Blood Vessels, Migraine, and Stroke

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See related article, pages 3145–3151.

The relation between migraine and stroke has been well recognized and has been the focus of several publications.1–3 Despite many hypotheses linking the 2 disorders, the precise mechanisms are unknown, and not surprisingly very complex. In this issue of Stroke, Pezzini and colleagues4 add to this complexity by suggesting that migraine with aura may “mediate” the influence of specific genotypes on stroke risk. How might this interesting association come about biologically? At the present time, we don’t know. Investigators believe that migraine is a complex genetic disorder5 in which multiple genes confer a small stroke risk burden together with a large impact from environmental events such as stress. However, genes responsible for causing common migraine subtypes such as migraine with and without aura are unknown as of this writing; therefore, it remains obscure whether a genetic component is involved in the link between migraine and stroke, and hence the study by Pezzini and colleagues is of particular interest.

The methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism constitutes an interesting target to further evaluate the biological link between migraine and stroke. MTHFR catalyzes the conversion of 5,10 methylene tetrahydrofolate into 5-methyl-tetrahydrofolate, the predominant form of folate within blood. Folate is used in multiple biochemical pathways including replication of DNA, metabolism of homocysteine as well as other methyl transfer reactions. The MTHFR C677T gene polymorphism has been associated with migraine in some6,7 but not all studies8,9 and is associated with an increase in homocysteine, a stroke risk factor causing endothelium dysfunction.10,11 Pezzini and colleagues investigate whether the MTHFR polymorphism and migraine independently lead to stroke or whether there is evidence that migraine mediates the association between this polymorphism and stroke. To evaluate these different associations in their data, the authors first test whether the polymorphism is associated with migraine among individuals without stroke and second, in a different study sample, whether the MTHFR polymorphism and migraine are associated with stroke risk. Statistical models can help to specify causal (ie, biological) relationships under specific assumptions. These assumptions include the absence of selection bias, use of appropriate control for potential confounding factors, as well as excluding the possibility of unmeasured confounders.12 However, although the data support (1) a link between the MTHFR polymorphism and both migraine with aura and ischemic stroke, and (2) an association between migraine with aura and ischemic stroke, future studies should directly observe whether the effect of the MTHFR polymorphism on ischemic stroke is mediated (ie, has different effect sizes) according to migraine aura status within the patient population. Pezzini and colleagues provide an important first step in suggesting an interrelationship between the MTHFR polymorphism, migraine with aura, and ischemic stroke. However, additional studies are now warranted to confirm these provocative findings and to clarify important points raised by this article.

Of course, an association between migraine headache and vascular dysfunction is not new. For example, the syndrome of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a vascular disorder that causes migraine headaches early in life, and stroke after age 30. Mutations in the notch-3 gene cause a diagnostic phenotype in vascular smooth muscle and a disturbance in cerebral blood flow regulation, at least in an animal experimental study.13 Precisely how this mutation causes stroke (not to mention migraine) remains unclear, but importantly, notch-3 appears to be expressed exclusively in vascular smooth muscle within adult brain. Both migraine with aura and CADASIL have been linked to significant changes in white matter. The lesion distribution within white matter is regionally distinct in CADASIL and usually greater in extent than in migraine with aura. Some studies suggest that migraineurs with aura also show a higher risk for cerebellar lesions that appear vascular in nature as they reportedly localize to watershed zones.14 Arteriovenous malformations and small angiomas sometimes cause attacks of migraine with aura, further linking blood vessel abnormalities to a migraine with aura phenotype.

More subtle mechanisms may be invoked to link typical forms of migraine and risk for stroke. For example, humans harboring mutations that disrupt the microcirculation and vascular regulation may be challenged by repeated events such as those accompanying migraine with aura. Cortical spreading depression (CSD) has been implicated as a key biological event causing aura and is characterized by intense, propagating depolarization of neurons and glia. During aura and CSD, hyperperfusion occurs early, whereas hypoperfusion often develops in a delayed fashion, and flow may be

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reduced in some patients by as much as 40% to 50%. Although a recent study suggested that functional arterial properties are altered in patients with migraine,15 the extent to which migraine or CSD reduces endothelium-dependent relaxation (eg, disturbed in hyperhomocytinemia possibly due to MTHFR C677T gene polymorphism), reduces blood flow or disrupts the microcirculation and its endothelial lining, and predisposes to stroke in a patient with migraine susceptibility remains to be solved. It has been well established that ischemia or hypoxia are particularly able to evoke CSD,16 and platelet stickiness has been implicated in migraine as well. It should also be noted that homocysteine in increasing amounts suppresses Na⁺-K⁺-ATPase activity in parietal, prefrontal, and cingulated cortex of rats, raising alternative possibilities for both migraine and stroke pathogenesis.17 Hence, the possibilities for this association extend beyond the cerebral blood vessel wall to possibly implicate neurons and glia as well.

The findings by Pezzini and colleagues are provocative and await confirmation. They do serve to remind us of the potential link between cerebral blood vessels and migraine with aura and its complex relationship to stroke and the neurovascular unit.

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References

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