Are migraineurs naturally born "well-hearted"?

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Migraine is a common episodic brain disorder characterized by recurrent attacks of disabling headache.[1] In one-third of patients, headache is preceded or accompanied by aura symptoms, which are transient and fully reversible hemispheric neurologic symptoms. In the absence of any objective marker, the diagnosis of migraine is clinical and based on the criteria proposed by the International Headache Society, which distinguish migraine without aura (patients who have never had an aura) and migraine with aura (patients who have had at least 2 auras, irrespective of the number of attacks without aura they have had).[1]

Migraine affects about 15% of the occidental population and predominates in women. Family and twin studies have shown that migraine is polygenic, with an overall heritability nearing 50%.[2]

Migraine is viewed as a benign condition, probably because the migraineurs who seek care are mostly young or middle-aged adults and because attacks tend to improve and eventually disappear with aging. However, accumulating data show that migraine is an independent risk factor for vascular disorders. Clinic- and population-based studies have shown that migraine with aura (and not migraine without aura) doubles the risk of ischemic stroke, especially in women younger than 45 years who are free of any other vascular risk factors (with the exception of smoking and use of oral contraceptives, which further increase the risk).[3,4] Cortical spreading depression, the surrogate of migraine aura, has been proposed as the main link between migraine and ischemic stroke through an increased vulnerability to cerebral ischemia.[5] Several studies and a recent meta-analysis have also shown that migraine, especially migraine with aura, is associated with an increased risk of coronary artery diseases (CADs), including angina, myocardial infarction, and coronary revascularization procedures.[6] The mechanisms linking migraine to CAD are totally unknown.

In this issue of *Neurology® Genetics*, Winsvold et al.[7] studied shared genetic susceptibility underlying migraine and CAD. Their main hypothesis was that shared genetic variations might explain part of the observed epidemiologic link between migraine and CAD. The authors analyzed 2 large existing genome-wide association studies (GWAS) for migraine and CAD. Using 4 separate methods, they found that some genetic loci are indeed associated with both migraine and CAD. However, and probably contrary to expectations, they found no overlap of genetic risk loci between migraine with aura and CAD. Moreover, the genetic variations that overlap between migraine without aura and CAD are protective.[7] In other words, patients with migraine without aura seem to have a lower load of genetic factors increasing the risk of CAD, and patients with migraine with aura do not have more risk loci increasing the risk of CAD than controls.

We now need to understand why migraineurs who are born with a protective or neutral genetic risk profile for CAD end up with an increased risk of coronary events. Other genetic factors could play a role. GWAS are efficient at identifying common genetic variants that each have a small functional effect. The most recent meta-analysis of GWAS has identified 42 variants associated with migraine, of which 7 are specific for migraine without aura and none is specific for migraine with aura.[8] One hypothesis is that the mode of inheritance of migraine with aura differs from the complex polygenic inheritance of migraine without aura and involves rare variants that each exert more important functional effects. Furthermore, it has been suggested that migraine with aura could be associated not only with an increased neuronal excitability and vulnerability to cerebral ischemia because of the consequences of cortical spreading depression but also with an increased cardiac and cellular vulnerability.[9] Some rare genetic variants, which cannot be captured by the GWAS approach, could be implicated in both migraine with aura and CAD. Second, nongenetic factors could play a role. Migraine has been associated with adverse life style,

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obesity, avoidance of physical activity, smoking, unfavorable cholesterol profiles, and depression, which all increase the risk of CAD.[4] Hypercoagulable states and endothelial dysfunction, both of which have been associated with migraine, could also play a role.[4] It is important to emphasize that the use of triptans and ergots to abort migraine headache cannot explain the epidemiologic link between migraine and CAD.[10] These vasoconstrictive migraine medications are contraindicated in patients who have had a stroke or a CAD or who have uncontrolled hypertension.

Practically, physicians should inform patients affected by migraine with aura of the increased risk of stroke and CAD, detect and treat conventional modifiable vascular risk factors, and especially encourage smoking cessation and regular physical activity.

While more data are needed to understand the molecular mechanisms underlying the association between migraine and CAD, this study shows that common genetic variants are not major players in this association.

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