INSIGHTS INTO THE PATHOPHYSIOLOGY OF MIGRAINE

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Overview of Presentation

Clinical Features

Pathophysiology

Effective Treatments

CLINICAL FEATURES:
- Throbbing / Pounding
- Worsening with Activity
- Photophobia / Phonophobia
- Nausea and Vomiting
- Allodynia
- Misdiagnosis as Sinus Headache
- Misdiagnosis as Tension-Type Headache
- Medication Overuse Headache (MOH)
- Common triggers
- Family history

EFFECTIVE TREATMENT:
- Migraine specific acute treatments- triptans
- DHE vs. triptan site(s) of action
- Early vs. late treatment
- Treatment while experiencing allodynia
- Rescue with NSAID's or steroids
- MOA for preventative pharmaceuticals
- MOA of osteopathic manipulation
- MOA of blocks, stimulators, OT-A, TCMS
- New targets- CGRP, Sub P, NKA, etc.
Objectives:

- List the (ICHD-3 beta) diagnostic criteria for migraine headache and apply them effectively in clinical practice.
- Briefly explain the pathophysiology behind the main clinical features seen in migraine.
- Describe the site and mechanism(s) of action of at least three acute and three preventative treatments for migraine.

Migraine Prevalence Compared With Other Neurologic Diseases

- MS = multiple sclerosis
- PD+HD = Parkinson disease + Huntington disease
- AD = Alzheimer’s disease

Migraine: A Disabling Headache Disorder

- Burden
  - Among the world’s 20 most disabling diseases (WHO)
  - Indirectly costs employers up to $13 billion per year
  - Direct medical costs exceed $1 billion per year
  - “same level of disability as dementia, quadriplegia and acute psychosis”

WHO = World Health Organization.


A Sophisticated Array of Effective Treatment Options

PREVENTATIVE:
- Dietary modification
- Trigger identification & avoidance
- Exercise
- Sleep hygiene / improvement
- Biofeedback
- Stress management & relaxation
- Acupuncture
- Osteopathic manipulation
- Nutraceuticals
- Herbal preparations
- Pharmaceuticals
- Onabotulinum Toxin A injections
- Peripheral nerve blockade / stimulation

ABORTIVE:
- Biofeedback and progressive relaxation
- Sleep induction
- Acupuncture
- Osteopathic manipulation
- Biofeedback
- Nutraceuticals
- Herbal preparations
- Occipital nerve blocks
- Trigeminal nerve blocks
- Neurostimulation
- Triptans
- Ergots & DHE
- NSAID’s
- Antiemetics
- IV infusions
Migraine Without Aura: International Headache Society Criteria

A. At least 5 attacks fulfilling criteria B through D

B. Headache attacks: 4 to 72 hours

C. Headache with at least 2 of the following characteristics
   1. Unilateral
   2. Pulsating
   3. Moderate or severe pain intensity
   4. Aggravation by or causing avoidance of routine physical activity

D. During headache at least 1 of the following:
   1. Nausea and/or vomiting
   2. Photophobia and phonophobia

E. Not attributed to another disorder

Migraine With Aura: International Headache Society Criteria

A. At least 2 attacks fulfilling criteria B through D

B. Aura consisting of at least 1 of the following, but no motor weakness
   1. Fully reversible visual symptoms*
   2. Fully reversible sensory symptoms*
   3. Fully reversible dysphasic speech disturbance

C. At least 2 of the following
   1. Homonymous visual symptoms and/or unilateral sensory symptoms
   2. ≥1 aura symptom over ≥5 minutes, and/or different aura symptoms in succession over ≥5 minutes
   3. Each symptom: ≥5 and ≤60 minutes

D. Headache fulfilling criteria B through D for migraine without aura begins during the aura or follows aura within 60 minutes

E. Not attributed to another disorder

*Including positive features and/or negative features.

The Natural Course of a Typical Migraine Attack

Premonitory phase
Aura
Headache phase
Resolution
Postdrome

Theoretical Model of a Migraine Cycle

Trigger
Initiating mechanisms
Low threshold
Perpetuating mechanisms
Resolving mechanisms

Adapted with permission from Linde M. Acta Neurol Scand. 2006;114:71-83.
Adapted from Expert Review Neurother. 4(3) 391-430 (2004) with permission of Future Drugs Ltd.
Migraine Triggers and Precipitants

- N=1,207 patients with migraine
- 75.9% reported triggers
  - 40.4% infrequently
  - 26.7% frequently
  - 8.8% very frequently

Adapted with permission from Kelman L. Cephalalgia. 2007; 27:394–402.

Migraine Pathophysiology: Proposed Mechanisms

- Genetic predisposition
- Cortical neuronal hyperexcitability
- Abnormal brainstem function

Aura

CSD

Activation and peripheral sensitization of TGVS

Neurogenic inflammation

Central sensitization

HEADACHE

Adapted with permission from Pietrobon D. Neuroscientist. 2005; 11:373–388.
The Primary Cause of the Migraine Headache Lies in the Brain

- Genetic predisposition in some patients
- Cortical neuronal hyperexcitability and/or brainstem dysfunction
- Trigger: Cortical Spreading Depression (?)
- Activation & sensitization of the TGVS
- Prolonged headache pain of migraine

The “vascular theory” not supported by experimental evidence:

→ migraine does not start in the blood vessels

TGVS = trigeminovascular system.

Migraine Pathophysiology: Central Role of the Trigeminovascular System

TGVS activated

PAIN

CSD

Dura

Trigeminal nerves

CSD = cortical spreading depression;
TNC = trigeminal nucleus caudalis.
Parasympathetic Contribution to Migraine Pathophysiology


FHM: a rare inherited form of migraine
Genetically heterogenous autosomal dominant

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Consequence</th>
</tr>
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<tbody>
<tr>
<td>FHM-1</td>
<td>CACNA1A</td>
<td>P/Q Ca(^{2+}) channels</td>
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<tr>
<td></td>
<td></td>
<td>↑ presynaptic Ca(^{2+})</td>
</tr>
<tr>
<td>FHM-2</td>
<td>ATP1A2</td>
<td>Na(^{+})/K(^{+})-ATPase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ K(^{+}) and glutamate clearance</td>
</tr>
<tr>
<td>FHM-3</td>
<td>SCN1A</td>
<td>Na(^{+}) channel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Persistent Na(^{+}) influx</td>
</tr>
</tbody>
</table>

FHM = familial hemiplegic migraine.
**Familial Hemiplegic Migraine: Functional Implications of Gene Mutations**

- **FHM-1**
  - CACNA1A gene
  - Cav2.1 Ca²⁺
  - Gain of function

- **FHM-2**
  - ATP1A2 gene
  - α₂-subunit Na⁺/K⁺ ATPase pump
  - Loss of function

- **FHM-3**
  - SCN1A gene
  - Nav1.1 Sodium channel
  - Gain of function

↑Glu/↑K⁺

CSD

Synaptic metabolism (including glucose uptake)


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**Cortical Neuronal Hyper excitability: Multiple Mechanisms**

- Enhanced release of excitatory neurotransmitters
  - For example, elevated plasma glutamate concentration in patients with migraine
  - Identified genetic mutations in FHM
- Reduced intracortical inhibition
- Low brain Mg²⁺
- Altered brain energy metabolism

NMDA = N-methyl-D-aspartate.

Initiating Mechanisms of Headache Pain: Cortical Spreading Depression

- Wave of intense cortical neuron activity
  - $↑$ rCBF
- Followed by neuronal suppression
  - $↓$ rCBF
  - Often coincides with headache onset
- Velocity: 2–3 mm/min
- Underlies visual aura
- Occurs in clinically silent areas of the cortex?
  - Migraine without aura

rCBF = regional cerebral blood flow.


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Initiating Mechanisms of Migraine: Brainstem Dysfunction

- Dysfunction in areas involved in central control of nociception
  - PAG
- Induces migraine?
  - Brainstem generator
- Facilitates activation and sensitization of TNC neurons?
  - Decreased descending inhibition during a migraine attack

PAG = periaqueductal gray region
Adapted with permission from Pietrobon D. Nat Rev Neurosci. 2003;4:386–389.
Activation of the Trigeminovascular System and Pain Generation

Adapted with permission from Iadecola C. *Nat Med*. 2002;8:110–112.

Activation of the Trigeminovascular System: Physiologic Impact

**Meningeal events**
- Inflammation
- Peripheral sensitization

**Brainstem events**
- Pain signal to CNS
- Central sensitization
- Allodynia

Neurogenic Inflammation Meninges

- CGRP and substance P activate mast cells
- Mast cell degranulation
  - Histamine
  - NGF
  - Serotonin
  - Proinflammatory cytokines
    - TNFα, IL-1, IL-6

Vasodilation of Cerebral Vessels

Hypothesis: Serotonin Presynaptically Inhibits CGRP Release in Active Trigeminal Nociceptors

During headache pain: Trigeminal nociceptors become activated

Serotonin
Serotonin receptor
CGRP

5-HT receptors activated
CGRP release inhibited


Pain Signaling to CNS

Neuronal Sensitization and Migraine

Peripheral Sensitization and Migraine

**Neurogenic inflammation**

- **Peripheral sensitization**
  - Response threshold of meningeal TGVS nociceptors
  - Response amplitude

- Early: within ~ 20 min of the onset of pain
- Can last for up to 2 hours
- Throbbing pain
- Worsened by movement
- Drives central sensitization

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**Central Sensitization and Migraine**

**Peripheral sensitization**
- ↑ incoming stimulation from the trigeminal nerve

**Central sensitization**
- Neuronal hyperexcitability in the TNC
  - Possibly due to: CGRP, Ca²⁺, glutamate (NMDA)

- ▪ Later: within ~60 min of the onset of pain
  - ▪ Can last up to 10 hours
- ▪ Allodynia
- ▪ Prolongation of the attack
- ▪ Drives sensitization of higher-order neurons

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**Measurable Neuropeptide Levels in the External Jugular Vein During Migraine Attacks**

<table>
<thead>
<tr>
<th></th>
<th>VIP</th>
<th>Substance P</th>
<th>CGRP</th>
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<tbody>
<tr>
<td>Migraine without aura</td>
<td>± 0</td>
<td>± 0</td>
<td>↑</td>
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<tr>
<td>Migraine with aura</td>
<td>± 0</td>
<td>± 0</td>
<td>↑</td>
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<tr>
<td>Trigeminal neuralgia</td>
<td>± 0</td>
<td>± 0</td>
<td>↑</td>
</tr>
<tr>
<td>Cluster headache</td>
<td>↑</td>
<td>± 0</td>
<td>↑</td>
</tr>
<tr>
<td>Chronic paroxysmal headache</td>
<td>↑</td>
<td>± 0</td>
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± 0 = no change from before headache.
↑ = significant increase in neuropeptide level.

Activation of the Trigeminovascular System: Primary Neuromediators in Migraine

<table>
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<tr>
<th>Neuro-peptides</th>
<th>Origin of Release</th>
<th>Suggested Meningeal Actions</th>
<th>Brain-stem</th>
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<tr>
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<tr>
<td>Glutamate</td>
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CGRP = calcitonin gene–related peptide; VIP = vasoactive intestinal peptide.

CGRP: Central Role in Migraine

- Main neuropeptide released by activated TGVS neurons in migraine
  - Major neuropeptide of the TGVS
- Infusion in susceptible individual induces migraine
- During migraine: increased in jugular venous blood, cerebrospinal fluid, saliva
  - Also elevated in blood between attacks
- Physiologic actions:
  - Vasodilation
  - Meningeal mast cell degranulation
  - Activation of second-order neurons in the TNC

CGRP Receptor

Adapted with permission from Brain SD, Grant AD. Physiol Rev. 2004;84:903–934.

Substance P: Role in Migraine?

- Member of the tachykinin neuropeptide family
  - Substance P
  - Neurokinin A
- Coexpressed and coreleased with CGRP
  - Less abundant than CGRP in trigeminal neurons
- Role in migraine—if any—poorly understood
  - Substance P blood levels not increased during headache phase
  - Substance P does not appear involved in vascular nociception
  - Substance P mediates dural plasma extravasation

Substance P Receptors

Glutamate: Central Role in Migraine

- Increased brain levels of glutamate may underlie cortical hyperexcitability in patients with migraine

- CSD
  - Is propagated by glutamate
  - Can be induced by NMDA and Mg²⁺ depletion (which releases NMDA receptors)

- Trigeminovascular activation
  - Glutamate-positive neurons found in all migraine pain-relay centers
  - All glutamate receptor subtypes expressed on the trigeminal system

- Pain signaling to CNS and central sensitization
  - Involves glutamate

Ramadan NM. CNS Spectr. 2003;8:446–449.
Nitric Oxide and Migraine

- Potent vasodilator
- NO donors induce migraine in susceptible humans
- NOS-containing fibers found around cranial blood vessels
  - Parasympathetic fibers
  - Trigeminal sensory fibers
- May contribute to vasodilation and activation of the TGVS nociceptive nerve terminals
- Role as a neurotransmitter
  - NOS expressed in trigeminal nerve cell bodies
  - May be involved in the activation and/or sensitization of TNC neurons

NOS = nitric oxide synthase.
Ramadan NM et al. Pharmacol Ther. 2006;112:199–212;

Migraine Pathophysiology: Summary

Initiation
- Genetic predisposition
- Cortical neuronal hyperexcitability
- Abnormal brainstem function
- (?)

Pain generation/perpetuation
- Activation of TGVS Neuromediator release (CGRP, glutamate)
- +
- Neurogenic inflammation
- Peripheral sensitization
- Central sensitization
- +
- HEADACHE
- (+)

TGVS = trigeminovascular system.
Adapted with permission from Pietrobon D. Neuroscientist. 2005;11:373–386.