Pathophysiology of Migraine

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Migraine Attacks

<table>
<thead>
<tr>
<th>Phase</th>
<th>Duration</th>
<th>Symptoms</th>
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<tbody>
<tr>
<td>Prodrome phase</td>
<td>~ up to 80% of patients, ~ hours to days</td>
<td>moodiness, difficulty concentrating, fatigue, GI, muscle/neck stiffness, fluid retention, yawning, cravings</td>
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<tr>
<td>Aura phase</td>
<td>(~ 20% of patients): &lt; 60 min</td>
<td>symptoms: visual, paresthesias, cognitive, behavioral, perceptual sensory &gt; motor, positive &gt; negative, dynamic &gt; static</td>
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<tr>
<td>Headache phase</td>
<td>~4 hours to 3 days</td>
<td>pain: hemi-cranial, throbbing, moderate to severe</td>
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<td>sensitivities: light, sound, odor, touch (allodynia), movement (vertigo)</td>
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<td>autonomic: nausea (~90%), vomiting, gastric atony, sinus congestion</td>
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<tr>
<td>Recovery phase</td>
<td></td>
<td>moodiness, fatigue, GI, muscle stiffness, diuresis</td>
</tr>
</tbody>
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Phases of a Migraine Attack

What Initiates Migraine?

For 82% of patients, premonitory features were followed by a migraine headache within 72 hours more than 50% of the time.


Migraine Premonitory Symptoms

Triggers for Migraine

- Chemical triggers - little proof but often reported by patients
  - Estrogens - OCPs, HRTs
  - Caffeine / chocolate
  - Tobacco smoke - nicotine, carbon monoxide?
  - Odors: perfumes, diesel, etc.
  - MSG - beware "natural" products
  - Processed, pickled or fermented foods or meats – nitrates / nitrites?
  - Some dairy products - aged cheeses, yogurt, sour cream (tyramines?)
  - Nuts
  - Alcohols (e.g. red wines) / Balsamic vinegar
  - Some fruits & vegetables - citrus, avocados, bananas, raisins, plums, beans, onions, aspartame

- Weather triggers – surprisingly strong evidence

Migraine Prevalence


Chronobiology of Migraine

- Migraine occurs more often on awakening
  - 3582 Attacks in 1698 Patients
- At the onset of menses
  - 1966 Attacks in 1208 Women

Fox and Davis, Headache 38: 436 (1998)

Cugini Chronobiol Internat. 7:467 (1990)

What Causes Aura in Migraine?

**Migraine Aura and Spreading Depression**

Lashley's aura (1941)

*Inferred propagation: 2 – 3 mm/min*

Leão’s Spreading Depression (1944)

*Observed Propagation: 2 – 3 mm/min*

Human Perception

Rabbit Cortex

Lashley Arch Neurol Psych 46:333 (1941)
Leão J Neurophysiol 7:359 (1944)

**Spreading Depression & Calcium Waves: Animal Observations**

Rat Cortex

Provoked CSD

"Optical Intrinsic Signal" Imaging

Courtesy Andrew Charles:
http://n81-67.medsch.ucla.edu/charleslab/

**“Imaging” Migraine Aura**

Spreading Oligemia

Cerebral Blood Flow by PET imaging

Spreading Depression?

Blood oxygenation level-dependent (BOLD) functional MR imaging
Hadjikhani et al. PNAS. 98:4687 (2001)
The Search for Migraine Susceptibility Genes

- Twins analyses
  ~ 30 to 60% heritable
- Segregation Analyses
  predominantly polygenic / multifactorial
- Monogenic variants
  e.g. FHM

FHM Mutation Convergence

Gain of Function:
- Faster recovery of Na⁺ channel
- Increased Ca²⁺ transport

Loss of Function:
- Decreased glutamate transport
- Decreased Na⁺/K⁺ transport

**FHM1 Mutations and CSD**

*Increased CSD Propagation Velocity*

*Lowered CSD Triggering Threshold*


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**FHM1 Mutations and CSD**

FHM1 knock-in mice have more pronounced CSD phenotypes if...
- greater mutant gene dosage
- female vs. male mice
- mutations that also lead to more severe human phenotypes

Eikermann-Haerter et al., JCI 119:99 (2009)

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**FHM1 Mutations and CSD**

CSD changes in female FHM1 mice are...
- largely normalized by ovariectomy or aging
- largely restored by adding estradiol to ovariectomized mice

Eikermann-Haerter et al., JCI 119:99 (2009)
FHM1 Mutations and CSD

Severity of CSD-induced hemiparesis in FHM1 mice correlates with degree of CSD propagation into striatum.


Problems with FHM Mice as Migraine Models

CACNL1A4 (FHM1) and ATP1A2 (FHM2) mutations are rare in SHM – only 8 of 100 SHM patients had variant genotypes, of which at least 6 variants were believed to be non-pathogenic

Patients with FHM do not develop migraine attacks to intravenous CGRP

Thomsen et al, Cephalalgia 28:914 (2008)

The visual cortex of migraineurs is intrinsically hyperexcitable...

Aurone SK et al, Cephalalgia 2003;23:258–263.
Suppression of Cortical Spreading Depression

Cortical spreading depression events were reduced 40% to 80% vs. controls (p<0.05) with long-term treatment with topiramate or valproate. Similar observations were made for propranolol, amitriptyline, and methysergide.


What Causes Headache in Migraine?

Wolff’s Observations

Only some Intracranial structures Are pain – sensitive:

Some regions of Dura mater Meningeal vessels, large cerebral vessels & sinuses Muscles of scalp, head and neck Nerves: 5th, 7th, 9th, 10th, C1, C2 Wolff proposed a vascular etiology for migraine

Wolff Headache 1st ed (1948)
**Cortical Blood Flow in Migraine**

**Wolff’s vascular hypothesis:**
spreading oligemia produces aura
then, prolonged hyperemia produces headache

*But...*

◆ Most patients don’t have aura
◆ Recent 3T MRA data found no MMA hyperemia during NTG-induced migraine


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**Serotonin in Migraine**

▲ In migraine attacks, blood levels of serotonin drop and urine levels of serotonin metabolites rise.

▲ Drugs which deplete platelet serotonin (e.g. reserpine) may trigger migraine-like attacks.

▲ Intravenous serotonin relieves migraine.

▲ Serotonin is implicated in mechanisms for many conditions co-morbid with migraine (e.g. depression, sleep, etc.).

Sicutari Headache 6:109 (1966)
Kimball et al. Neurol Minneap 10:107 (1960)

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**Serotonin (5-HT) Receptors and Migraine Therapies**

Adapted from: *The Triptans*. 2001
Trigeminovascular System


Is Aura Linked to Headache?

© 2001 Karen LeBlanc

Trigeminovascular System: Migraine Pathways

Proposed mechanisms of CSD-mediated brainstem activation, dural vasodilation, & sterile inflammation

What Causes Migraine Without Aura?

Cortical Spreading Depression without aura?


What Causes Hypersensitivity in Migraine?

Migrain Duet - Jeanette Abulafia

Nervous System Sensitization in Migraine

The Migraine Threshold

- Lifestyle Changes
- Preventive Medications
- Behavioral Therapy
- Genetic Factors
- Biohythms
- Head Trauma
- Overuse of Acute Medications
- Hormonal trigger
- Missed meal
- Muscle tension in neck
- Lack of sleep
- Work/home stresses

Adapted from: Migraine in Women, A. MacGregor, Martin Dunitz, 1999

And... What Terminates Migraine?

Through a Glass Darkly
- Janet Morgan Mel

Midbrain Periaqueductal Grey (PAG): Migraine “Generator” or “Suppressor”?

- Blood flow increases transiently during migraine attack and then sumatriptan treatment
- Non-heme iron steadily accumulates with duration of migraine illness (Is migraine neurodegenerative?)
**Migraine Integration**

Migraine is an episodic CNS disorder with predominantly sensory, autonomic, and cognitive manifestations.

![Diagram showing the pathophysiology of migraine with images of brain scans labeled as left-sided pain and right-sided pain.](Diagram Image)

**References**