Migraine makes the stroke grow faster?

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Long associated with increased incidence of stroke,[1,2] migraine has been linked with mechanisms involving the vasculature (vasospasm, arterial dissection, endothelial dysfunction, venous thrombosis), heart (patent foramen ovale), and blood (hypercoagulability).[3] Since cerebral ischemia can induce cortical spreading depression, the physiologic process underlying aura, migraine with aura may theoretically represent a TIA equivalent in a subset of people. In addition to the heightened occurrence of stroke in migraineurs, a growing body of evidence suggests more dire consequences when stroke occurs, with experiments in mice with the familial hemiplegic migraine mutation showing hastened and larger infarct size.[4]

In this issue of *Neurology*®, Mawet et al.[5] investigate the hypothesis that history of migraine predisposes to faster infarct growth through a case-control design of persons with stroke, including chart documentation of migraine status and MRI within 72 hours of the stroke. The primary cohort included 2 groups: 45 migraineurs (11 with aura) and 27 controls. The authors determined the degree of recruitment of the ischemic penumbra into the infarct core by calculating diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) MRI lesion volumes. They then compared the proportion of persons in each group with no-mismatch, a pattern presumed to represent completed stroke. They defined no mismatch as DWI lesion volume >83% of PWI lesion volume. In this study, migraine, particularly migraine with aura, more frequently showed the no-mismatch pattern, even when adjusted for time to MRI. This suggests accelerated loss of viable tissue at risk, as shown in the migraine mouse model.[4] Important clinical implications include that migraineurs have a shorter therapeutic window with acute stroke, and that migraine prophylaxis, by raising the threshold for spreading depolarization, may lower the tissue at risk during stroke.

The study has several limitations beyond the small sample size. The retrospective design may bias diagnosis of migraine and its subtypes. MRI equipment and software may have changed during the 11-year recruitment period. Exclusion of small lesions may create bias, since some data show a higher proportion of lacunar strokes in migraineurs.[6]

Perhaps the most important limitation of this study, however, is that it provides only a snapshot of evolving stroke at a given moment. Interpretations of that picture may vary and have important ramifications on the clinical implications of the findings. The greater proportion of no-mismatch in the migraine group may result, as the authors posit, from increased tissue demand in even moderately oligemic tissue, thus predisposing incorporation of the penumbra into the ischemic core. Alternatively, the smaller penumbra-to-core ratio in migraineurs may reflect more robust compensatory mechanisms to circulatory dysfunction, thus putting less tissue at risk from the outset. Findings that mice preconditioned with transient ischemia show increased ischemic tolerance to induced stroke, and consequently, decreased brain damage support this line of thinking.[7] Although final lesion size was not reported by the authors, a preliminary report by another group of clinical investigators demonstrated an association between history of migraine aura and (3-fold) larger infarcts.[8] This supports the authors' interpretation of malignant ischemic progression in migraine. Furthermore, recent experiments in mice showing that chronic treatment with medications used in migraine prophylaxis (topiramate, lamotrigine) decreased susceptibility to spreading depression and improved tissue and neurologic outcomes.[9]

The finding that only 22% of those in the migraine group exhibited no-mismatch on MRI suggests that there are influences other than migraine that predispose to this pattern. Identifying the clinical and genetic factors rendering this sizable subset more vulnerable to ischemia and testing treatments for prevention will be important goals of future investigations.

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