



Highlights from the Presidential Symposium

The 14th Congress of the International Headache Society

September 10-13, 2009

Philadelphia, Pennsylvania

Independence from Headache

Hosted by the American Headache Society and the International Headache Society

Tightening the Links between Migraine and Blood Vessels

Chair: Michael A. Moskowitz, MD, President, International Headache Society

Dr. Moskowitz, professor of neurology at Harvard Medical College and Massachusetts General Hospital, provided not only a warm welcome to the attendees of the 14th Congress of the International Headache Society (IHC), but also a challenge. He asked that everyone consider the bidirectional connection between vascular and neuronal features that contribute to onset of migraine and risk of morbidities that also arise from their relationship.

The first presenter, Dr. David Dodick, professor of neurology, Mayo Clinic, Scottsdale, Arizona, spoke about *Migraine and Vascular Disease: The Clinical Spectrum*. He introduced the 'vascular-neural hypothesis' of migraine (ie, neurogenic inflammation of meningeal vessels provoked by peptides released from trigeminal sensory neurons), and inquired as to its feasibility versus either a separate and distinct vascular or neural theory. He provided evidence that suggests 'neurovascular coupling,' meaning migraine associated with blood vessel inflammation, may function as both an upstream etiology and a downstream result.

Strong epidemiological evidence indicates that migraine, especially migraine with aura, is associated with increased risk of ischemic stroke. Dr. Dodick reiterated data that demonstrate cortical spreading depression, referred to as CSD (slowly propagating wave of cortical depolarization with an initial hyperemia followed by prolonged hypoperfusion), is associated with migraine with aura. Endothelial cells are the first to respond to a microvascular insult, such as hypoxia. Previous studies, conducted by Dr. Gretchen Tietjen, have demonstrated the presence of genetic biomarkers of endothelial dysfunction associated with mutant and inherited vasculopathies, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), retinal vasculopathy with cerebral leukodystrophy (RVCL), and hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL). Other study findings show evidence of increased endothelial activation, a component of endothelial dysfunction, in patients with migraine with aura. Results from the CAMERA I study showed that patients with migraine with aura with one attack or more per month were at highest risk of



developing deep white matter lesions in the posterior circulation. The origin of these deep white matter lesions is not known. Collectively, these findings suggest that migraine with aura and ischemic stroke may be the end phenotype of common pathogenic mechanisms.

The bidirectional relationship suggests that in some instances migraine with aura may initiate an ischemic event via cerebral microcirculatory vasoconstriction as a result of cortical spreading depression and oligemia, intracerebral great vessel spasm, or microvascular endothelial dysfunction. Alternately, migraine with aura may predispose the patient to interictal episodic cerebral ischemia, which affects endothelial function, and perhaps other physiologic mechanisms of cardiovascular disease.

The research evidence translates to a promise of clinical outcomes improvement by means of biomarker screening designed to identify patients with migraine with aura at high risk for ischemic stroke. From a drug discovery perspective, new therapeutic targets may be realized, and molecular interventions or other targeted therapies may be introduced.

The second speaker, Dr. Tobias Kurth, Faculty of Medicine, University Pierre et Marie Curie, Paris, France, presented: *Migraine as a Risk factor for Vascular and Cerebrovascular Disease*.

Dr. Kurth presented compelling epidemiologic evidence of migraine with aura associated with ischemic stroke. Women with migraine with aura who are younger than 45 years of age, those who smoke cigarettes, and those who are prescribed oral contraceptives are all at greatest risk of ischemic stroke. Dr. Kurth was quick to caution that migraine *without* aura is *not* a marker for ischemic stroke.

In light of the evidence derived from several studies, Dr. Kurth suggests that the Framingham Risk Score may be a reliable method to stratify cardiovascular risk in patients with migraine with aura. It was noted that the odds of having an elevated Framingham Risk Score for coronary heart disease were approximately doubled for migraineurs with aura. Ischemic stroke has been associated with a high migraine with aura attack frequency. Dr. Kurth mentioned that mechanisms that evoke ischemic stroke and myocardial infarction in the migraine population may be separate and distinct. Further research focused on processes associated with microvascular endothelial response in patients with migraine with aura compared to a healthy control group is needed.

Dr. Moskowitz was the third speaker and presented: *Experiential Evidence Linking Migraine and the Blood Vessel*.

Cortical spreading depression (CSD) associated with migraine, stroke, traumatic brain injury, and subarachnoid hemorrhage, serves as both a trigger and provokes consequences of oxidative, vascular, and cytotoxic stress. Genetic predisposition and



non-genetic modulators are considered culprit. Ischemic injury serves as the trigger for aura. CSD correlates with decreased perfusion. The depth and duration of reduction in blood flow impacts CSD. For example, CSD initiated by a reduction in perfusion without presence of an infarct is an ultra-transient event that comes and goes without resultant tissue damage.

Several cardiovascular factors were mentioned that may act as both triggers of and responses to CSD, migraine with aura, and ischemic stroke. They include:

- Microemboli
- Endothelial injury, chemical or sheer stress-induced
- Compromised vessel compliance; volume-pressure relationship (ie, vascular tone and compliance)
- Platelet aggregation; rheologic sheer stress
- Vessel wall trauma/injury
- Release of vasoactive substances in response to stress or injury
- Heart and tributary vessels may be implicated in a subset of patients

Drugs formulated for the prevention of migraine raise the threshold for evoking CSD.

The final speaker was Dr. Rami Burstein, associate professor of anesthesia, Harvard Medical School and Massachusetts General Hospital. His presentation was entitled: *Transitioning from the Vessel/Brain to Headache Pathogenesis*.

Dr. Burstein discussed that in animal models, it has been shown CSD does not activate the trigeminal vascular neurons of the dorsal horn, but will activate meningeal nociceptors, which likely leads to the throbbing pain of migraine. The studies also showed that CSD once activated can resolve and, without further CSD stimulus, can reactivate. Excision of the sphenopalatine ganglion reduces the likelihood of neuronal activation. The assumption is that in humans, CSD is a nociceptive event predicated on the activation of the meningeal nociceptors.