Prevention Strategies for Pediatric Headaches

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Disclosures

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NIH, CHRF research foundation, Curelator
NIH – Advisory Board, Common Data Elements
Migraine Research Foundation – Advisory Board
Assoc Ed – Headache, Cephalalgia, The Journal of Headache Pain
Advisory Board – Alder, Amgen, Curelator, Depomed, Impax, Lilly, Teva
Objectives

• To understand the latest update on prevention of headaches in children and adolescents
• To develop a treatment strategy for prevention of headaches in children and adolescents.
Classification of Headache

- Migraine without aura
- Migraine with aura
  - Migraine with typical aura
  - Migraine with brainstem aura
  - Hemiplegic migraine
  - Retinal migraine
- Chronic migraine
- Complications of migraine
  - Status migrainosus
  - Persistent aura without infarction
  - Migrainous infarction
  - Migraine aura-triggered seizure
- Probable migraine
  - Without aura
  - With aura
- Episodic syndromes that may be associated with migraine
  - Recurrent gastrointestinal disturbance
    - Cyclical vomiting syndrome
    - Abdominal migraine
  - Benign paroxysmal vertigo
  - Benign paroxysmal torticollis
Why Migraine

• Migraine prevalence
  • 4% of young children
  • Up to 10.5% of children age 5-15
  • Up to 28% age 15-19
  • Adults 12% (17.1% women, 5.6% men)

• Migraine pathophysiology
  • Migraine as a genetic disease
  • Early intervention may have lifetime implications

• Migraine Impact
  • Up to 200,000 lost school days in US
  • $17 billion (1998) direct and $17 billion indirect cost
  • Individual cost (2006)
    • Direct $127 to $7089
    • Indirect $709 to $4453
  • Chronic Mig vs Episodic Mig (2016)
    • CM – Direct ($4943), Indirect ($3300)
    • EM – Direct ($1705), Indirect ($943)
    • Pharma – CM ($3925), EM ($1196)
  • Potential progression to refractory headaches if not treated
Why Migraine – Global Burden of Disease


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<td>Osteoarth</td>
<td>Depression</td>
<td>COPD</td>
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Rate of change 2005-15
-0.19 to 0.03  -0.03 to 0.01  0.01 to 0.06  0.06 to 0.09  0.09 to 0.15
0.15 to 0.19  0.19 to 0.24  0.24 to 0.29  0.29 to 0.42  0.42 to 0.63
Changes in Character with Age

- 5659 patients headache characteristics compared
- Age 4 to 18, mean 11.95 ± 3.53
- Analysis of diagnostic criteria across the developmental ages
- McKenzie Miller, summer student
Menstrual Effects

• Is Puberty the Reason?
• Reviewed Headache Center Database
  • 896 girls, age 9 to 18
  • Clinically asked
    • Had first period
    • Headaches worsen with periods
    • Monthly pattern of worsening headaches
Urinary Hormone Effect (Adults)

Martin et al, Headache, 2005
Urinary Hormone Effect
Martin et al, Cephalalgia, 2017

• Adult studies revealed hormonal fluctuations could predict headache
• What role does development have in this influence
• Stratification across 3 ages
  • 8-11 years old
  • 12-15 years old
  • 16-17 years old
• Daily urine samples
  • Estrone glucuronide (ElG), pregnandiol glucuronide (PdG)
  • 96.2% of days with sample collection
• Diary of headache characteristics and presentation
Pubertal Urinary Menstrual Level Changes

- **Urinary Estrone Glucuronide (ug/dL)**
  - 8 to 11
  - 8 to 15
  - 12 to 15
  - 12 to 17
  - 16 to 17

- **Urinary Pregnandiol Glucuronide (ug/CL)**
  - 8 to 11
  - 8 to 15
  - 12 to 15
  - 12 to 17
  - 16 to 17
Urinary Hormone Effect (Children and Adolescents)
Family History
Migraine Twin Children
Svensson et al, *Cephalalgia* 1999

- 1480 Swedish twins
  - Born between Apr 1985 and Dec 1986
  - 8 to 9 year olds
  - Clinical Dx based on ICHD-I

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<th>Twin pairs</th>
<th>N</th>
<th>-/-</th>
<th>+/+</th>
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<tr>
<td>DZ Boys</td>
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<td>142</td>
<td>36</td>
<td>5</td>
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<tr>
<td>MZ Girls</td>
<td>164</td>
<td>127</td>
<td>24</td>
<td>13</td>
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<tr>
<td>DZ Girls</td>
<td>200</td>
<td>155</td>
<td>38</td>
<td>7</td>
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<td>DZ Us</td>
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<td>227</td>
<td>80</td>
<td>7</td>
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<tr>
<td>Total</td>
<td>1039</td>
<td>797</td>
<td>199</td>
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Table 5. Estimates of components of variance in 8 to 9-year-old boys and girls.

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<th>$a^2$</th>
<th>$c^2$</th>
<th>$e^2$</th>
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<td>Estimate</td>
<td>0.70</td>
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<td>95% CI</td>
<td>0.54–0.82</td>
<td>-</td>
<td>0.18–0.46</td>
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</table>

$a^2$ = Additive genetic effects (heritability); $c^2$ = shared environmental effects; $e^2$ = nonshared environmental effects.
Migraine Gene Candidates
Persico et al, Neurogenetics 2015

• Examined by groupings
  • Neurological Candidates
  • Vascular Candidates
  • Hormonal Candidates
  • Inflammatory Candidates
### Migraine Gene Candidates

**Persico et al, Neurogenetics 2015**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Beta Coeff. (95% CI)</th>
<th>N-SNPs analyzed</th>
<th>Associated SNPs/IVSs</th>
<th>P-value</th>
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<tr>
<td>DDC</td>
<td>7.91 (3.79, 11.92)</td>
<td>323</td>
<td>Spanish</td>
<td>15</td>
<td>592</td>
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<tr>
<td>MAOA</td>
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<td>Spanish</td>
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<tr>
<td>HTR2B</td>
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<td>SLC6A4</td>
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<td><strong>GABA-related genes</strong></td>
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**Table 3: Positive association findings with migraine candidate genes**

- **DDC**: 7.91 (3.79, 11.92) (Spanish, 15 SNPs analyzed, P-value: 0.009 (MA), Ref: 592)
- **5HT1A**: 8.04 (177 SNPs analyzed, P-value: 0.019, Ref: 602)
- **MAOA**: 4.02 (273 SNPs analyzed, P-value: 0.002 (MA), Ref: 602)
- **HTR2B**: 3.00 (209 SNPs analyzed, P-value: 0.002 (MA), Ref: 602)
- **SLC6A4**: 5.15 (237 SNPs analyzed, P-value: 0.002 (MA), Ref: 602)

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**Notes:**
- P-values are significant (P < 0.05).
- MA indicates major allele.
- SNPs: Single Nucleotide Polymorphisms.
- IVSs: Introns.
# Migraine Gene Candidates

Persico et al, Neurogenetics 2015

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**Table 4: Positive association findings with vascular candidate genes**
# Migraine Gene Candidates

Persico et al, Neurogenetics 2015

<table>
<thead>
<tr>
<th>Gene</th>
<th>Locus</th>
<th>Cases</th>
<th>Controls</th>
<th>Ethnicity</th>
<th>n. SNPs analyzed</th>
<th>Associated SNPs/polymorphisms</th>
<th>P value</th>
<th>Refs</th>
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<tbody>
<tr>
<td>ESR1</td>
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<td>1</td>
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### Migraine Gene Candidates

Persico et al, Neurogenetics 2015

<table>
<thead>
<tr>
<th>Gene</th>
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<th>Cases</th>
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<th>n. SNPs analyzed</th>
<th>Associated SNPs/polymorphisms</th>
<th>P value</th>
<th>Refs</th>
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</tbody>
</table>

*Table 6: Positive association findings with inflammatory candidate genes.*
MEG

• Migraineurs frequently note that it is hard to think during an acute attack

• MEG can measure cortical function
  • Finger tapping (200 trials, randomly presented clicks in right or left ear to tap fingers)
  • Mis-matched negativity

• Compared subjects with acute migraine seen in the acute headache unit vs. controls
MEG Methodology
Guo et al, PLoS ONE 2012
Delayed Movement-evoked Response in migraine
Movement-evoked Magnetic Fields (MEFs) in Children with Migraine (left)
Preventive Treatment
Pathophysiology to direct strategies

• Changing Characteristics
• Menstrual development
• Genetic basis
  • Neuronal
  • Vascular
  • Hormonal
  • Inflammatory
• Hypersensitive nervous system
Preventative Treatment Barriers

• What works best
• Need to reduce to <1/week
• May require 8-10 weeks to achieve dose
• Up to 16 weeks to reach full response
• Adherence
Treatment of Migraine
Preventive
Reviewed by Igarashi et al., 1992, Welch 1993

• Anticonvulsants
  • Phenobarbital
  • Phenytoin
  • Carbamazepine
  • Valproic acid

• Antiserotonergic
  • Methysergide
  • Cyproheptadine

• Antidepressants
  • Amitriptyline
  • Imipramine
  • Phenelzine
  • SSRIs

• NSAIDs
  • Aspirin
  • Naproxen
  • Indomethacin
  • Ketoprofen

• Beta-blockers
  • Propranolol, metoprolol, timolol
    nadolol, atenolol
  • Not alprenolol, osprenolol, acebutolol

• Ca-channel blockers
• Vitamin B₂ (riboflavin)
• Biofeedback
Gaps in Prevention

• Very limited number of studies in pediatric and adolescent headaches
• Translation from adults studies may be problematic
  • Are they really generalizable
• Prevention does not only mean medication
AEDs for Migraine
Wheller, 2000

• GABAergic Agents
  • Valproate
  • Gabapentin
  • Tiagabine
  • Vigabatrin

• Other compounds
  • Topiramate
  • Levetiracetam
  • Zonisamide
  • Pregabalin
  • Oxcarbazepine
  • Lamotrigine
Treatment of Migraine - Prophylactic

- Amitriptyline
  - Non-specific re-uptake inhibitor
  - Effects on
    - Serotonergic receptors
    - Adrenergic receptors
    - Cholinergic receptors
    - Histaminergic receptors
CHAMP Study Design

Real World Approach

• Subjects to reflect patients seen in typical headache, neurological and pediatric practice

• Subjects are children and adolescents, ages 8 to 17 years old

• Consistent headache frequency that indicates need for prophylaxis (>4 headaches per month)

• Standardized dosing of most commonly used preventative medication
  • AMI 1 mg/kg/day
  • TPM 2 mg/kg/day

Study Design

Primary and Secondary Outcomes

• Greater than 50% reduction in migraine frequency
• Absolute reduction in monthly migraine frequency
• Reduction in migraine disability
• Tolerability of drug therapies
Definitions

• Headache Frequency
  • Headache Day – any headache in 24 hour period midnight to midnight
  • Headache Episode – any headache, start to headache free
  • Migraine Day – any headache with ICHD Migraine characteristics in 24 hour period
  • Migraine Episode – any migraine from start to headache free
Baseline Results

Table 2.—History of Headache Characteristics at Screening Visit†

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>1st Week</th>
<th>2nd Week</th>
<th>3rd Week</th>
<th>4th Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Headaches Per Week</td>
<td>1.00</td>
<td>0.90</td>
<td>0.80</td>
<td>0.70</td>
</tr>
<tr>
<td>Mean Number of Headaches</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>

- Headache changes activity level
- Activity or play made headache worse*
CHAMP results

• Primary - > 50% reduction in headache frequency (day)
  • 28 days prior to randomization vs 28 days prior to end of treatment phase

• Secondary
  • Headache Disability – PedMIDAS; compare randomization to end of treatment
  • Tolerability – whether or not subject completed entire 24 weeks

• Additional Secondary
  • Absolute reduction in headache frequency
  • Side effects
CHAMP results – Consort

488 Patients Assessed for eligibility

- 21 (4%) Were not randomized due to early study closure
- 106 (22%) Were excluded
- 81 Did not meet inclusion criteria
  Primary reasons for ineligibility included: headache frequency (38), PedsMIDAS Disability Score (23), and other medical conditions (15)
- 25 Declined to participate
  - 13 Unwilling but eligibility otherwise confirmed
  - 12 Unwilling and eligibility unknown
  Primary reasons for declining to participate included: concerns about side effects (4), did not have enough time (3), other reasons (12)

361 Randomized

144 were assigned to receive Amifptyline
12 were not included in primary analysis due to DSMB recommended early study closure

145 were assigned to receive Topiramate
15 were not included in primary analysis due to DSMB recommended early study closure

72 were assigned to receive Placebo
6 were not included in primary analysis due to DSMB recommended early study closure

132 were included in primary analysis
  - 104 with endpoint data
  - 28 with imputed data
  - 2 missing headache diary data
  - 7 drug withdrawal due to tolerability
  - 9 lost to follow-up
  - 10 terminated early due to other reasons

130 were included in primary analysis
  - 101 with endpoint data
  - 29 with imputed data
  - 1 missing headache diary data
  - 6 drug withdrawal due to tolerability
  - 6 lost to follow-up
  - 14 terminated early due to other reasons

66 were included in primary analysis
  - 50 with endpoint data
  - 7 with imputed data
  - 0 missing headache diary data
  - 1 drug withdrawal due to tolerability
  - 2 lost to follow-up
  - 4 terminated early due to other reasons
Primary (>50%)

- Primary – all subjects without data considered failures
- Last Observation Carried Forward – most recent visit with 28 day calendar
- Multiple Imputation – methods with multiple chains
- Observed data – all subjects with baseline and last 28 days
Primary (>50% distribution)

Based on data submitted as of 06Jan2016
Neutriceuticals
Neuronal Theory of Migraine

• **Cortical hyperexcitability**
  • Mitochondrial Association
    • Riboflavin
    • CoEnzyme Q10
    • Carnitine
    • Mitochondrial disorders
Riboflavin

- Involved in initial stages of electron transport
- Deficient in some migraineers
- Prophylactic response similar to VPA

- Barile, Eur J Biochem 267:4888 2000
Riboflavin
Schoenen et al., 1998

- 54 patients in Belgium and Luxemburg
- Double-blinded, randomized placebo-controlled trial
- Reduction in HA frequency and headache days

- 50% “responders”
  - Riboflavin 59%
  - placebo 15%

- Number needed to treat
  - 2.3 (for adverse events 33.3)
  - vs Divalproex - 1.6 (for adverse events 2.4)

- ? Increases complex I and II, ∴ mitochondrial
Riboflavin
CoEnzyme Q10

- Geromel et al, 2002

- Rozen et al, 2002 *Cephalalgia*
Q10 and CCHMC
Hershey et al, Headache 2007
Q10 and CCHMC
Slater et al, Headache 2011
Vitamin D
Vitamin D

• Neurological implications of Vitamin D
  • Association with Multiple Sclerosis
  • Association with early dementia
  • Association with chronic pain conditions

• Increasing incidence of Vitamin D deficiency
Vitamin D
Coping Skills in Chronic Migraine

• NIH/NINDS
• Chronic Migraine (>15 days per month)
• PedMIDAS restriction (>20 and <140)
• No Medication Overuse
• Randomized to Coping Skills vs. Education Control
• 8 year treatment, 20 week treatment phase, 12 month follow-up
• Enrollment and Treatment phase complete, 12 month follow-up pending
Coping Skills in Chronic Migraine

**Figure 1a**

Frequency of Headache Days Per Month

- **Baseline**
- **Posttest**
- **3mo FU**
- **6mo FU**
- **9mo FU**
- **12mo FU**

Comparison: CTL vs TX

- **p < .003, TX < CTL**
- **p < .001, TX < CTL**

**Figure 1b**

PedMidas Score

- **Baseline**
- **Posttest**
- **3mo FU**
- **6mo FU**
- **9mo FU**
- **12mo FU**

Comparison: CTL vs TX

- **p = .01, TX < CTL**
- **p < .001, TX < CTL**
Where do we go from here?

- Children and adolescents with real world migraine get better
  - 50 to 70% with a >50% reduction in headache frequency
  - Mean frequency at end down to almost 1 per week
  - Thus, multidisciplinary care works
- Biochemical effect of medication is not the reason
- Is the reason expectation of response?
- What do we do with the 30-40% that don’t get better?
Expectation of Response

Cormier et al, Pain 2016
Trajectory Response

[Graph showing trajectory response over time with different treatments]
Putting it all together – a treatment strategy

• Patients and parents present because headaches are impacting their lives “Need to do something”

• Baseline of CHAMP shows that just because you diagnosis, provide acute treatment, and introduce healthy habits, it’s not enough

• Expectation of response is needed
  • Pharmaceutical expectation
  • Cognitive Behavioral Therapy
  • Wait and see
  • “The Expert Effect”
Strategies

• Migraine in pediatrics and adolescents can be diagnosed with standardized criteria

• The “why” of migraine is multifactorial, but likely a genetic basis with environmental factors

• A multidisciplinary treatment plan is ideal

• Plan must include education of the patient and addressing barriers while enhancing expectation

• SMART and MOST designs may be the next way to go
Thank you
Thank you

• Headache Center
  • Scott Powers, PhD, FAHS
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  • Shannon White, DNP
  • Jessica Weberding, PNP
  • Mimi Miller, FNP
  • Shawna Hess, PNP
  • Ann Segers, RN
  • Paula Manning, RN
  • Judy Bush, RN
  • Anne Jordan-Lynch, PhD
  • Shalonda Slater, PhD
  • Antoinette Green
  • Janelle Allen

• Collaborators
  • AMI/TPM Comp Effectiveness
    • Chris Coffey, PhD
    • Dixie Ecklund
    • Linda Porter, PhD
    • Deborah Hirtz, MD
  • Genomics
    • Frank Sharp, MD
    • Yang Tang, MD, PhD
    • Paul Horn, PhD
  • Allodynia
    • Rami Burstein, MD, PhD
    • Paul Winner, DO
  • MEG
    • Jing Xiang, MD, PhD
    • Milena Korostenskaja, PhD
  • Menstrual Hormonal Levels
    • Vince Martin, MD
    • Timothy Houle, PhD