Migraine Pathophysiology

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Objectives: By the end of this course participants will be able to:

1. Describe the role of cortical spreading depression in migraine aura.
2. Describe the role of the trigeminovascular system in migraine headache
3. Describe the current state of genetic findings for migraine susceptibility.
4. Describe the current state of neuroimaging for migraine.

Key facts

1. Migraine is a recurrent episodic neurologic state with widespread effects on multiple body systems.
2. Migraine attacks characteristically unfold and recur in phases (premonitory, aura, headache, post-drome) with symptoms particular for each phase. These symptoms may include headache (often unilateral throbbing), heightened and distorted sensation (e.g. allodynia, photophobia, phonophobia), cognitive changes (e.g. dysphasia), and autonomic dysfunction (e.g. nausea, rhinorrhea).
3. Expression of migraine attacks is influenced by cyclic (e.g. hormonal, circadian), environmental (e.g. chemical triggers), and heritable factors (approximately 50% of expressivity).
4. Migraine aura typically comprises transient positive sensory (visual, somesthetic, vestibular), cognitive (dysphasic speech), or motor (hemiplegic) symptoms. Multiple lines of evidence indicate that aura is related to the phenomenon of cortical spreading depression (CSD), a wave of massive depolarization propagating at ~3mm/min across cortex followed by prolonged cortical refractoriness. CSD may be triggered by excessive glutamatergic excitatory neurotransmission, heightened extracellular potassium, brain trauma, or other factors.
5. Rare mutations have been identified in several genes leading to Mendelian inheritance of susceptibility to migraine variant syndromes. Mutations in three genes lead to a similar phenotype of aura with prolonged hemiparesis (Familial Hemiplegic Migraine (FHM)). Each of these genes (FHM1 - CACNL1A4, FHM2 - ATP1A2, FHM3 - SCN1A) codes for an ion channel or
pump (calcium channel, Na+/K+ ATPase Pump, voltage-gated Na+ channel, respectively) expressed on neuronal and/or astrocyte membranes. These gene mutations lead convergently to enhanced cortical glutamatergic excitatory neurotransmission. Mouse models expressing FHM1 mutations have reduced thresholds to provoking CSD, reduced cutaneous sensory thresholds, and other traits consistent with human migraine.

5. Migraine headache is associated with activation of bipolar trigeminal and upper cervical (C2, C3) nerve root afferents that innervate both dural and cutaneous receptive fields (distally) and converge on second order sensory neurons (centrally) in the medullary trigeminal nucleus caudalis (TNC) and dorsal horn. Projections from TNC neurons ascend to thalamus and then to cortex for perception of pain.

6. TNC activation also leads to activation of the pontine parasympathetic superior salivatory nucleus and sphenopalatine ganglion neurons to innervate the dura (trigemino-vascular reflex TVR). Key neurotransmitters/neuromodulators of the TVR include calcitonin gene-related peptide (CGRP), PS, VIP, NO, and PACAP. In rodent models, experimentally provoked CSD leads to activation of the TVR.

7. Functional brain imaging studies (e.g. fMRI, PET) have identified further regions activated during migraine attacks, including the hypothalamus (during premonitory phase), the dorsal pons ipsilateral to headache (possibly a migraine “generator”), midbrain periaqueductal gray, posterior thalamus, and cortical regions identified as the “pain matrix” (e.g. insular, superior temporal gyrus, temporal pole).

References


