Chronic Migraine versus Chronic Pain: Similarities and Differences

Clinical Differences/Background

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Disclosure (36 months)

Migraine: Multiphasic Paroxysmal Neurologic Syndrome with Unique Clinical Symptomatology

- Nausea
- Visual Changes, Numbness/Tingling, Language Dysfunction, Cognitive Dysfunction, Brainstem Symptoms
- Headache
- Cutaneous Allodynia

Premonitory Aura Headache Postdrome


Migraine: Unique Biology


Migraine: Unique Targets/Pharmacology


Migraine: Unique Genetic Inheritance Patterns

Pain Matrix: Not Unique to Migraine

Chronic migraine and chronic pain conditions

- Children and adults with migraine or frequent headache are at increased risk of concurrent non-headache pain, especially musculoskeletal pain and arthritis
- Multiple pain conditions is a negative prognostic category for pain recovery
- Possible reasons for this association
  - Unidirectional causality
  - Shared endogenous or exogenous risk factors or life stressors
  - Genetic factors involved in endogenous pain modulation
Migraine is progressive in some

83% Persistent Episodic Migraine
2.5% Chronic Migraine
14.5% Other Outcomes

Chronic Migraine Has Greater Psychiatric and Medical Comorbidities than Episodic Migraine

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>Episodic Migraine (n=16,605)</th>
<th>Chronic Migraine (n=455)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Depression(^a)</td>
<td>17.2%</td>
<td>30.2%</td>
<td>2.1 (17.4-2.5)</td>
</tr>
<tr>
<td>Anxiety Disorders(^b)</td>
<td>16.8%</td>
<td>30.2%</td>
<td>1.9 (1.6-2.2)</td>
</tr>
<tr>
<td>Other Chronic Pain Disorders(^b)</td>
<td>15.1%</td>
<td>31.5%</td>
<td>2.6 (2.2-3.1)</td>
</tr>
</tbody>
</table>

\(^a\) Defined as PHQ-9 sum score ≥15
\(^b\) Based on subject report of physician diagnosis

Comorbid Pain Predicts Onset and Persistence of Chronic Migraine: Results From the Cameo Study

Examined:
Number of pain locations occurring most or all of the time; excluding head pain, 8 pain locations were possible
Cross-sectional relationship of number of pain locations and migraine type for:
- Episodic Migraine
- Chronic Migraine (not daily)
- Daily Chronic Migraine
Predictive validity of the number of pain locations on:
- Onset of chronic migraine among episodic migraineurs
- Persistence of chronic migraine (binary logistic regression analysis)

Noncephalic pain is marker for headache pain chronicity: Both Onset and Persistence

- The odds of CM onset among those with baseline EM increased by 30% (95% CI 1.21–1.40, p<0.001) for each additional non-cephalic pain site at baseline
- Individuals with CM were 15% (95% CI 1.07–1.25, p<0.001) more likely to have persistent EM for each additional non-cephalic pain site at baseline.

Number of Pain Locations By Migraine Group:
Cross-sectional Analysis

<table>
<thead>
<tr>
<th>Migraine Group</th>
<th>Mean (SD) number of pain locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic Migraine (0-14 Headache Days/Month)</td>
<td>0.87 (0.40)</td>
</tr>
<tr>
<td>Chronic Migraine, Non-daily (15-29 Headache Days/Month)</td>
<td>1.82 (1.9-3.2)</td>
</tr>
<tr>
<td>Daily Chronic Migraine (30 Headache Days/Month)</td>
<td>2.67 (1.46)</td>
</tr>
</tbody>
</table>

 RR: 2.04 (95% CI, 1.9−2.2)
Non-daily RR: 1.46 (95% CI, 1.13−1.89)
Number of Pain Locations and the Onset Of Chronic Migraine in Patients With Episodic Migraine Over 3 Months

<table>
<thead>
<tr>
<th>Baseline Headache Status</th>
<th>Unadjusted</th>
<th>Adjusted for Demographics</th>
<th>Adjusted for Demographics and Baseline Headache Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic Migraine (Transition to Chronic Migraine)</td>
<td>43% (OR 1.43 [95% CI, 1.33–1.53])</td>
<td>42% (OR 1.42 [95% CI, 1.33–1.53])</td>
<td>30% (OR 1.30 [95% CI, 1.21–1.40])</td>
</tr>
<tr>
<td>Chronic Migraine (Remaining Chronic Migraine)</td>
<td>16% (OR 1.16 [95% CI, 1.08–1.25])</td>
<td>15% (OR 1.15 [95% CI, 1.07–1.25])</td>
<td>6% (OR 1.06 [95% CI, 0.97–1.16])</td>
</tr>
</tbody>
</table>

Bolded values are statistically significant.

Increased Odds of Chronic Migraine with Each Additional Pain Location

Note: OR for 2 pain locations = 1.96; OR for 3 pain locations = 2.7

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Note: OR for 2 pain locations = 1.96; OR for 3 pain locations = 2.7

Childhood maltreatment/emotional abuse is a risk factor for headache chronification

<table>
<thead>
<tr>
<th>Physical abuse</th>
<th>Sexual abuse</th>
<th>Emotional abuse</th>
<th>Physical neglect</th>
<th>Emotional neglect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic migraine</td>
<td>1.79 (1.17–2.77)**</td>
<td>1.44 (0.90–2.38)</td>
<td>2.05 (1.36–3.07)**</td>
<td>1.49 (0.88–2.54)*</td>
</tr>
<tr>
<td>Transformed migraine</td>
<td>2.14 (1.35–3.36)**</td>
<td>1.71 (1.07–2.70)*</td>
<td>2.25 (1.36–3.68)**</td>
<td>1.81 (1.15–2.80)*</td>
</tr>
<tr>
<td>Daily tension headache</td>
<td>1.25 (0.79–2.00)</td>
<td>1.49 (0.60–3.52)</td>
<td>1.54 (0.64–3.25)*</td>
<td>1.33 (0.62–2.91)</td>
</tr>
<tr>
<td>Sexually abused</td>
<td>1.45 (1.04–2.03)</td>
<td>1.47 (0.62–3.55)</td>
<td>1.54 (0.64–3.25)*</td>
<td>1.33 (0.62–2.91)</td>
</tr>
<tr>
<td>Migraine-related</td>
<td>1.21 (0.76–1.94)</td>
<td>1.17 (0.73–1.82)</td>
<td>1.59 (0.90–2.81)</td>
<td>1.09 (0.69–1.79)</td>
</tr>
</tbody>
</table>

*P = .05; **P < .01, ***P < .001.

Childhood maltreatment in those with migraine increases risk of development of comorbid pain conditions

<table>
<thead>
<tr>
<th>Irritable bowel syndrome 31%</th>
<th>Comorbid pain conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis 25%</td>
<td>≥1 (61%)</td>
</tr>
<tr>
<td>Fibromyalgia 10%</td>
<td>2 (18%)</td>
</tr>
<tr>
<td>Interstitial cystitis 6.5%</td>
<td>≥3 (13%)</td>
</tr>
<tr>
<td>Endometriosis 15%</td>
<td>Emotional abuse OR 1.88 (1.22–2.33)</td>
</tr>
<tr>
<td></td>
<td>Physical neglect OR 1.73 (1.22–2.46)</td>
</tr>
</tbody>
</table>
Depression and anxiety associated with three pain conditions: results from a nationally representative sample

<table>
<thead>
<tr>
<th>Pain Category</th>
<th>Depression</th>
<th>Panic attacks</th>
<th>Generalized anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1.81 (1.21, 2.71)**</td>
<td>1.57 (0.86, 2.87)</td>
<td>5.83 (2.03, 11.6) ***</td>
</tr>
<tr>
<td>Migraine</td>
<td>2.14 (1.48, 3.1) ***</td>
<td>2.37 (1.42, 3.99) ***</td>
<td>3.13 (1.56, 6.3) ***</td>
</tr>
<tr>
<td>Back Pain</td>
<td>2.76 (1.24, 2.5) **</td>
<td>2.33 (1.40, 3.73) ***</td>
<td>2.87 (1.41, 5.81) **</td>
</tr>
<tr>
<td>Multiple pain conditions</td>
<td>3.39 (2.52, 4.55) ***</td>
<td>5.22 (3.61, 7.56) ***</td>
<td>6.91 (4.01, 11.9) ***</td>
</tr>
</tbody>
</table>

**P<0.01  
***P<0.001

Severity of Depression Predicts New Onset Chronic Migraine

Data from AMPP Study, 2005–2007

<table>
<thead>
<tr>
<th>Severity</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>2.53*</td>
<td>(1.52–4.21)</td>
</tr>
<tr>
<td>Moderately–Severe</td>
<td>2.35*</td>
<td>(1.53–3.62)</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.77*</td>
<td>(1.25–2.52)</td>
</tr>
<tr>
<td>None/Mild</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05

Prevalence of Comorbid Pain Conditions and Severity of Alodynia

Frequency and total number of pain conditions increased with increase in severity of alodynia

Data from AMPP Study, 2005–2007

<table>
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<tr>
<th>Severity of cutaneous alodynia (Number of symptoms)</th>
<th>Total number of pain conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/Mild</td>
<td>1</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Severe</td>
<td>4</td>
</tr>
<tr>
<td>&gt;3</td>
<td>5</td>
</tr>
</tbody>
</table>
Functional Pain Disorders

- Stress - most common reported trigger of migraine
  - Effects of stress may be cumulative
  - Frequency of attacks a risk factor for migraine chronification
  - Sensitized state promotes vulnerability to triggers (i.e., stress)

Perceived triggers of primary headache disorders: A meta-analysis

Understanding Migraine through the Lens of Maladaptive Stress Responses: A Model Disease of Allostasis Load
Modification of allostatic overload by targeting multiple stressors


Medications
Injections
Neutraceuticals
Neurostimulation
Mindfulness
Yoga

Biofeedback assisted relaxation therapy, CBT
Trigger avoidance
Low/no caffeine, histamine, aspartame, MSG, glycemic index
Targeting the stress response itself: kappa opioid receptors

Acute stress produces adaptive physiological responses critical for survival – “fight or flight”

Chronic stress is maladaptive and induces:
- Anxiety: open field, elevated plus maze, novel object
- Depression: social defeat and avoidance
- Drug seeking behavior:

All of these effects are blocked by KOR antagonists

Relevance to stress-related functional pain disorders?

Dynorphin, KOR signaling and stress

Brain Stress Circuit

CRF → CRFR → Dynorphin → KOR

- Stress induces release of CRF and opioid peptides including dynorphin.
- Dynorphin-KOR system may be sensitized in functional pain disorders.

KOR antagonists may be beneficial in protecting from stress-related disorders

Priming model of functional pain

Repeated use/overuse of opioids or triptans can induce a state of latent sensitization characterized by lowered thresholds to triggers (e.g., stress).

In naïve animals, stress elicits a transient response.
In primed animals, the same stress exposure now promotes pain.

No tissue injury
**Summary**

Migraine has a biology, genetic inheritance, clinical profile, and pharmacotherapy that is distinct from chronic pain.

Chronic migraine and chronic pain:

- Have unidirectional and ‘dose-dependent’ relationship
- Share risk factors (e.g. allodynia, obesity, psychiatric disease, genetic)
- Share an association with stress
- Physiology of stress response opens up new targets (kappa opioid receptor) for drug therapy