Chronic Migraine Pathophysiology

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Learning Objectives

At the conclusion of this talk, participants will be able to:

- Recognize that episodic and chronic migraine involve overlapping trigeminovascular mechanisms
- Know the role of allodynia and central sensitization in chronic migraine
- Explain how activation of brain regions are involved in the pathophysiology of migraine

The understanding of migraine pathophysiology has changed dramatically from the old vascular theory. Vasodilation is not linked to the genesis of migraine pain.[1] Cerebral and meningeal blood vessels are not dilated during migraine induced by nitroglycerin[2] or sildenafil. Some drugs that induce significant cerebral vasodilation do not cause migraine (e.g. vasoactive intestinal peptide).

Magnetic Resonance Angiography (MRA) of intracranial and extracranial arteries in patients with 19 patients with spontaneous migraine with aura found no extracranial artery dilation during attacks and only slight intracranial artery dilation during attacks. Effective treatment with sumatriptan caused no intracranial vasoconstriction.[3]

The central genesis of migraine may occur in the hypothalamus, especially during prodrome, in the cortex during aura, or in the upper brainstem at onset. All of these areas have been implicated in migraine pathophysiology, and wide spread activation with central sensitization and allodynia is seen in both episodes of migraine at peak and in the progression to chronic migraine (CM).

Allodynia is defined as a state in which non-nociceptive stimuli are perceived of as painful. In migraine, allodynia represents the sensitization of V1, as a region of spontaneous pain, then expands via activation of trigeminocervical complex neurons. The spread occurs both ipsilaterally and contralaterally as thalamic neurons become involved. The presumed mechanism of allodynia is sensitization, and the entire process is more common in CM than episodic migraine (EM).

The actual point of onset of migraine is unknown. Some hypothesize that the migraine sequence begins with aura and cortical spreading depression or cortical spreading depolarization. Others believe activation is in the periaqueductal gray (PAG) or hypothalamus. Some believe the beginning of attacks is in the dura/meninges.[4]

In any case, the migraine pain, whether in EM or CM, is caused by at least some peripheral meningeal processes, including vasodilation and neurogenic inflammation. These, in turn, stimulate first order nociceptive neurons which have cell bodies in the semilunar trigeminal ganglion and terminate in the trigeminocervical complex. Second order neurons are trigeminothalamic, terminating in thalamus, and third order neurons proceed to the sensory cortex.

Peripheral sensitization occurs with the first order neuron activation and may be represented clinically by throbbing pain.[5] Central sensitization accompanies firing of second and third order neurons and may become autonomous, with continued spontaneous firing. Again, the clinical manifestation of central sensitization is allodynia, which is also linked to more refractory pain in terms of treatment.

When the first order neurons terminate in the trigeminocervical complex, they synapse in neurons at the cervicomedullary junction and the dorsal horn of the spinal cord. This may account for the neck pain so common in migraine, generally as referred pain rather than as a problem related to neck pathology.

Persistent brainstem activation from recurrent attacks may play a role in progression from EM to CM. Brainstem neurotransmitters released are similar in CM and EM. Iron deposition in the PAG is related to frequency of attacks.[6] Pontine lesions cause CM-like headache.

Cortical spreading depression (CSD) is a misnomer, as the actual pathophysiological events that occur represent neuronal excitation and depolarization and can occur in brainstem and cerebellum as well as cortex. Blood flow necessarily increases during CSD, and after neuronal firing, a decrease in blood flow occurs with the post-ictal neuronal state.[7] Generally, the decreased blood flow does not reach ischemic levels.

CSD clearly occurs with migraine aura, and can occur in migraine without aura in at least some patients.[8] The debate continues as to whether CSD precedes all migraine attacks; this seems unlikely.

Others continue to opine that migraine onset is in the PAG. Initially noted at migraine onset on PET,[9] a subsequent fMRI located the dorsal raphe/PAG activation contralaterally from the pain.[10]

The PAG appears central in migraine pathophysiology. Triptans,[11] ergots,[12] calcium channel blockers, and opioids all bind there. The pivotal endogenous vasodilator calcitonin gene-related peptide (CGRP) also binds there.

P/Q calcium channels are where the mutation for Familial Hemiplegic Migraine Type 1 occurs. These converge in the PAG. Agatoxin, a P/Q channel antagonists binds there.[13]

It is also possible that migraine originates in the hypothalamus or pain matrix. There is evidence for hypothalamic activation in prodrome,[14] and during, and after migraine attacks, in postdrome.[15]

As EM progresses to CM, it is likely that there is thalamic sensitization with with extended allodynia. Burstein and colleagues found that sensory neurons in rat posterior thalamus were activated and sensitized by dural chemical stimulation. The thalamic sensory neurons exhibited long-lasting hyperexcitability to innocuous (brush, pressure) and noxious (pinch, heat) paw stimulation. Innocuous, extracephalic skin stimuli not producing neuronal firing at baseline (e.g., brush) became as effective as noxious stimuli (e.g., pinch) in eliciting large bouts of neuronal firing after sensitization was established. In migraine patients, fMRI BOLD showed brush and heat stimulation of the hand produced larger BOLD responses in the posterior thalamus during migraine with extracephalic allodynia than interictally.[16,17]

Both structural and functional changes in brain occur as CM develops. There is decreased gray matter density or volume in structures in the pain matrix involved in descending pain modulation, including cingulate cortex, insula, prefrontal cortex, Amygdala, parietal cortex, and superior temporal gyrus and temporal pole. [18-20]

Changes of consequence do not occur everywhere in the brain as migraine continues to occur. For example, there was much publicity when the prospective CAMERA MRI study suggested deep white matter lesions and cerebellar infarcts were associated with long-standing migraine, especially in women with migraine with aura.[21]

However, longitudinal follow up in the CAMERA-2 trial was described over 8.5 (7.9-9.2) years. The study was case matched, with controls (*n*=83/140), migraine with

aura (114/162), and migraine without aura (89/134). There was a slight increased risk of progression of deep white matter lesions in women but not in men with migraine, and no increase in progression of the brainstem hyperintensities in patients with migraine compared with controls. There turned out be no increased risk of posterior circulation infarcts in patients with migraine compared with controls.[22] The patients had normal neurologic exams, and addition trials found no difference in cognitive function in patients with white matter lesions compared with the controls.

The progression of migraine and the severity of migraine has also been probed by genetic studies. Many families with Familial Hemiplegic Migraine have mutations in CACNA1A, ATP1A2, and SCN1A genes, coding for abnormalities that result in increased glutamatergic tone. Some families with familial migraine have mutations in genes in TRESK and CK1δ. Migraine susceptibility loci include PRDM16, TRPM8, LRP1, ZNF555, ADARB2, GRM7, HTR7, MEF2D, TGFBR2, PHACTR1, and ASTN2.

The area of greatest excitement in migraine treatment is in medications targeting CGRP. How CGRP participates in the progression from EM to CM is not known. We do know that CGRP is released into the jugular venous system during migraine attacks.[23] CGRP infusion evokes migraine,[24] and serum CGRP levels are elevated in CM. CGRP receptor antagonists effectively abort migraine attacks.[25-27] Anti-CGRP and anti-CGRP receptor monoclonal antibodies prevent both EM and CM, suggesting both a pivotal role for CGRP and shared pathophysiology in EM and CM.[28-31]

Many questions on CGRP, migraine pathophysiology, and the role of CGRP in the chronification of EM to CM remain. These include: Where is it released? Where are its receptors? Where is the primary site of action as a mechanism of migraine? How can we design better therapies targeting CGRP?

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