Headaches –“its all in your head”

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Migraines – very common and often disabling!

Global Burden of Disease Study 2015
- Common, multifactorial, disabling, recurrent, hereditary neurovascular headache disorder
- Migraine is the 3rd most prevalent medical disorder on the planet
- Migraine accounts for > 50% of the disability burden attributable to all neurological disease worldwide.
- Overall, 4th ranking cause among women and the 6th ranking cause of all disease-associated disability worldwide.
- 2.1 million ER visits/year
- $13 billion lost/year in productivity

• First mention of “hemicrania” is cited by the Oxford dictionary as 1597
• Even mentioned by Hippocrates in his writings
• Julius Caesar thought to have suffered from migraines
• Lewis Carroll – Alice in Wonderland, possibly migraine with visual aura
Diagnostic criteria for Migraine without aura

A. At least five attacks fulfilling criteria B through D

B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)

C. Headache has at least two of the following characteristics:
   Unilateral location/Pulsating quality/Moderate or severe pain intensity
   Aggravation by routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:
   Nausea, vomiting, or both
   Photophobia and phonophobia

E. Not better accounted for by another ICHD-3b diagnosis

Reference: Cephalalgia. 2013 Jul;33(9):627-8
Diagnostic criteria for Migraine with aura

- A. At least two attacks fulfilling criterion B and C

- B. One or more of the following fully reversible aura symptoms:
  Visual/Sensory/Speech and/or language
  Motor /Brainstem/Retinal

- C. At least two of the following four characteristics:
  At least one aura symptom spreads gradually over ≥5 minutes, and/or two or more symptoms occur in succession
  Each individual aura symptom lasts 5 to 60 minutes
  At least one aura symptom is unilateral
  The aura is accompanied, or followed within 60 minutes, by headache

- D. Not better accounted for by another ICHD-3b diagnosis, and transient ischemic attack has been excluded

Reference: Cephalalgia. 2013 Jul;33(9):627-8
Migraine Pathophysiology

- Migraine is not just a headache (premonitory phase-hours to days, aura phase-<60 minutes, headache phase-hours to days and recovery phase-hours to days)
- Complex neurological disorder that affects multiple cortical, subcortical, and brainstem areas that regulate autonomic, affective, cognitive, and sensory functions.
- Primary neuronal event resulting in a trigeminovascular reflex causing neurogenic inflammation

doi: 10.1523/JNEUROSCI.0373-15.2015
Migraine pathophysiology

- Once popular vascular theory is no longer considered viable
- Trigeminal activation causes inflammatory changes in the pain-sensitive meninges
- Trigeminal nucleus caudalis -> thalamus->sensory cortex
- Substance P, Calcitonin gene-related peptide (CGRP – a potent vasodilator), neurokinin A result in neurogenic inflammation
- Cortical spreading depression is thought to cause aura, activate trigeminal afferent and alter BBB
- Sensitization – neurons become increasingly responsive to nociceptive and non-nociceptive stimulation, responsible for many migraine symptoms
Cortical Spreading Depression

- Massive wave of depolarization, propagating at 2 to 4 mm/min, followed by suppressed cortical activity
- Fluxes in extracellular glutamate and K+
- Changes in vascular tone

Blood oxygenation level-dependent (BOLD) functional MR imaging

Migraine Pathophysiology

- Role of Serotonin in generation of migraine unclear
- Elevated CGRP levels normalized after serotonin (1b/1d) agonist/triptan
- Complex genetic basis, KCNK18 and CSNK1D genes have been implicated in migraine with aura
- Interestingly, narcotics have no effect on CGRP or Serotonin receptors
- Familial hemiplegic migraines associated with mutations in four genes
Role of Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists in Migraine

- Triptans are a first-line treatment for migraines
  - Side-effects (e.g., chest pain, pressure, asthenia, paraesthesia, dysaesthesia and hyperaesthesia, throat tightness)
  - Triptans are vasoconstrictors
    - Contraindicated in patients with history, symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular disease
  - Serotonin syndrome risk when triptans are used in combination with SSRIs or SNRIs
- CGRP is a potent neuropeptide neurotransmitter
  - Released from peripheral and central nerve endings during migraine and cluster headache
- CGRP receptor antagonists
  - Block the action of CGRP, thus inhibiting migraine pain transmission
  - Inhibit vasodilation
## Trigeminal Autonomic Cephalalgias

<table>
<thead>
<tr>
<th></th>
<th>Cluster Headache</th>
<th>Paroxysmal Hemicrania</th>
<th>SUNCT/SUNA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>M&gt;F</td>
<td>F=M</td>
<td>F=M</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Attack frequency (/day)</td>
<td>1 to 8</td>
<td>11</td>
<td>10-200</td>
</tr>
<tr>
<td>- Duration (minutes)</td>
<td>15-180</td>
<td>2-30</td>
<td>5-240 s</td>
</tr>
<tr>
<td><strong>Cranial autonomic features</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes++</td>
</tr>
<tr>
<td><strong>Migrainous features</strong></td>
<td>50%</td>
<td>65%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Alcohol trigger</strong></td>
<td>90%</td>
<td>10%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Cutaneous trigger</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Rx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sumatriptan s/c</td>
<td>90%</td>
<td>20%</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>- Indomethacin</td>
<td>No effect</td>
<td>100%</td>
<td>No effect</td>
</tr>
<tr>
<td>- Oxygen</td>
<td>75%</td>
<td>No effect</td>
<td>No effect</td>
</tr>
</tbody>
</table>

*(After Cohen et al., Brain 2006;129:2746 and Cittadini et al., Brain 2008;131:1142) Nausea/photophobia/phonophobia*
Cranial Autonomic Symptoms
1. Conjunctival injection, lacrimation, or both
2. Nasal congestion, or rhinorrhea, or both
3. Eyelid oedema
4. Forehead and facial sweating
5. Forehead/facial flushing
6. Sense of fullness in the ear
7. Miosis, or ptosis, or both

Trigeminal-autonomic reflex

thalamus

thalamus

CGRP PACAP
V ganglion

dura mater

superior salivary n.

sphenopalatine ganglion (pterygopalatine)

VIP PACAP

nitric oxide synthase

CGRP: calcitonin gene-related peptide
PACAP: pituitary adenylate cyclase activating peptide

Goadsby & Lipton Brain 1997;120:193
2SNOOP4 – Secondary causes

- Systemic symptoms (fever, weight loss) or Secondary risk factors (HIV or cancer)
- Neuro symptoms/signs (confusion, impaired consciousness, focal deficits, etc)
- Onset – sudden/abrupt or split-second
- Older age (>50)
- Postural worsening
- Precipitated by Valsalva
- Pregnancy
- Progressive (sudden change in character, frequency or severity)

Secondary Headache disorders

**Reversible Cerebral Vasoconstriction Syndrome (RCVS)**
- recurrent thunderclap in first 7 days is a strong indicator
- peaks at 3 weeks

**Idiopathic Intracranial Hypertension (IIH)**
- consider it even if no papilledema, visual disturbance, pulsatile tinnitus, etc
What is this?
Treatment of Acute Migraines

General guidelines:

- Educate and Encourage migraine sufferers
- Use migraine specific agents (eg, triptans, dihydroergotamine)
- Select a non‐oral route of administration if significant nausea or vomiting
- Consider a self‐administered rescue medication for patients with severe migraines
- Guard against medication overuse headache (MOH)
Triptans (serotonin 5HT 1B/1D agonists)

- Sumatriptan (Imitrex) 6mg sc, 20 NS, 50-100 po
- Naratriptan (Amerge) 2.5 po
- Rizatriptan (Maxalt) 10 mg po
- Zolmitriptan (Zomig) 2.5-5 mg po, NS
- Almotriptan (Axert) 12.5 mg po
- Frovatriptan (Frova) 2.5 mg po
- Eletriptan (Relpax) 40 mg po

Comparative efficacy of triptans for the abortive treatment of migraine: A multiple treatment comparison meta-analysis, Cephalalgia Vol 34, pp. 258 – 267, October 2013
Acute Migraine Rx in ER

- Either Sumatriptan (6 mg s.c) and/or antiemetic (such as metoclopramide 10 mg IV, prochlorperazine, or chlorpromazine) or
- Dihydroergotamine (DHE) 1 mg IV + Metoclopramide 10 mg IV reasonable alternatives
- DHE contraindicated in patients with ischemic vascular disease involving cardiac, cerebrovascular, or peripheral circulations
- Add Dexamethasone (10 to 25 mg IV or IM) to reduce the risk of early headache recurrence
- Avoid opioids/more likely to return to the emergency department with a headache within seven days of the original visit
- Other alternatives for acute HA treatment: (Intranasal lidocaine 4% (sphenopalatine ganglion blockade?)/Occipital nerve blockade/Valproate(Depacon®) 500 mg IV/Magnesium Sulfate-1-4 g IV
New class of triptans (5HT-1F blockers) - Lasmiditan

- Trigeminal Pathway (unlike blood vessels with triptans)
- 5-HT1F receptor (unlike 5-HT 1B/1D with triptans)
- CNS Penetrant – Yes
- Vasoconstrictor - No
- Phase 3 trials ongoing
CHRONIC MIGRAINE

SPONSORED BY THE AMERICAN HEADACHE SOCIETY AND THE AMERICAN MIGRAINE FOUNDATION

General Facts

It is estimated that up to 144 million people in the world have CM. This is as many people as those who watched the Super Bowl and the Oscars combined.

Between 3 and 7 million people in the US have CM.

CM occurs when individuals meet criteria for migraine and average 15 or more headache days/month for at least 3 months.

Both migraine and CM are 2–3 times more common in women than men.

1.3% of women and 0.5% of men in the US meet criteria for CM.

The number of women with CM (3.2 million) is approximately the same as every person in Iowa.
Treatment of Chronic Migraines

- Topiramate and onabotulinumtoxinA - at least two randomized placebo-controlled trials supporting their use in prophylaxis.

- Lower quality evidence for Valproate, Gabapentin, Tizanidine, Amitriptyline, Atenolol, Memantine, Zonisamide, and Pregabalin

- In clinical practice, we use Propranolol and Amitriptyline more often, used due to favorable side effect profile

- Always consider co-morbidities when choosing a prophylactic med.
Chronic migraine treatment

- Serotonin syndrome results from 5HT-1A/2A receptor activation, not by Triptans (5-HT 1B/1D)
- No to Butterbur or Gabapentin
- Yes to Lisinopril per Agency for Healthcare Research and Quality (Pub No 13-EHC068-1-EF, April 2013)
- CHAMP trial (NEJM Jan 2017; 376:115-124): No difference between Amitriptyline, Topiramate and Placebo in Pediatric migraines
- Adding Propranolol to Topiramate did not improve CM in adults
- However, adding Behavioral management does help overall
Transcranial Magnetic Stimulation

- FDA approved for acute treatment of migraines with aura
- The Lancet Neurology, Volume 9, Issue 4, 373 - 380
NeuroModulation

- SupraOrbital transcutaneous stimulation
- Cefaly device
Non-Invasive Vagus Nerve Stimulator (nVNS)

- pain relief in about half of patients, and complete pain relief in about 20% of patients, within 2 hours of using the device
Other non-pharmacologic options

- SphenoCath/Sphenopalatine ganglion block/Trigeminal nerve block
- Cooling Helmet
- Theraspecs for photophobia
Complimentary and Integrative Medicine (CAM)

- Herbs, supplements, aromatherapy
- Ayurveda, homeopathy
- Hypnosis, biofeedback, meditation
- 50% of chronic migraine patients use CAM
- AAN recommendation (probably effective - Level B) Feverfew, Riboflavin 200mg bid, Magnesium, CoQ10 is possibly effective
- Butterbur root may contain hepatotoxic alkaloids, so AAN withdrew support
- And yes, there is NO evidence to support “ear piercing”
DUDE, ENOUGH!

YOU’RE GIVING ME A HEADACHE