Deep Phenotyping and the Search for Biomarkers in Chronic Daily Headache,

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CHRONIC DAILY HEADACHE

“I shall not today attempt further to define the kinds of material I understand to be embraced within that shorthand description and perhaps I could never succeed in intelligibly doing so. But I know it when I see it.”
Which of the following matches the previous quote?

- Pornography
- Great art
- Bad Pastrami
- Chronic Headache
- All of the above
The Road to hell is paved with bad assumptions

- Headache is a NEUROTIC condition
- Headache is primarily a conversion disorder or somatization disorder
- Migraine is primarily a vascular disease
- Chronic daily headache is differentiated from its episodic counterpart only by frequency and duration
Misdiagnosis

Side-locked?
Autonomic features?
Duration?
Chronification pattern?
Intractable headache or Intractable patient?

- “It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has.”

William Osler
Migraine Transformation

Approximately 14% of migraine sufferers progress to CDH (TM with or without acute medication overuse).
CDH, chronic daily headache; TM, transformed migraine.
Natural History vs. Clinical Course

No Migraine \[\xrightarrow{\lambda_1} \xleftarrow{\lambda_2}\] LFEM 0-9 d/mo \[\xrightarrow{\lambda_3} \xleftarrow{\lambda_4}\] HFEM 10-15 d/mo \[\xrightarrow{\lambda_6} \xleftarrow{\lambda_5}\] Chronic Migraine

\[\lambda = \text{Transition Rate}\]
\[\text{LFEM} = \text{low-frequency episodic migraine}\]
\[\text{HFEM} = \text{high-frequency episodic migraine}\]

Presumed Pathophysiology

- Hyperexcitability of the cortex
- Dysmodulation of the pain system in the brainstem
- Sensitization of the trigeminal vascular system
  - Peripheral
  - Central
Overview of the Pathophysiology of Chronic Migraine

- **Structural brain changes**
  - Changes in cortical gray matter
  - Increased iron deposition in pain-related structures
  - Subcortical white matter lesions and cerebellar infarct-like lesions

- **Functional brain changes**
  - Focal changes in brain metabolism
  - Increased cortical excitability
  - Central sensitization

- **Pharmacologic changes**
  - Excitatory transmitters
  - Paradoxical effects of opioids
Activation and Free Radical Damage to Brain Stem Nociceptive Brain Centers in Chronic Daily Headache

- Periaqueductal gray (PAG), substantia nigra (SN), and red nucleus (RN) are structures implicated in nociception and autonomic dysfunction
- Evidence for persistent flow activation and hyperoxia of SN and RN in migraine (fMRI)
- CDH patients showed increased iron deposition in PAG consistent with duration of illness (high-resolution MRI)
- May indicate free radical damage (FRD) induced persistent dysfunction in CDH
- FRD from repeated attacks may account for migraine transformation from episodic to persistent

fMRI, functional magnetic resonance imaging.
Brain Iron Accumulation in Migraine

Iron accumulation in PAG correlates with duration of illness

CA, cerebral aqueduct; CDH, chronic daily headache; EM, episodic migraine; PAG, periaqueductal gray; RN, red nucleus; SN, substantia nigra.

Duration of Migraine in Years vs. Allodynia

Pearson’s Correlation of Duration of Migraine in Years vs. Allodynia=.21 (N=295)

Frequency of Migraine Attacks vs. Allodynia


Pearson’s Correlation of Frequency of Migraines per Month vs. Allodynia=.35 (N=291)
Central Sensitization

- Repetitive migraine attacks can cause repetitive central sensitization\(^1\)
- Generates free radicals that damage PAG\(^2\)
  - Facilitates migraine progression
- Cutaneous allodynia is a marker for central sensitization\(^3\)

CM, chronic migraine; PAG, periaqueductal gray matter.
Central Sensitization

*Sensitization of trigeminovascular neurons in nucleus caudalis mediates cutaneous allodynia*

Opioid-Induced Hyperalgesia

- Paradoxical increased pain sensitivity in response to opioids\(^1\)
  - May be responsible for declining levels of analgesia or worsening of pain while receiving opioids
- Can occur with even brief durations of therapy\(^2\)

Possible Mechanisms of Opioid-Induced Hyperalgesia

- Inhibition of inhibitory circuits
- Direct excitatory effects—cytokines—glial activation
- Activation of “dormant” opioid receptor subtypes (ie, δ receptors)
- Increased cortical excitability and cortical spreading depression
Clinical Correlates of Opioid-Induced Hyperalgesia in Migraine

- Worsening of the frequency and severity of migraine
- Development of frequent nonmigrainous headache
- Allodynia
- Diffuse spread of what was initially a more focal headache
- Need for increasing the dose and frequency of opioid use
- Refractoriness to preventive medications, nonopioid analgesics, including NSAIDs and triptans
Presumed Mechanism of Therapy for Chronic Migraine
Mechanisms of the Antinociceptive Effect of Subcutaneous OnabotulinumtoxinA: Inhibition of Peripheral and Central Nociceptive Processing

Various doses BTX-A into the intraplantar fat pad 5 days before subcutaneous formalin

- Subjectively (Lifting/Licking):
  - Decreased pain response 46%

- Peripherally
  - Dose-dependent decreased release of Glu at site of peripheral inflammation

- Centrally
  - Reduced c-fos expression
  - Decreased electrical activity of WDR neurons in spinal cord

MOH patients show both reversible and irreversible changes

- Ventromedial prefrontal cortex changes appear reversible and attributable to acute headache
- Substantia nigra/ventral tegmental dysfunctions are persistent and associated with MOH

What do we do while we wait to get the definitions and pathophysiology sorted?

- Clinical Management of Refractory Headache
Causes of Treatment Failure

**Diagnosis Incomplete or Incorrect**
- Secondary headache
- Misdiagnosed primary headache

**Inadequate Pharmacotherapy**
- Inadequate dose of acute/prophylactic treatment
- Ineffective medications
- Poor initial strategy
- Premature cessation
- Wrong route
- Noncompliance

**Failure of Nonpharmacologic Therapy**
- Physical medicine
- Cognitive therapies

**Unidentified Exacerbating Factors**
- Analgesic or caffeine overuse
- Medications
- Dietary factors
- Lifestyle - sleep etc

**Patient Factors**
- Poor insight/understanding of disorder
- Comorbid conditions such as anxiety and depression
- Unrealistic expectations
- Genetics
Two Common Misdiagnoses in Intractable Headache

- Idiopathic low pressure headache typically results from a CSF leak
- Headache is *initially* orthostatic and bilateral, often occipital predominant
- With time the orthostatic feature may fade. Other symptoms include changes in hearing, dizziness and diplopia
- Headache is consistently side-locked
- There are ipsilateral autonomic features
- Patient has not had or has had an inadequate trial of indomethacin
Two Common Misdiagnoses in Intractable Headache

- Idiopathic low CSF pressure headache from a spontaneous leak
- Headache is initially orthostatic and bilateral, often occipital, pressure like
- With time, the orthostatic feature fades, other symptoms emerge, including changes in hearing, dizziness, and diplopia
- The great majority of people improve spontaneously although it can take many months, others may require patch/surgery
- More commonly seen in hyperflexible patients

Chronic SIH

Headache is consistently side-locked, may be hemicephalic, behind the eye, cervical
There are ipsilateral autonomic features which can be subtle, including fullness in one year, flushing of one side of forehead, or stuffy nostril
Patient has not had or has had an inadequate trial of indomethacin. May report partial response to other NSAIDS, but not to Migraine medications

Hemicrania Continua
Two Common Missed Diagnoses

- Global headache, initially orthosatic, may be occipitally predominant
- Orthostatic features may fade over time, may c/o tinnitus, light headedness, dbl vision
- Often seen in patients with hyperflexible joints

- Side-locked headache, often waxing a waning is severity
- Autonomic features ipsilateral to head pain
- Absent or inadequate trial of indomethacin, partial response to other NSAID’s
Headache attributed to Chiari malformation type I (CM1)
Imaging in Treatment failure

- Previous negative imaging-
  - Consider targets for secondary headache
    - Sphenoid sinus
    - Cervical-occipital junction
    - Pituitary Sella
    - Nasopharyngeal region
    - Clival lesions
    - CSF leak(s)
Summary of Definitional Issues

1. Should we distinguish refractory to abortive from refractory to preventives?
2. Should patients with 1 year of severe headaches be viewed differently than those with 30 years?
3. What is the role of disability?
4. Should psychiatric co-morbidities be part of the definition?
5. Should Medical comorbidities that may be related to chronic headache play a role in assessment?
6. What role should medication overuse play in the definition?
7. How important is the role of white matter changes, iron deposition, etc.?
8. How important are genetics in defining refractoriness?
9. Should the definition allow for refractoriness that may change over time?
Hot Button Issues in Refractory Headache

- **Subsets of Refractory Patients**
  - By age: Adolescents with difficult headaches are approached differently than adults. Patients over age 70 present unique challenges.
  - by headache type: Types of headaches should be separated, Chronic migraine is most common but other types include refractory trigeminal autonomic cephalgia’s, New Daily Persistent Headache, post-traumatic and chronic tension type headache.

- **Level of refractoriness**
  - Duration of refractoriness
  - Refractoriness with psychiatric co morbidities
  - Refractoriness with medical comorbidities
  - Refractoriness with varying degree of disability.
Thank you for your time

Please feel free to contact me with questions or comments
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