Disclosures

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Learning Objectives

- Identify the migraine types and the neuroinflammatory peptides that play a role in migraine pathogenesis, and how they affect migraine pathways
- Describe current and emerging treatment options for migraine
- Recognize how CGRP targeted therapies can modulate treatment
- Incorporate optimal acute and preventive treatment of migraine in special populations
Clinical Updates in Migraine: Dawn of a New Day

Epidemiology

13% prevalence in US in any given year
18% women; 6-7% men
One of leading causes of disability world-wide
High socio-economic burden
Most common neurologic disease seen in primary care
Migraine most common type of primary headache seen in a primary care office
Not enough neurologists or headache specialists to see the 39 million Americans with migraine

Disability of Migraine

- 2nd leading cause of years lived with disability world-wide
- 6th most common disabling illness in the world
- Peaks in ages 22-55 for men and women
- Affects 1 in every 4 households in US


The Prevalence of Migraine in Primary Care

12% Population
29% Primary Care Waiting Room
94% Out-Patient with a Complaint of Headache

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Migraine – Most Common Headache in Clinical Practice

• Patients seen in primary care
• IHS diagnosis based on diary review

N = 377
IHS = International Headache Society

Migraine-type
Episodic Tension-type
Unclassifiable

94%
3%
3%


They’re Here...
(In My Waiting Room That Is)

• >37% of women of reproductive age in a physician’s waiting room have migraine
• People with episodic tension headache rarely seek medical advice
• Other primary headache disorders infrequently appear in a primary care office
• Chronic condition – they will need a lifetime of care, they will need a good PCP
  • Only 520 certified headache specialists in the United States

PCP = primary care physician
Diagnosis

Diagnosis of Migraine

At least 5 attacks lasting 4-72 hours with at least 2 of the following:
1. Unilateral location
2. Pulsating quality
3. Moderate to severe pain
4. Aggravation or avoidance of physical activity

During the headache at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
3. Not better accounted for by another ICHD-3 diagnosis
Migraine With Aura

At least 2 attacks with 1 or more of the following fully reversible aura symptoms:
1. Visual
2. Sensory
3. Speech and/or language
4. Motor
5. Brainstem
6. Retinal

At least 3 of the following:
1. At least 1 aura symptom spreads gradually over >5 minutes
2. 2 or more occur in succession
3. Each aura symptom lasts 5-60 minutes
4. At least one aura symptom is unilateral
5. At least one aura symptom is positive
6. Aura accompanied or followed by headache within 60 minutes


Phases of Migraine Attack

1. Premonitory or Prodrome1-3 (up to 24 hrs) (5-60 mins)
2. Headache (4-72 hrs)
3. Postdrome1,3
4. Interictal1,5

Symptoms:
- Fatigue
- Depression
- Nausea
- Neck pain
- Photophobia
- Phonophobia
- Yawning

59-63%

Fatigue
Depression
Nausea
Neck pain
Photophobia
Phonophobia
Yawning

Tension-type Headache

At least 10 episodes of headache fulfilling the following:

A. Lasting from 30 minute to 7 days

B. At least 2 of the following:
   1. Bilateral
   2. Pressing or tightening (non-pulsating)
   3. Mild-moderate intensity
   4. Not aggravated by routine physical activity

C. Both of the following:
   1. No nausea or vomiting
   2. No more than one of photophobia or phonophobia

Not accounted for by another ICHD-3 diagnosis


Cluster Headache

At least 5 attacks of the following:

1. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes when untreated

Either or both of the following:

1. At least one of the following symptoms or signs, ipsilateral to the headache-conjunctival injection and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial swelling, miosis and/or ptosis

2. A sense of restlessness or agitation

Occurring with a frequency between one every other day and 8 per day

Not accounted for by another ICHD-3 diagnosis
**Cluster Headache**

**Episodic Cluster**
- At least 2 cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of 3 months or greater
- Cluster periods usually last between 2 weeks and 3 months
- Majority of cluster are episodic
- Age onset both episodic and cluster 20-40 years old
- Men affected 3x more than women

**Chronic Cluster**
- Cluster headache attacks lasting for 1 year or longer without remission or with remission periods lasting less than 3 months
- About 10-15% of cluster patients
- Triggers include alcohol, histamine or nitroglycerin for both cluster types
- Often referred to as the “suicide” headache

**“Sinus” Headache**
- Term no longer recognized by ICHD-3
- Headache attributed to acute rhinosinusitis is part of ICHD-3 classification and is a secondary headache (not primary)
- Headache has developed in temporal relation to onset of rhinosinusitis
- Headache significantly improves or resolves in parallel with resolution of rhinosinusitis

### ID Migraine

**During the last 3 months, did you have the following with your headaches?**

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>You felt nauseated or sick to your stomach?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light bothered you (a lot more than when you don’t have headaches)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Your headaches limited your ability to work, study, or do what you needed to do?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 2/3 for migraine
- Sensitivity: 0.81
- Specificity: 0.75

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### Classification of Migraine

- **Episodic** - less than 15 days per month of headache
- **Infrequent Episodic** - <4 headache days/month
- **Frequent Episodic** - 4 to <15 migraine headache days/month
- **Chronic** - 15 or more headache days per month of which 8 or more meet criteria for migraine for at least 3 months
- **Migraine may or may not be associated with medication overuse**

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Evolution of CM from EM

- Patients may transition among these 3 migraine states in the direction of increasing and decreasing frequency
- Transitions occur over weeks to months
- CM develops in individuals with EM at the rate of 2.5% per year

![Image of migraine state evolution diagram](https://example.com/migraine-diagram.png)


Patient Characteristics of EM vs CM

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>EM</th>
<th>CM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache frequency, days/mo</td>
<td>&lt;15</td>
<td>≥15</td>
</tr>
<tr>
<td>Report severe headache (%)</td>
<td>78.1</td>
<td>92.4*</td>
</tr>
<tr>
<td>Duration of headache pain without medication (mean h)</td>
<td>38.8</td>
<td>65.1*</td>
</tr>
<tr>
<td>Duration of headache pain with medication (mean h)</td>
<td>12.8</td>
<td>24.1*</td>
</tr>
<tr>
<td><strong>Sociodemographic Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race, % white</td>
<td>87.3</td>
<td>90.7</td>
</tr>
<tr>
<td>Women, %</td>
<td>80.0</td>
<td>78.6</td>
</tr>
<tr>
<td>Low household income, % &lt;$22,500/y</td>
<td>24.9</td>
<td>29.9*</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression, %</td>
<td>17.2</td>
<td>30.2*</td>
</tr>
<tr>
<td>Anxiety, %</td>
<td>18.8</td>
<td>30.2*</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>21.0</td>
<td>25.5*</td>
</tr>
<tr>
<td>Cutaneous allodynia, %</td>
<td>63.2</td>
<td>68.3*</td>
</tr>
</tbody>
</table>

*Indicates statistical significance (P<0.05) between EM and CM

**When Is it Not a Migraine?**

- **Primary Headaches**
  - Migraine
  - Tension-type
  - Cluster
  - Miscellaneous headaches unassociated with structural lesions

- **Secondary Headaches**
  - Post-traumatic
  - Vascular disorders
    - Stroke, hemorrhage
  - Nonvascular intracranial disorder
    - Neoplasm, meningitis, low or high CSF pressures
  - Substances/withdrawal
  - Systemic infection or metabolic disorder
  - Cranial, extracerebral lesions

CSF = cerebral spinal fluid
Not Missing a Secondary Headache

• Key point – migraine patients can have or develop a secondary headache
• Red flag, “Worse headache ever”
• SNOOP mnemonic
• Choosing wisely; blood work and brain scan are not a routine part of a headache work-up

Worrisome Headache
“Red Flags”

‘SNOOP4’ – When in doubt, investigate the atypical!
Systemic symptoms (fever, weight loss); or
  • Secondary risk factors – underlying disease (HIV, systemic cancer)
  • Neurologic symptoms or abnormal signs (confusion, impaired alertness, or consciousness)
  • Onset: Sudden, abrupt, or split-second (first, worst)
  • Older: New onset and progressive headache, especially in middle age >50 (giant cell arteritis)
  • Pattern change: First headache or different, change in type of headache
    • Postural aggravation
    • Papilledema
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**Diagnostic Imaging**

- Headache merits neuroimaging in special circumstances only (immunosuppression, thunderclap onset, new onset pregnancy)
- 0.4% yield potentially treatable lesions in patients with nontraumatic migraine
- Focal neurologic deficits increase likelihood of finding an abnormality


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Pathophysiology of Migraine

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Migraine: Is it Vascular?

Current Theory of Migraine Pathophysiology

- **Vascular Theory**
  - Pain caused by:
    - Constriction of blood vessels in the cranium
    - Rebound vasodilation

- **Neurogenic Theory**
  - Pain caused by interaction between:
    - Cortical spreading depression (cortex)
    - Trigeminal system

- **Neurovascular Theory**
  - Pain caused by combination of:
    - Cortical spreading depression (cortex)
    - Trigeminal system
    - Cranial vascular changes brought about by release of neuropeptides and proinflammatory substances

Migraine Is a Complex Disease With Peripheral and Central Components

**Peripheral components**¹:
- Trigeminal afferents (CGRP)
- Meningeal vasculature
- Resident immune cells

**Central components**²:
- Trigeminal efferent (CGRP)
- Trigeminal cervical complex
- Thalamus
- Cortex

CGRP = calcitonin gene related peptide

1. Ferrari, MD. Lancet Neurology. 2015; 14(1);65-80; Figure Ferrari, MD. Lancet Neurology. 2015; 14(1);65-80.

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Key Steps in Migraine Evolution

- Trigeminovascular system gets activated
- Trigeminal nerves release neurotransmitters and neuropeptides such as CGRP
- Nociceptive (painful) signals can be transmitted through this pathway during a migraine
- Primary afferents of the trigeminal ganglion innervate the dura and dura vasculature and synapse onto the trigeminocervical complex in brainstem (2nd order neurons)
- Transmission of pain can travel up to thalamus and cortex
What is CGRP?

- Calcitonin gene-related peptide – a 37 amino acid polypeptide in neurons and glial cells (universally present)
- Receptors to CGRP are located throughout the trigeminal system and multiple brain regions (as well as other locations throughout the body)
- CGRP is a vasodilator and causes neurogenic inflammation
- CGRP modulates pain signaling

CGRP and Migraine: Where is the Evidence?

- CGRP levels elevated during migraine attack (measured external jugular vein)¹
- Infusion of CGRP in migraine patients can cause migraine²
- Infusion of CGRP blocking medication can resolve a migraine attack in a migraine individual³
- Development of new targeted CGRP blocking molecules show promise in migraine treatment (including large monoclonal antibodies and small molecule oral medications called “gepants”)

Role of CGRP in Migraine

CGRP elevated in spontaneous migraine\(^1\)

IV infusion of CGRP induces headache\(^2\)

Successful acute migraine therapy lowers CGRP\(^3\)

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Role of CGRP in Migraine Pathophysiology

Neurogenic Inflammation

Peripheral Sensitization

Central Sensitization

CGRP causes vasodilation and mast cell degranulation indirectly activating nociceptors*

Felt as initial headache

CGRP stimulates cytokine release, thereby stimulating trigeminal neurons*

Felt as throbbing pain and sensitivity to movement

CGRP enhances synaptic excitability*

Felt as cutaneous allodynia and photophobia

* To date, dural mast cell degranulation has not been observed in humans

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CGRP Ligand and Receptor Distribution

CGRP neurons innervate multiple systems such as cardiovascular, respiratory, endocrine, GI and central and peripheral nervous systems.

- CGRP is a 37 amino acid peptide
- \( \alpha \)-CGRP is found predominately in CNS and PNS
- \( \beta \)-CGRP is mainly found in enteric nervous system

CGRPs most basic functions include:

- Vasodilation
- Inflammation/Immune modulation
- Sensory stimuli perception

Role of CGRP in Other Selected Systems

**Respiratory system**
- CGRP is abundant in lungs and vasodilates pulmonary arterioles
- CGRP protects against pulmonary hypertension in animal models

**Wound healing**
- CGRP produces vasodilation and inflammation in the skin
- Depletion of CGRP, by capsaicin, reduced wound healing in rats
- Impaired wound healing, angiogenesis and enhanced inflammation in CGRP KO mice

**Diabetes and obesity**
- Potential for protective and causative roles for CGRP in diabetes
- CGRP dampens insulin release and CGRP KO mice are resistant to diet-induced obesity
- Possible connection between lower CGRP and impaired wound healing, neuropathy and cardiovascular disease common in diabetes

**Ischemia**
- CGRP plays a protective role against ischemia in the gut, kidney, brain, and heart
- CGRP KO mice are more susceptible to ischemic injury and have impaired recovery
- Endogenous but not exogenous CGRP protects against myocardial infarction

GI = gastrointestinal
CNS = central nervous system
PNS = peripheral nervous system

CGRP is an Endothelial Dependent and Independent Vasodilator

Endogenous CGRP works locally, but not systemically, as a potent vasodilator on the endothelium and smooth muscle.

Bi-directional communication between vessels and the nervous system occurs without changes in vascular tone.

CGRP alone is not the key mediator of the physiologic regulation of blood pressure.

Mixed evidence for the protective role of CGRP in cardiac ischemia and cerebral ischemia.

Summary of CGRP

CGRP is found throughout the body and contributes to the pathophysiology of many diseases, including migraine.

CGRP signaling within the trigeminovascular system contributes to:
  - Neurogenic Inflammation
  - Peripheral and central sensitization
  - Ultimately enhancing transmission of pain signaling.


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Thank You!

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