What is a migraine?

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Migraine is a highly disabling, complex neurological disorder characterized by recurrent headache attacks of moderate to severe pain often accompanied by other symptoms[1]:

Photophobia | Nausea | Phonophobia

While pain is typically unilateral, **~4 in 10 patients** report bilateral pain during migraine attacks[2]

More than 1 billion people live with migraine globally; approximately 40 million in the United States[3,4]

2nd
Most prevalent **neurological disease** in the US[a,4]

~3×
More common in females than males (3:1 ratio)[5]

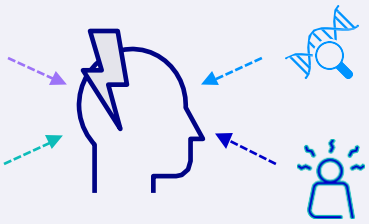
25–55 years
Most common in the **productive years**[6]

Activation of the trigeminovascular system is a component of migraine pathophysiology

Migraine pathophysiology is multifactorial[7-10]

PNS activation: the trigeminal ganglion in the PNS relays trigeminovascular nociceptive input from the meningeal nerves and vessels to the CNS[10]

CNS sensitization: presents as a **prolonged** but **reversible activation** of the central nociceptive pathways and manifests as **pain hypersensitivity**[11]



Genetic predisposition: a combination of genetic variations associated with migraine inherited from a parent[7,8]

Triggers: multiple factors can culminate in a migraine episode, e.g., stress, not eating, hormones in women, and weather[9]

The trigeminovascular system innervates the meninges and intracranial vasculature[12]

Trigeminovascular system activation during a migraine attack may result in:

Release of neuropeptides ▸ **Vasodilation** of intracranial nerves ▸ **Neurogenic inflammation** in the brainstem and thalamus ▸ **Pain sensitization** due to increased nociceptive response

CGRP is the primary neuropeptide released by trigeminal nerve endings in the meninges[10]

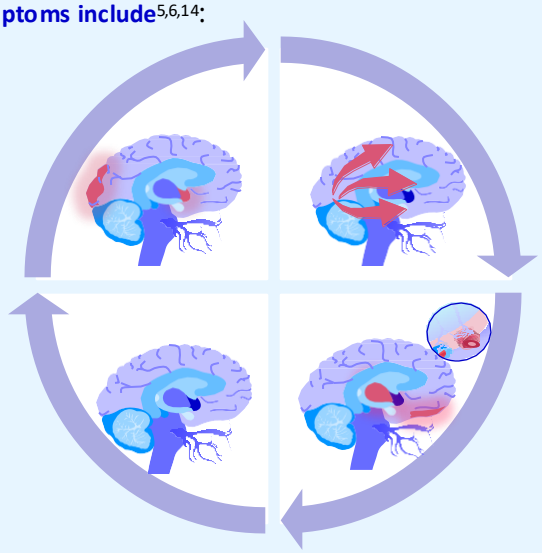
CGRP release upon trigeminovascular system activation may lead to:

Vasodilation of intracranial arteries[10,13]

Promotion of local **inflammation**[10,13]

Modulation of **nociceptive pain signaling**[13]

There are four stages of migraine; symptoms include[5,6,14]:



PRODROME

Few hours–days

Activation of hypothalamic region

- Impaired concentration
- Mental slowness
- Neck pain/stiffness
- Water retention

POSTDROME

24–48 hours

Altered brain-blood flow

Symptoms include:
- Asthenia
- Tiredness
- Somnolence
- Difficulty with concentration
- Cognitive difficulties

AURA

~1 in 3 people with migraine experience aura with some or every attack[2]

5–60 minutes

Cortical spreading depression

Symptoms include:
- Visual disturbances
- Paresthesia
- Expressive language dysfunction
- Motor dysfunction

HEADACHE

4–72 hours

Activation of trigeminovascular system

Symptoms include:
- Nausea, vomiting
- Photophobia
- Phonophobia

Stages can occur sequentially or overlap, and some may not occur at all for some patients.[15,16] Interictal periods occur between migraine attacks, during which symptoms may persist, and individuals remain susceptible to the next attack[5,14]

[a]Tension-type headache is the most prevalent neurological disease

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A genetic component to migraine susceptibility exists[16]

According to the American Migraine Foundation:

If **1 parent** has migraine, there is a **50%** chance their child will too[7]

If **both** parents have migraine, there is a **75%** chance their child will too[7]

Migraine triggers are unique and specific to each patient; commonly reported triggers include[9b]:

- **Stress** 80%
- **Hormones in women** 65%
- **Not eating** 57%
- **Weather** 53%
- **Sleep disturbance** 50%

The ICHD-3 provides diagnostic criteria for three main categories of migraine[1]

Migraine categories				
Migraine *without* aura History of ≥5 attacks	Headache attacks lasting **4–72 hours** *(when untreated or unsuccessfully treated*	**With ≥2 of the following characteristics:** • Unilateral location • Pulsating quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity	**Accompanied by ≥1 of the following symptoms:** • Nausea and/or vomiting • Photophobia • Phonophobia	Symptoms not better accounted for by another ICHD-3 diagnosis
Migraine *with* aura[c] History of ≥2 attacks	Recurrent migraine aura symptoms lasting **5–60 minutes** that accompany or are followed **within 60 minutes** by a headache	**With ≥3 of the following characteristics:** • ≥1 aura symptom that spreads gradually over ≥5 minutes • ≥2 aura symptoms that occur in succession • Individual aura symptoms of 5– 60 minutes • ≥1 unilateral[d] aura symptom • ≥1 positive aura symptom e.g., scintillations /pins and needles • Aura with/followed by headache within 60 min	**≥1 of the following fully reversible aura symptoms:** • Visual • Sensory • Speech and/or language • Motor • Brainstem • Retinal	Symptoms not better accounted for by another ICHD-3 diagnosis Transient ischemic attack should be excluded

Episodic migraine

- Headache or migraine occurring on < **15 days/month**
- **Does not fulfill** the diagnostic criteria for chronic migraine

Chronic migraine

- Headache occurring on **≥15 days/month for >3 months**
- With features of migraine **on ≥8 days/month**

Abbreviations

BBB, blood-brain barrier; CGRP, calcitonin gene-related peptide; CNS, central nervous system; ICDH-3, International Classification of Headache Disorders 3rd Edition; PNS, peripheral nervous system.

Footnotes

[b]Based on a retrospective study of 1750 patients with migraine; [c]Migraine with aura can be subcategorized as typical aura, brainstem aura (≥2 brainstem symptoms, e.g., dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, decreased consciousness), hemiplegic migraine (motor weakness) or retinal migraine (monocular visual disturbances); [d]Aphasia is always unilateral while dysarthria may or may not be.

References

1. Gupta J, Gaurkar SS. *Cureus* 2022;14(8):e28347; **2.** Eigenbrodt AK, et al. *Nat Rev Neurol* 2021;17:501–14; **3.** GBD 2016 Headache Collaborators. *Lancet Neurol* 2018;17:954–76; **4.** GBD 2017 US Neurological Disorders Collaborators. *JAMA Neurol* 2021;78:165–76; **5.** Andreou AP, Edvinsson L. *J Headache Pain* 2019;20:117; **6.** Dodick DW. *Lancet* 2018;391:1315–30; **7.** American Migraine Foundation. Facts about migraine 2019(https://americanmigrainefoundation.org/resource-library/migraine-facts/); **8.** Polderman TJC, et al. *Nat Genet* 2015;47:702.709; **9.** Kelman L. *Cephalalgia* 2007;27:394–402; ; **10.** Ashina M, et al. *Lancet Neurol* 2019;18:795–804 ; **11.** Woolf, CJ. *Pain* 2011;152:S2-S15**; 12.** Ashina M. *N Engl J Med* 2020;383;1866–76; **13.** Edvinsson L, et al. *Nat Rev Neurol* 2018;14:338–50; **14.** Ferrari MD, et al. *Nat Rev Dis Primers* 2022;8:2; **15.** Khan J, et al. *Biomed Pharmacother* 2021;139:111557; **16.** American Migraine Foundation. Migraine prodrome: symptoms and prevention 2022(https://americanmigrainefoundation.org/resource-library/migraine-prodrome-symptoms prevention/).

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