Migraine as a Risk Factor for Stroke

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The following summary discusses several presentations concerning the relationship between migraines and stroke, including epidemiology, genetics, and mechanisms, in an effort to explain the link between migraines with aura and stroke.

Migraine and Stroke: Epidemiological Evidence

Migraines are relatively common, occurring in about 12% of the population. Migraines that are associated with aura, a more serious form of migraine, occur in 20% to 40% of migraineurs [Lipton et al. *Headache* 2001]. Gretchen E. Tietjen, MD, University of Toledo, Toledo, Ohio, presented epidemiological evidence for the relationship between migraine with aura and stroke. Results from meta-analyses indicate that migraine with aura is associated with a 2-fold increased risk of stroke (RR, 2.16; 95% CI, 1.53 to 3.03) compared with those without migraine, whereas migraine without aura is not associated with risk of stroke (RR, 1.23; 95% CI, 0.90 to 1.69). Stroke risk is doubled in women with migraine. Age <45 years, smoking, and oral contraceptive use further increased the risk [Schurks et al. *BMJ* 2009]. In persons with migraine with aura, frequency of migraines has also been found to be related to stroke risk, with those experiencing >12/year at higher risk (OR, 10.4; 95% CI, 2.18 to 49.4) [Donaghy et al. *J Neurol Neurosurg Psychiatry* 2002]. Several studies have shown that migraine is associated with cardiovascular (CV) risk factors [Bigal et al. *Neurology* 2010; Bushnell et al. *BMJ* 2009; Scher et al. *Neurology* 2005), but the migraine-with-aura-related stroke risk is highest in those with the most favorable CV risk profiles [Kurth et al. *BMJ* 2008]. Results from a recent study that investigated the predictive value of major CV factors in young adults with ischemic stroke showed the risk of migraine with aura increased with decreasing number of CV risk factors (OR, 0.50; 95% CI, 0.24 to 0.99 for 2 factors or more), increasing number of thrombophilic variants (OR, 2.21; 95% CI, 1.05 to 4.68 for carriers of at least 1 of the 2), and the presence of right-to-left atrial shunt (OR, 2.41; 95% CI, 1.37 to 3.45), as compared with patients without migraine. None of these factors affected the risk of migraine without aura [Pezzini A et al. *Stroke* 2011].

Migraine and Stroke: Genetic Evidence

Arn van den Maagdenberg, PhD, Leiden University Medical Center, The Netherlands, presented data that showed the genetic link between migraine and ischemic stroke. Bolay and colleagues [Bolay et al. *Nat Med* 2002] suggested that cortical spreading depression (CSD), which underlies the migraine aura, may also cause headache itself by activating the trigeminovascular system). Prof. van den Maagdenberg believes genetic mutations that affect these mechanisms can help explain the pathophysiology of migraines.

Genetic studies of monogenic subtypes of migraine, such as familial hemiplegic migraine (FHM), revealed gene mutations in components of ion transport systems, including the voltage-gated Ca^{2+} channel gene CACNA1A; the ATP1A2 gene, which encodes the alpha2 subunit of the Na^+/K^+ pump; and the gene SCN1A, which encodes a subunit of voltage-gated Na^+ channels that is essential for the generation and propagation of action potentials. Mutations in these ion transporter genes, in addition to hemiplegic migraine, may also cause cerebral ataxia, seizures, fatal mild head trauma-induced edema, and recurrent stroke.

Migraine and stroke (or small vessel disease) are linked by at least two other monogenic disorders: cerebral autosomal dominant arteriopathy with subcortical infarcts and

leukoencephalopathy (CADASIL), and retinal vasculopathy with cerebral leukodystrophy (RVCL). CADASIL is the most common form of hereditary stroke and is characterized by progressive white matter degeneration and smooth muscle cell abnormalities. About 30% of CADASIL patients also have migraine with aura, often as the presenting clinical symptom. RVCL is a lesser-known disease in which migraine can be prominent in certain families.

Transgenic mouse models with monogenic migraine gene mutations were generated (Eikermann-Haerter et al. *Ann Neurol* 2009; van den Maagdenberg et al. *Neuron* 2004), of which the S218L missense mutation in the CACNA1A gene causes a particularly dramatic hemiplegic migraine syndrome that is associated with cerebellar ataxia, seizures, and severe, sometimes fatal, brain edema triggered by only mild head trauma. S218L mutant mice display an exquisite sensitivity to CSD, with a vastly reduced triggering threshold, an increased propagation velocity, and frequent multiple CSD events after a single stimulus. In contrast, mice that bear the R192Q missense CACNA1A mutation, which in humans causes a milder form of hemiplegic migraine, typically exhibit only a single CSD event after one triggering stimulus [van den Maagdenberg et al. *Ann Neurol* 2010].

Cellular and transgenic mouse studies suggest that neuronal hyperexcitability and increased susceptibility to CSD, the correlate of migraine aura, are important molecular mechanisms in migraine. Normalizing glutamatergic neurotransmission in R192Q mutant mice in cortical slice preparations also normalized CSD susceptibility, showing a causative link between enhanced glutamate release and CSD facilitation [Tottene et al. *Neuron* 2009]. A key role for glutamate in migraine pathophysiology is also shown by increased levels in CSF and plasma of migraine patients. Using genetically modified animal models may help delineate the link between the migraines and stroke, Prof. van den Maagdenber concluded.

Migraine and Stroke: Experimental Insights into Mechanisms

Cenk Ayata, MD, Massachusetts General Hospital, Boston, Massachusetts, presented data from animal models of migraine and stroke that may help explain the mechanism(s) that links these two highly prevalent disorders. In one animal model that used CSD as a surrogate for migraine with aura, Nozari and colleagues demonstrated that particulate or air-induced microemboli triggered CSD, often without causing microinfarction, suggesting that a subset of migraine auras may belong to a spectrum of hypoperfusion disorders, along with transient ischemic attacks and silent infarcts [Nozari et al. *Ann Neurol* 2010].

Dr. Ayata also showed data suggesting that transgenic mice that expressed CACNA1A migraine gene mutations exhibit an increased susceptibility to not only CSD but also anoxic depolarization and peri-infarct depolarizations, thereby hastening the growth of the ischemic core. As a result, mutant mice develop considerably larger infarctions and worse neurological outcomes, including high mortality. This mechanism is a result of tissue hyperexcitability, independent of vascular factors. Because hyperexcitability is a phenotype that is shared between rare monogenic forms of migraine with aura and more common but genetically complex forms, Dr. Ayata suggested that brain hyperexcitability may be a common mechanism that worsens ischemic outcome in migraineurs.

Dr. Ayata cautioned, however, that these two mechanisms are not the only mechanisms that explain the link between migraine and stroke and that they may be operational in only a subset of migraineurs.