulted in a 10-fold increased risk of ischemic stroke when compared with women without migraine who did not smoke and did not use oral contraceptives, which is consistent with previous observations. Because of the potential underestimation of effect, the data by MacClellan and colleagues do not provide conclusive evidence that oral contraceptive use does not further increase the risk of ischemic stroke among women with migraine with aura. However, the data strongly indicate that women with migraine with aura who use oral contraceptives should be strictly advised to quit smoking.

There are further notable results of the study. First, although limited by small numbers, the presence of a patent foramen ovale did not substantially increase the risk of ischemic stroke among women with PMVA, indicating that this congenital heart disease is unlikely to explain a large amount of the migraine-ischemic stroke association. Second, with regard to ischemic stroke subtypes, the proportion of lacunar infarction and ischemic stroke of undetermined origin but not atherosclerotic and cardioembolic strokes was higher among women with PMVA. This pattern differs from nonmigraine stroke patients in whom the two latter subtypes are more common. In addition, there was no anatomic predilection of infarcts, which is consistent with findings from a large prospective cohort study but in contrast to others.

In summary, the data of MacClellan as well as the data of others suggest that the migraine-ischemic stroke association...
is modified by several factors, including migraine frequency and duration, and that potential biological mechanisms are likely complex. Many issues, however, remain unclear and future research is warranted to identify subgroups of patients with migraine with aura who are at particular increased risk of ischemic stroke. When considering potential consequences for migraineurs with aura, one has to keep in mind that very few of these patients are at high risk for ischemic stroke. There is, however, consistent evidence that smoking substantially increases the risk of ischemic stroke among young women with migraine, in particular if they additionally use oral contraceptives. Recommendations for such patients not to smoke have long been available. The data from this important study by MacClellan and colleagues, however, underscore that continued efforts are needed to communicate this scientific finding to patients.

Disclosures
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