PATHOPHYSIOLOGY
Structures Related with Headache

Blood vessels that become dilated (enlarged) or constricted

Muscles around the eyes that become strained due to overwork or poor vision correction

Sinuses that become swollen due to allergies, colds, or infections

Teeth that are decayed or damaged

Nerves that transmit abnormal pain signals

Joints in the jaw and neck that are overused or become damaged

Muscles in the neck and head that become tight or tense
Primary vs. Secondary Headache

**Primary Headache**
Not a symptom of or caused by another disease or condition

**Secondary Headache**
A symptom of or caused by an underlying disease or condition, such as tumor or infection

# PRIMARY HEADACHE

<table>
<thead>
<tr>
<th>Type of Headache</th>
<th>Pain Location</th>
<th>Quality of Pain</th>
<th>Pain Severity</th>
<th>Duration</th>
<th>Unique Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>![Image]</td>
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<td>![Image]</td>
<td>![Image]</td>
<td>neurological dysfunction nausea, photophobia, phonophobia, parasthesions, disorientation, mental cloudiness and &quot;TRIGGERS&quot;.</td>
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</tbody>
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Causes of Primary Headaches

• No underlying disease is responsible for the symptoms
• Caused by problems with or over-activity of pain structures in the brain
• Some primary headaches can be triggered by lifestyle factors:
  • Alcohol – especially red wine
  • Certain foods (e.g., processed meats containing nitrates)
  • Changes in sleep or lack of sleep
  • Poor posture
  • Skipped meals
  • Stress

## Causes of Secondary Headaches

- Acute sinusitis
- Arterial tears
- Blood clot in the brain (non-stroke)
- Brain aneurysm
- Brain arteriovenous malformation
- Carbon monoxide poisoning
- Chiari malformation
- Concussion
- Dehydration
- Dental problems
- Ear infection (middle ear)
- Encephalitis
- Giant cell arteritis
- Glaucoma
- Hangovers
- Influenza
- Intracranial hematoma
- Medications to treat other disorders
- Meningitis
- Monosodium glutamate
- Overuse of pain medication
- Panic attacks
- Post-concussion syndrome
- Pressure from tight-fitting headgear
- Pseudotumor cerebri
- Toxoplasmosis
- Trigeminal neuralgia

A wide range of possible causes with varying severity

Proposed Mechanisms of Migraine

- Abnormal cortical activity
  - Hyperexcitable brain (\(\uparrow\text{Ca}^{++}, \uparrow\text{Glu}, \downarrow\text{Mg}^{++}\))
- Cortical Spreading Depression
- Activation/Sensitization of TGVS
  - Vasodilation
  - Neurogenic Inflammation
  - Central Sensitization
- Abnormal brain stem function
  - Excitation of brain stem, PAG, etc.
- Headache Pain

TGVS = trigeminal vascular sensitization.
Migraine Mechanisms

• Trigeminal vascular system serves as a common pathway for migraine with and without aura
• How migraine pain is triggered and the cascade of events following original activation are not completely understood
• Connection between cortical spreading depression (CSD) and activation of trigeminal nerve afferents
  • Activation of trigeminal nerve → a series of meningeal and brainstem events consistent with what is observed during a migraine attack
  • Triggering CSD → long-lasting blood flow increase in middle meningeal artery
  • Increased blood flow depends on trigeminal and parasympathetic activation

Migraine Mechanisms

• Bidirectional conduction along trigeminal nerve sensitizes surround nerve fibers
• Conveys painful stimuli to trigeminal nucleus caudalis in brainstem for transmission to higher centers
• Leads to the throbbing pain, nausea, photophobia, and phonophobia that characterize migraine

Migraine and Sensitization

• Patients often report increased sensory sensitivity during a migraine attack

• Symptoms may be regulated by central or peripheral mechanisms
  • Peripheral sensitization → throbbing, exacerbation of pain with movement
  • Central sensitization → cutaneous allodynia (increased sensitivity to touch)

Central Sensitization in Migraine

- Migrateurs develop increased sensitivity to stimuli due to increased excitability.
- About 2/3 of migraine patients suffered from cutaneous allodynia during attacks due to central sensitization.

![Diagram](https://via.placeholder.com/150)

1) Trigeminal ganglion
2) Spinal cord neurons at base of skull
3) Thalamus

Inflammatory pain

Sensitized neurons
Normal neurons

The Process of Migraine Pain

1. Trigeminal Activation
2. Neuropeptide Release
   - Neurokinin A
   - Substance P
   - CGRP
   - Vasodilation
   - Neurogenic Inflammation
3. Meningeal Vasodilation
4. Central Pain Transmission
Migraine Aura

Only 15% of patients with migraine experience aura

- Rate of expansion calculated at ~3-6 mm/min
- Initial hyperemia is followed by oligemia, which spreads from the occipital cortex at a rate of 2 to 6 mm/min
- Headache usually starts while cerebral blood flow is diminished
SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
Cluster Headaches (Trigeminal Autonomic Cephalalgias)

- Attacks of severe, strictly unilateral pain that is orbital, supraorbital, temporal, or any combination of these
- Duration: 15 minutes to 3 hours
- Frequency: one every other day to eight times/day
- Associated symptoms:
  - Ipsilateral conjunctival injection
  - Lacrimation
  - Nasal congestion
  - Rhinorrhea
  - Forehead and facial sweating
  - Miosis
  - Ptosis and/or eyelid edema
  - Restlessness/agitation

Pathogenesis of Cluster Headaches (Trigeminal Autonomic Cephalalgias)

A unifying pathophysiologic explanation of cluster headache is not yet available

Pathophysiology of Cluster Headaches

- May involve an autosomal dominant gene
- Carotid and ophthalmic artery vasodilation and an increased sensitivity to vasodilator stimuli during an attack may be triggered by trigeminal parasympathetic reflexes
- May involve autonomic function abnormality with increased parasympathetic drive and decreased sympathetic function
- May be a disorder of circadian rhythm: attacks often begin during sleep
- Reduced oxygenation may trigger attacks
  - Increased prevalence of sleep apnea in patients with cluster headaches

Tension-Type Headache

- Depression
- Anxiety
- Stress
- Noise
- Alcohol
- Medications

- Transient stabbing pain
- Episodic
- Chronic

Persistent, variably severe headache
Tension-Type Headache (TTH)

- Very common: lifetime prevalence 30 to 78%
- Four subtypes:
  - Infrequent episodic
  - Frequent episodic
  - Chronic
  - Probable
- Increased pericranial tenderness with manual palpation
  - Typically interictal, further increased during actual headache, and increases with intensity and frequency of headaches

It can be difficult to discriminate between TTH and migraine without aura

Patients with frequent headaches often suffer from both disorders

Pathophysiology of Tension-Type Headache (TTH)

- Complex and multifactorial pathology with contributions from central and peripheral factors\(^2\)
- May be due to abnormal neuronal sensitivity and pain facilitation – not abnormal muscle contraction
- Associated with exteroceptive suppression, abnormal platelet serotonin, and decreased cerebrospinal fluid beta-endorphin
- Extracranial myofascial nociception and hypersensitivity of neurons in the trigeminal nucleus caudalis may play a role
- May involve central sensitization at spinal dorsal horn/trigeminal nucleus due to prolonged nociceptive inputs from pericranial myofascial tissues

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Menstrual Migraine

- ~60% of female migraine sufferers have menstrual migraines
- Reduced estrogen at menstruation can trigger migraine in many women
- May be more persistent, painful, and resistant to treatment than migraines that occur at other times
- ICHD criteria: Migraine without aura occurring between 2 days prior and 3 days after the onset of menses and in 2 of 3 menstrual cycles
  - Some women experience migraine perimenstrually
- Headache diary should be used to record timing of menstrual migraines
Estrogen Levels and Menstrual Migraine

Literature Cited


