Key Words
cortical spreading depression, aura, oligemia, calcitonin
gene related peptide, P/Q channel

Objectives
At the conclusion of this program, participants should be able to:
1. Identify the typical features of migraine aura.
2. Describe the pathophysiologic mechanisms behind migraine aura.
3. Correlate the physiology of cortical spreading depression to the clinical phenomena of migraine aura.

CME Questions
1. Migraine aura is associated with which of the following conditions:
   a. Cortical spreading depression
   b. Vascular ischemia
   c. Vasoconstriction
   d. Spike and wave activity
   e. Cortical hypothermia

2. Spreading depression advances along the cortex at a rate of:
   a. 1cm/minute
   b. 2cm/minute
   c. 1mm/minute
   d. 3mm/minute
   e. 8mm/minute

3. Which of the following features is not typical of migraine visual aura?
   a. Gradual buildup
   b. Lasts 15-30 minutes
   c. Positive visual phenomena
   d. Precedes the headache
   e. Monocular
EDITORIAL

Migraine, Aura, and Cortical Spreading Depression: Why Are We Still Talking about It?

Few things are pathognomonic in medical practice, but the clinical history of the scintillating scotoma marching slowly across the visual field is one of the closest to being a clinical home run. It is the very nature of migraine aura, its progression and usually remarkable respect for the midline that has fascinated neurologists for centuries, even those not yet enamoured of headache. So it has been fitting that migraine aura would be the subject of detailed study in humans, and its animal homologue—cortical spreading depression (CSD)—similarly analysed and dissected. However, much of the study of aura has been based on a seldom-questioned, even unstated hypothesis that migraine aura, along with headache, forms a necessary sequential and pathophysiologically connected phenomenon. The concept that aura in some way generates the rest of the attack, particularly being pivotal to the pain, has been assumed for many years. The results of Ebersberger and colleagues’ question this neat and tidy view. The hypothesis that aura might be the trigger for migraine, simply stated, is that the aura process activates trigeminal afferents, thus causing the pain and the cascade of events that we recognise as migraine. To some extent to promote discussion, but equally because it has struck me as clinically implausible, I will set out the case that migraine aura is a parallel track process to the pain. The concept being that aura is triggered or facilitated by the same process that is responsible for the pain and other symptoms; a process that resides and is governed by the brain.

Considering migraine aura itself: Only some 15–20% of migraineurs have aura by standard criteria. Aura is typically visual or sensory, and only rarely motor. Migraine aura is accompanied by a spreading oligemia first reported by Olesen’s pioneering studies supported and extended by the elegant work of the Boston Group. Some remarkable recent observations of an initial hyperemic phase secure the validity of comparisons of migraine aura with cortical spreading depression. What has emerged very clearly from both the Copenhagen Group and the Boston group is that the headache phase begins while oligemia is still present. The first lesson from aura studies is that headache is not necessarily due to reactive vasodilatation as Wolff had considered, although these studies themselves did not examine large vessels. If aura indeed only occurs in, at most, one fifth of migraineurs, it cannot easily account for headache in the vast majority of sufferers. It has been suggested that clinically silent aura may occur to account for the majority of patients who have migraine without aura. Evidence such as a well-documented case of bilateral spreading oligemia observed with positron emission tomography (PET) might support this view. However, this is one case and it is challenging to describe visual change in the setting of the PET scanner. Moreover, it may be unattractive to explain most patients by a phenomenon that is completely speculative in order to save an explanation that applies to a minority, even a minority of migraineurs with aura.

What is the clinical evidence that migraine aura may not be the trigger for the pain and other symptoms? First, if unilateral aura triggers headache then it must be contralateral to the pain. Although this is very often the case, there are very well documented cases in which it is not. So sad is the clinical reality that I have seen an ophthalmologist who sought consultation simply because the aura was homolateral and he was concerned that this meant it could not be migraine aura. Second, patients with aura but no headache offer a significant challenge to the hypothesis that aura triggers pain. In practice aura without headache is uncommon but certainly seen often enough to demand explanation. Third, aura does not necessarily precede headache; although this is the general rule, again patients in whom aura occurs with the onset of headache or even after hours or days of headache are the uncommon but well-recognised. Fourth, genetic analysis is starting to separate aura and headache. Ferrari and Frants have shown that the P/Q channel implicated in migraine may be implicated in migraine with aura but not migraine without aura. Is this the, or an, aura susceptibility gene? Last, a recently published study of intranasal ketamine in the treatment of aura in familial hemiplegic migraine demonstrated that for some patients ketamine could reproducibly abort the aura, but this did not effect the headache. Remarkably, and disturbing for pharmacogenomics, patients with the same P/Q channel gene mutation had completely different responses to ketamine!

Set on this clinical background, Ebersberger and colleagues have studied CSD in the rat and asked how it
might activate trigeminal neurons, to explore a plausible biological mechanism for aura-generating headache. It was shown some years ago that repeated induction of spreading depression in the rat could increase Fos-like immunoreactive protein (FLP) expression in the trigeminal nucleus caudalis. Subsequently, it was argued that FLP may be due to mechanisms other than the induction of CSD, such as neuronal activation by the injection process as a consequence of direct dural irritation. This was hotly disputed at the time. In the new study, the authors have recorded from neurons in the trigeminal nucleus caudalis of the rat during induction of CSD. Further, they attempted to determine if CSD would induce plasma protein extravasation (PPE) in the dura mater and then looked in vitro at whether the chemical changes elicited by CSD would alter calcitonin gene-related peptide (CGRP) or prostaglandin PGE2 in the dura mater. They found no trigeminal neuronal activation, no PPE after CSD, and no local dura change in CGRP or PGE2. Absence of CGRP release is a pivotal negative finding, because it is a reliable finding in migraine patients during headache that can link human and experimental studies. They conclude that FLP expression after CSD induction was an artefact of direct dural stimulation. The study is negative and one must be cautious with negative studies. However, it is totally consistent with the clinically based analysis presented above.

Where do these data leave us? The new data taken with the clinical picture demand a reappraisal of the hypothesis that aura triggers headache. The data suggest that CSD is not a noxious stimulus as such and not a sufficient stimulus to induce trigeminovascular nociceptive activation. A plausible hypothesis might be that migraine aura is a parallel process permitted by the basic migraine pathophysiology. This hypothesis would predict that aura and headache would be dissociated genetically, expressed with headache but not necessarily before it, and have no completely fixed laterality between the headache side and the aura symptoms. The clinical facts all fit this hypothesis. These considerations lead to one inescapable and fundamental question: What is the source of the pain in migraine? If not vascular change and not the aura process, at least in isolation, then what causes the pain? A radical possibility is that migraine pain is more to do with the abnormal perception of the normal than the activation of nociceptive pathways in the classical way that pain is generated. A change in brain state not a ramp function as Professor Patrick Wall recently explained it (personal communication). This has been suggested on the basis of experimental and human observations. Is this so radical? What is photophobia but normal light exaggerated, so to speak, by the brain; and what is phonophobia but normal sound apparently amplified, again by the brain? Certainly the observations of cortical excitability and the observed interictal electrophysiological changes would support this notion.

Why are we talking about aura again? Because a careful analysis of the clinical features and plausible biological studies can inform, challenge, and focus our minds on one of the commonest neurological maladies. Perhaps migraine is an episodic disorder of sensory sensitivity whose basic understanding and generation will be found in the brain and whose pathophysiological behaviour will not respect classical pain physiology. We must know the answer to this question if we want new preventatives and to provide patients with a coherent explanation for the condition. Perhaps Living’s view of a primary brain nerve storm will be much closer than the more classical vascular view that has held so much unjustified sway for more than 300 years.

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References
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CME Answers

1. a
2. d
3. e