Disclosures

- Salary support from the NIH (K23 10896737)
- Grant support from GSK for an investigator-initiated grant

Self Assessment Questions

1. Which of the following factors modify the risk of migraine in those with obesity?
   a) Age
   b) Sex
   c) Race
   d) All of the above

2. T/F: The hypothalamus plays an important role in migraine and in obesity.

3. Which of the following are obesity-related proteins or neurotransmitters which may participate in migraine pathophysiology?
   a) Adiponectin
   b) Interleukin-6
   c) Serotonin
   d) Resistin
   e) All of the above
Overview

• Migraine & Obesity Classification & Epidemiology
• Overlapping central & peripheral mechanisms
• Clues to novel migraine biomarkers?
  • Adipocytokines

What Is Migraine?

How Is It Diagnosed?

ICHD-II Definition of Migraine

• A. 5 attacks fulfilling criteria B-D
• B. Headache lasting 4-72 hours
• C. 2 of the following:
  • Unilateral
  • Moderate or severe
  • Aggravated by routine activity
  • Pulsating
• D. 1 of the following:
  • Nausea and/or vomiting
  • Photo and phonophobia
• E. Not attributed to another disorder
Demographic Factors Linked with Migraine Prevalence Estimates

- Women > Men
- Caucasian > African American > Asian
- Younger > Older

Studies Designed to Evaluate Migraine Prevalence Changes Across Time

<table>
<thead>
<tr>
<th>Pub Year</th>
<th>Design</th>
<th>HA DX</th>
<th>Age Range</th>
<th>1st Time</th>
<th>2nd Time</th>
<th>1st TP</th>
<th>2nd TP</th>
</tr>
</thead>
</table>

Risk Factors & Triggers

Not Readily Modifiable
- Female sex
- Caucasian Race
- Reproductive Age
- Low Socioeconomic status

Potentially Modifiable
- Obesity
- Fasting
- Lack of exercise
- Stressful life events
- Sleep disorders
Obesity: Definition, Epidemiology, & Practical Considerations

Obesity

- Excessive adipose tissue relative to lean body mass
  - i.e. adipose tissue to non-fat tissue

Obesity Trends Among U.S. Adults
Obesity Trends Among U.S. Adults

- BMI ≥ 30
  - 36% of women
  - 34% of men

Diseases Associated With Obesity

- GERD
- DVT
- Some cancers
- Infertility
- ESRD
- Abdominal hernias
- Liver disease
- Increased wound infections
- Gall bladder disease
- Gout
- Arthritis

- Pseudotumor Cerebri
- Stroke
- CAD/HTN
- Dyslipidemia
- Insulin Resistance
- Diabetes
- Metabolic Syndrome
- Depression
- Sleep apnea
- Migraine (All frequencies)
Practical Considerations For Evaluating Obesity

The Migraine & Obesity Association

Relationships between body mass index and well-being in young Australian women

- Australian Longitudinal Study on Women’s Health
- 14,000 Women, 18-23 years of age; controls w/ no headaches
- Overweight women were 12% (OR 1.12; CI: 1.0-1.25) & Obese women 47% more likely to report migraine or headache than normal weighted women, (OR 1.47; 95% CI: 1.2-1.73).

Episodic Headache & Obesity

Factors associated with the onset and remission of chronic daily headache in a population-based study

- Obese episodic headache participants had 5.5X greater risk of transforming into CDH at 11 months as compared to non-obese episodic headache participants, (OR 5.53; 95% CI:1.4-21.8).

Migraine & Obesity Epidemiology

- 15 general population, epidemiological studies
  - 13 cross-sectional & 2 longitudinal
  - 11 different general population databases


Prevalence of Migraine & Severe Headaches in Obesity (NHANES) and the Effect of Age and Sex

- CS-general population study
- BMI calculated based on measured height & weight to estimate obesity status
- Self-reported migraine & severe headaches
- 21,783 participants
  - 15,631 younger than 55
  - 6,152 participants 55 or older
## Prevalence of Migraine & Severe Headaches in Reproductive-aged Individuals with Obesity (NHANES)

- Younger, obese adults (≤ 55 years) show increased odds of migraine/severe HA
  - Women: OR 0.39; CI: 1.25, 1.56; men OR 0.38; CI: 1.20, 1.59
- Older, obese adults show no increased odds of migraine
  - Women: OR 0.86; CI: 0.68, 1.16; men: OR 0.77; CI: 0.54, 1.10

---

## The Influence of Age, Sex, & Race on the Episodic Migraine & Obesity Association (NCS-R)

- CS-general population study
- BMI based on self-reported height & weight
- Episodic migraine based on ICHD criteria
- 3,862 participants
  - 2,265 younger than 50
  - 1,598 participants 50 or older

- OR of EM in obese white individuals increased over 2-fold
  (OR 2.06; CI: 1.41, 3.01)

- OR of EM in obese women increased by 95%
  (OR 1.95; CI: 1.38, 2.76)

- OR of EM in obese individuals <50 increased by 80%
  (OR 1.80; CI: 1.20, 2.89)

- Odds of EM in those with obesity increased 81%
  (OR 1.81; CI: 1.27, 2.57; p=0.001)

---

### Notes:

- Peterlin et al. Headache 2010;50:52-62
Epidemiological Lessons

• Obesity is comorbid with migraine
  – Strongest in reproductive age
  – Risk of migraine increases with increasing obesity status.
  – Transformation to chronic daily headache is greater in obese individuals with episodic headache as compared to normal weighted episodic headache individuals.

Central & Peripheral Mechanisms

Overview

• Discuss the role of the hypothalamus
• Identify neurotransmitters & proteins targeted by existing migraine therapies that modulate feeding
• Discuss the role of adipocytokines
**Time of Onset of Migraine Attacks**

3,582 Migraine Attacks in 1698 Patients

- **Fox AW, Davis RL.** *Headache.* 1998;38:436-441.

**Fasting & Migraine**

- **Klebanov L.** *Cephalalgia.* 2007;27:394-402

**Interictal Insulin Sensitivity in Migraine**

- 30 mig vs 15 con
  - No preventive meds
  - No BMI > 24
- No sig difference in basal glucose/insulin levels
- OGTT sig ↑ in mig

*Rainero et al. Cephalalgia. 2005;25:593-597*
The Hypothalamus & Migraine

Activation of hypothalamus & brainstem in PET Scan of MO

Denuelle et al. Headache 2007;47:1418-1426

Snacking in Migraineurs

• Electronic HA diary study of 34 EM Patients
  - every AM & PM collected HA characteristics, activity level, eating behaviors
• Over 1000 entries were evaluated in which patients were HA-free in the 24 hrs prior to the next day

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>1.35</td>
<td>1.19 to 1.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No Food</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Early breakfast</td>
<td>0.93</td>
<td>0.85 to 1.04</td>
<td>0.28</td>
</tr>
<tr>
<td>Late dinner</td>
<td>0.79</td>
<td>0.55 to 1.15</td>
<td>0.22</td>
</tr>
<tr>
<td>Snack</td>
<td>0.6</td>
<td>0.40 to 0.90</td>
<td>0.013</td>
</tr>
</tbody>
</table>


Neuropeptides Affecting Feeding
& Adipose Tissue Function

• Drive to Feed
  - Norepinephrine
  - NPY
  - Opiods
  - Orexin
  - Ghrelin

• Satiety
  - Serotonin
  - Dopamine
  - Histamine
  - CGRP
  - Adiponectin
  - Leptin
NF-κβ & iNOS in Episodic Migraineurs

Peripheral Mechanisms in Migraine & The Drive To Feed

Adipose Tissue & Inflammation
Migraine & Cytokines

IL-6, TNF-α within 1 hr of onset of moderate to severe migraine attack

Sarchielli et al. Headache 2006;46:200-7

Are Adipokine Levels Altered In Migraine?

Adipocytokines
- Also called adipokines
- Predominantly secreted from adipocytes
- Roles in energy homeostasis & inflammation
- Includes:
  - Adiponectin (1995)
  - Leptin (1994)
  - Resistin (2001)
Characteristic Units of Adiponectin

- Full length
- LMW
- MMW
- HMW

Waki et al. J of Biol Chem 2003;278:40352-63

• Total 37 Caucasian women
  – 12 CM vs 13 EM vs 12 Controls
  – Normotensive, euthyroid, non-DM
  – Age & BMI-matched
  – Peripheral serum levels by EIA
  • T-ADP and ADP multimers (HMW, MMW, LMW)

Peterlin et al Neurology 2008;70:1909-1911

Adiponectin Levels in Chronic & Episodic Migraineurs (Baseline Pain States)

- T-ADP: 10.1 CM vs. 8.6 EM vs 7.5 µg/ml Controls, (p=0.024)
- HMW: 6.1 CM vs. 4.2 EM vs 3.9 µg/ml Controls, (p=0.003)

Peterlin et al Neurology 2008;70:1909-1911

Adiponectin Levels in CM & EM (Baseline Pain States)
### Baseline Serum Adiponectin Levels in Migraineurs

- 133 Men & Women
  - 68 Migraineurs (45 EM, 23 CM)
  - 54 HA-Free Controls
- Total ADP evaluated by EIA

- Total ADP increased in those with migraine (43.6±11.6) vs controls (36.6±9.7 ng/mL), p<0.001.

Duarte H et al. J Neurol Sci. 2014;342:186-188

### Baseline Leptin Levels in Migraine

- Interictal, Fasting LEP
  - 125 Participants (61 EM, 64 Con)
  - Crude LEP levels were decreased in EM (49±25) vs Con (49±25; p=0.05), but not significant after adjustment for fat mass calculation (BMI).
- Interictal, Fasting LEP
  - 64 non-obese women (40 EM, 44 Con)
  - Crude LEP increased in EM (15±10) vs Con (10±6; p=0.01), but not significant after adjustment for BMI (CR 2.3; CI0.51-10.10).
  - Note: Did not control for glucose, which was lower in EM vs Con

- LEP in EM before & after prevention
  - Open-label study
    - 25 mg/day amitriptyline (n=19)
    - 10 mg/day flunarazine (n=20)
  - LEP increased after 12 wks of tx with amitriptyline (17±2) vs baseline (7±1), p<0.05.
  - LEP increased after 12 wks of tx with flunarazine (13±2) vs baseline (7±1), p<0.01.

- Interictal, Fasting LEP
  - 84 non-obese women (40 EM; 44 Con)
  - Crude LEP increased in EM (15±10) vs Con (10±6; p<0.01), but not significant after adjustment for BMI, (OR 2.3; CI:0.51-10.10).

- Note: Did not control for glucose, which was lower in EM vs Con

Guldiken B et al. Headache 2008;48:1103-7

### Do Ictal Adipocytokine Levels Correlate with Migraine Pain Severity?

- Are Adipocytokine Levels Modulated by Treatment Response In Migraineurs?
"MAT" ATTACK!
ADPK Levels in EM Before & After Treatment

- Multicenter, R-DBPC trial
- Evaluated ictal ADPK levels before and after treatment in responders & non-responders
  - Sumatriptan/Naproxen Sodium vs Placebo
  - Responders defined as reduction in pain from moderate to severe to mild or no pain.
- Blood drawn 4 hrs before and 30-120 min after treatment
- ADPKs evaluated by EIA


MAT ATTACK: CONSORT FLOW DIAGRAM

- Assessed for eligibility (n=147)
- Excluded (n=111)
  - Not meeting inclusion criteria (n=48)
  - Declined to participate (n=17)
  - Did not present with acute attack (n=46)
- Randomized (n=36)
  - Suma/Nap (n=18)
  - Placebo (n=18)
- Analysed (n=17)
  - Excluded from analyses (n=1), blood not analyzed due to labelling error and unable to differentiate different time points

Do Adipokine Levels Correlate with Pain Severity in Episodic Migraine?

<table>
<thead>
<tr>
<th>Adipokine</th>
<th>Adjusted Pain Intensity Estimates (per 1 ug/mL increase)</th>
<th>0 to 10 scale</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment (Pain Onset)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Adiponectin (T-ADP)</td>
<td>-0.01</td>
<td>(-0.12, 0.11)</td>
<td>0.925</td>
</tr>
<tr>
<td>HMW/T-ADP</td>
<td>5.00</td>
<td>(1.82, 8.18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Leptin</td>
<td>-0.02</td>
<td>(-0.07, 0.04)</td>
<td>0.597</td>
</tr>
<tr>
<td>Resistin</td>
<td>0.07</td>
<td>(0.01, 0.13)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

Chai et al. Neurology 2015; In Press
Pretreatment Migraine Pain Severity with Quartile Changes in Adipokines

Are Adipokine Levels Modulated By Acute Abortive Treatment Response?

Ictal Adipokine Levels in Responders and Non-Responders
Is Adiponectin or Resistin a Migraine Biomarker?

The official NIH definition of a biomarker is:
“a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, a pathogenic processes, or a pharmacologic response to a therapeutic intervention.”


Future Research

• Utilize more definitive measures of obesity
  – MRI visceral and subcutaneous adipose tissue

• Unbiased techniques for examining obesity-related differences
  – Metabolomics; neuroimaging
  – Interictal & ictal blood marker trials

• Evaluate broader applicability in other pain disorders


In Summary…

• The hypothalamus plays an important role in migraine and the drive to feed or not to (satiety).

• Multiple neurotransmitters & proteins targeted by existing migraine therapies modulate satiety.

• Adipocytokines may be modulated by acute pain severity and treatment response in those with migraine.
Self Assessment Questions

1. Which of the following factors modify the risk of migraine in those with obesity?
   a) Age
   b) Sex
   c) Race
   d) All of the above

2. T/F: The hypothalamus plays an important role in migraine and in obesity.

3. Which of the following are obesity-related proteins or neurotransmitters which may participate in migraine pathophysiology?
   a) Adiponectin
   b) Interleukin-6
   c) Serotonin
   d) Resistin
   e) All of the above

Acknowledgements

• Collaborators
  – N. Cindy Chai, MD (UCSF)
  – Bizu Gelaye, PhD (Harvard)
  – Andrea L. Rosso, PhD (U of PA)
  – Jennifer Haythornthwaite, PhD (JHSOM)
  – Barbara A. Gower, PhD (UAB)
  – Tom Ward, MD (Dartmouth)
  – Alan M. Rapoport, MD (UCLA)
  – Ann I. Sheftell (Uniformed Services University)
  – Stewart J. Tepper, MD (Cleveland Clinic)
  – Gretchen Tietjen, MD (U of Toledo)

• Research Coordinators
  – Linda White, CRNP (JHSOM)
  – Sherry Nickelson (JHSOM)

• Research Assistants
  – Ming Li (JHSOM)
  – Nancy Nishie (JHSOM)

• Acknowledgements
  – Marilyn Albert, MD (JHSOM)
  – Fred Sheftell, MD (Past AHS Pres)

Questions or Observations

lpeterlin@jhmi.edu