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The pathophysiology of migraine: Complex process that begins with primary neuronal dysfunction.

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Pathophysiology

The pathophysiology of migraine is a complex process that begins with primary neuronal dysfunction.

A large number of chemical mediators produced at the site of tissue injury and inflammation can promote the excitation and sensitization of nociceptors (1,2). Inflammatory mediators of peripheral sensitizatio: Mediators such as bradykinin, histamine, serotonin (5-HT), and prostaglandin E2, (PGE2) have been shown to produce both excitation and mechanical sensitization of somatic and meningeal nociceptors (2).

The dural vascular structures are innervated by neurons arising from the trigeminal nucleus and dorsal portions of the upper cervical roots (1,2). Nowadays, the suggestions pose that multiple primary neuronal impairments lead to a series of intracranial and extracranial changes that cause migraines (1,3). These structures project onto second order neurons in the trigeminal cervical complex and trigeminal nucleus caudalis (TNC) (2,3). Fibers then ascend to the thalamus and sensory cortex. Pain is felt in the head and neck due to convergence of fibers from the trigeminal nerve via the trigeminal nucleus caudalis and upper cervical roots (3,4).

Pain can be modulated by both descending fibers from the hypothalamus, periaqueductal grey, locus coerulus and nucleus raphe magnus onto the TNC and by ascending fibers from the hypothalamus, locus coerulus, and periaqueductal grey (3,4).

The fifth cranial nerve is the common denominator for many headaches and facial pain pathologies currently known (1,2). Projecting from the trigeminal ganglion, in a bipolar manner, it connects to the brainstem and supplies various parts of the head and face with sensory innervation. Cortical spreading depression, originally only thought to occur in migraine with aura occurs in all migraines. This is a slow, self-propagating wave of cellular depolarization across the cerebral cortex that is associated with depression of neuronal activity and altered brain metabolism (4,5).

The trigeminal innervation of pain-producing intracranial structures. Surrounding the large cerebral vessels, pial vessels, large venous sinuses and dura mater is a plexus of largely unmyelinated fibers that arise from the ophthalmic division of the trigeminal ganglion and in the posterior fossa from the upper cervical dorsal roots (3,4).

This process also activates neurons in the TNC and causes the inflammatory process in the meningeal vascular structures to begin causing pain and headache. Brain matrix metalloproteinase is upregulated and this alters the permeability of the blood brain barrier (2,3).

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Central sensitization occurs during this process. Neurons become upregulated and sensitized to both nociceptive and non-nociceptive stimuli (4,5). This in turn causes peripheral sensitization where pain receptor fields are enlarged causing increased sensitivity to both noxious and non-noxious stimuli. Allodynia and exacerbation of pain by physical activity is thought to be caused by this process (3,4).

Chronic pain is maintained in part by central sensitization, a phenomenon of synaptic plasticity, and increased neuronal responsiveness in central pain pathways after painful insults. Accumulating evidence suggests that central sensitization is also driven by neuroinflammation in the peripheral and central nervous system (5,6).

A characteristic feature of neuroinflammation is the activation of glial cells, such as microglia and astrocytes, in the spinal cord and brain, leading to the release of proinflammatory cytokines and chemokines (6,7).

Recent studies suggest that central cytokines and chemokines are powerful neuromodulators and play a sufficient role in inducing hyperalgesia and allodynia after central nervous system administration. Sustained increase of cytokines and chemokines in the central nervous system also promotes chronic widespread pain that affects multiple body sites. Thus, neuroinflammation drives widespread chronic pain *via* central sensitization (6,7).

Migraine

Migraine is an episodic headache that lasts between 4 to 72 hours and fulfills the criteria established by The International Classification of Headache Disorders (ICHD), 3rd Edition is the standard by which headaches are categorized (8,9). In addition, at least one of the following characteristics must be present: Nausea or vomiting. Photophobia and phonophobia. Eighty percent of migraines have no aura (9,10).

Most patients with migraine do not have an aura, but when an aura occurs, it is defined as migraine with aura. Visual aura is most common and accounts for 90% of aura (10). This is typically a fortification spectra: zigzag lines that move across the visual field. Many different auras have been described: scintillating scotoma, kaleidoscope vision, pixelated vision, "orbs in the sky" to name a few. These last from 5 to 60 minutes and are followed by the headache (11).

On occasion, these occur without headache. Sensory disturbances are the second most common aura (pins and needles sensation, numbness) usually affecting the face and arm. Language disturbance (aphasia) is unusual as is motor weakness (12,13). When motor weakness occurs, it is classified as hemiplegic migraine. When vertigo, ataxia, diplopia or other brain stem symptoms occur, it is classified as migraine with brainstem aura. Other prodromal symptoms such as yawning, irritability, neck pain, food cravings, burst of energy, or fatigue may occur hours to days preceding the migraine (12).

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The two major categories are migraine with aura (once called "classical migraines") and migraine without aura (formerly known as "common migraines"). As per the International Headache Society, chronic migraine is defined as headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of migraine headache (11).

Migraine is a common and disabling condition reported in approximately 12% of the population. In the Global Burden of Disease Study by the World Health Organization, updated in 2013, migraine was found to be the sixth highest cause worldwide of years lost due to disability. Migraine attacks sometimes increase in frequency over time (11).

Chronic migraine treatment should primarily focus on prevention through use of medication and non-medication preventive strategies as well as addressing identified risk factors (12,13). Headache experts divide this process of transition into four distinct states:

- No migraine
- Low-frequency episodic migraine (less than 10 headache days per month)
- High-frequency episodic migraine (10-14 headache days per month)
- Chronic migraine (15 or more headache days per month; meaning that people with chronic migraine have a migraine or headache more often than not)

Treatment / Migraine

Always treat early in the attack before the headache progresses in severity. Whenever possible use migraine-specific medications such as triptans or dihydroergotamine. Contraindications are uncontrolled hypertension, cardiovascular and cerebrovascular disease (14,15).

Use a formulation based on migraine characteristics: nasal spray or subcutaneous formulation in someone with rapid onset headache or who has nausea and vomiting from the onset. Nonsteroidal anti-inflammatory drugs (NSAIDS) are useful alternatives when triptans are contraindicated. Avoid opioids and butalbital containing compounds since these are not only addictive, but rapidly cause medication overuse headache (MOH). Do not use abortive medications more than 10 days per month to avoid MOH (16,17).

Recent triptan development has focused on new administration methods and formulations, triptan combination therapies, treatment in menstrually related migraines, and novel serotonin receptor subtype agonists (5HTf) (18,19).

Serotonin–5-HT1F receptor agonists and migraine. Some, but not all, of the triptans as well as begin 5-HT1B/1D receptor agonists are also potent 5-HT1F receptor agonists. A notable example is naratriptan, which is highly potent by the injectable route (19,20).

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With the same second messenger activity as the 5HT1B and 5-HT1D receptors, adenylate cyclase inhibition and no contractile effects on blood vessels so far identified, it is a good novel neural target for migraine treatment. It can be shown that 5-HT1F activation inhibits trigeminal nucleus fos activation and neuronal firing in response to dural stimulation, the latter without cranial vascular effects (19,21).

The following are the currently available triptan formulations:

- Sumatriptan (Imitrex): 25, 50, 100 mg by mouth (usual dose 50 or 100 mg), 10, 20 mg (20 usual dose) nasal spray, 4, 6 mg subcutaneous (6 mg usual dose)
- Zolmitriptan (Zomig): 2.5, 5 mg by mouth, once daily, nasal spray
- Rizatriptan (Maxalt): 5, 10 mg by mouth, once daily (usual dose 10 mg, unless patient is on propranolol, then decrease to 5 mg)
- Almotriptan (Axert): 6.5, 12.5 mg by mouth (usual dose 12.5 mg)
- Eletriptan (Relpax): 20, 40 mg by mouth (usual dose 40 mg)
- Naratriptan (Amerge): by mouth 1, 2.5 mg (usual dose 2.5 mg)
- Frovatriptan (Frova): by mouth 2.5 mg PO
- Sumatriptan 85 mg + naproxen sodium 500 mg (Treximet): by mouth

The important components of headache management include:

- Accurate diagnosis
- Patient education
- Nonpharmacotherapy, including trigger management, lifestyle modification (diet and exercise), and behavioral therapy
- Avoid overuse of acute medications: limit to no more than 2 days a week or 10 days a month to prevent medication overuse headache
- Use of both prophylactic and abortive medications
- Headache diary, disability or the migraine-specific quality of life questionnaire to monitor response to treatment.

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The science of migraine

Peripheral senistization refers to a state where primary afferent nociceptive neurons exhibit increased responsiveness to external mechanical or thermal stimuli at the original site of inflammation or injury. Common symptoms of peripheral sensitization during migraine are the throbbing of the headache and its aggravation during routine physical activities that increase intracranial pressure such as coughing and bending over (22,23).

These effects are mediated by bradykinin, histamine, serotonic, prostaglandin E2 and a number of cytokines and other inflammatory mediators (23,24). In contrast, central sensitization refers to a condition where nociceptive neurons in the dorsal horn of the spinal cord exhibit increased excitability (25,26), increased synaptic strength, and enlargement of their receptive fields beyond the original site of inflammation or injury (26,27). Allodynia is the archetypical manifestation of central sensitization (25,27). It is mediated by central trigeminovascular neurons. Central sensitization undergoes an initiation phase and a maintenance phase, each mediated by different neurons (27).

Once initiated, maintenance of central sensitization can be activity-dependent or activity-independent. The activity-dependent form is the consequence of neurotransmitter and neuromodulator induced activation of multiple intracellular signalling pathways. Activity-independent sensitization develops slowly over several hours and lasts for prolonged periods. The pathways and time course of central sensitization have clinical relevance (27).

Early in a migraine attack, triptans are highly effective abortives. However, in patients whose migraine is accompanied by allodynia, the patient becomes increasingly resistant to triptan therapy as the allodynia develops (27).

There are a host of other migraine symptoms that have not been studied as thoroughly as allodynia. In some cases, distortion or intensification of other sensory modalities, as seen in photophobia, phonophobia, osmophobia, and vestibular symptoms, may be mediated by the same pathways and could have similar response or resistance to therapy (27).

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