ABUSE AND MIGRAINE: EPIDEMIOLOGY, MECHANISMS, & TREATMENT IMPLICATIONS

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Disclosure

• Owns stock in Johnson & Johnson and Stryker

• Served as medical advisor for Lilly and for Dr. Reddy’s
Objectives

At the completion of this presentation, participants will be able to discuss:

• **Epidemiology** linking abuse and migraine

• Potential **mechanisms** linking abuse and migraine

• **Treatment implications** of these associations
Early life stress is associated with migraine
Early Life Stress: Adverse childhood events (ACE)

- Sexual Abuse
- Physical Abuse
- Emotional Abuse
- Physical Neglect
- Emotional Neglect
- Separation from parent(s)
- Parental violence
- Parental substance abuse
- Parental mental illness
- Parental incarceration
<table>
<thead>
<tr>
<th>Authors/ Study design</th>
<th>Sample</th>
<th>HA Dx</th>
<th>Childhood Maltreatment History</th>
<th>Association of Headache and Maltreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felitti, 1991</td>
<td>231 adults, HMO sample</td>
<td>No specific headache dx</td>
<td>Childhood sexual abuse</td>
<td>Chronic headache twice as common in abused</td>
</tr>
<tr>
<td>McCauley et al., 1997</td>
<td>1931 women, multi-center primary care sample</td>
<td>No specific headache dx</td>
<td>Childhood physical and sexual abuse</td>
<td>Headache more common in abused, Prevalence ratio = 2.2, 95% CI 1.7-2.8</td>
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<tr>
<td>Golding, 1999</td>
<td>7502 pooled community-based sample of youth and adults</td>
<td>No specific headache dx</td>
<td>Childhood sexual abuse</td>
<td>Headache more common in abused, OR=1.9, 95% CI 1.2-3.0</td>
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<tr>
<td>Walker et al., 1999</td>
<td>1225 women, HMO random sample</td>
<td>No specific headache dx</td>
<td>Sexual abuse</td>
<td>HA more common in abused, OR = 1.3, 95% CI 1.1-1.6</td>
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<tr>
<td>Goodwin et al, 2003</td>
<td>3032 adults, community sample</td>
<td>Migraine</td>
<td>Childhood physical abuse</td>
<td>Migraine more common in frequently abused, OR = 2.7, 95% CI: 1.2-5.8</td>
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<tr>
<td>Authors/ Study design</td>
<td>Sample</td>
<td>HA Dx</td>
<td>Childhood Maltreatment History</td>
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<tr>
<td>Anda et al., 2011</td>
<td>17337 adults in HMO in San Diego</td>
<td>Frequent headache</td>
<td>Childhood abuse, including emotional, physical, sexual abuse plus other exposures</td>
<td>Frequent headaches were associated with emotional, physical, sexual abuse</td>
</tr>
<tr>
<td>ACE Study</td>
<td></td>
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</tr>
<tr>
<td>cross-sectional survey</td>
<td></td>
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<tr>
<td>Tietjen et al., 2015</td>
<td>9734 adults, nationally representative sample</td>
<td>Migraine, ETTH (ICHD2)</td>
<td>Emotional abuse, Emotional neglect, Sexual abuse modified CTQ</td>
<td>Migraine associated with emotional abuse</td>
</tr>
<tr>
<td>AMPP</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>cross-sectional survey</td>
<td></td>
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<tr>
<td>Brennenstuhl et al., 2015</td>
<td>22996 adults, nationally representative sample</td>
<td>Migraine</td>
<td>Sexual abuse physical abuse saw domestic violence</td>
<td>Migraine was associated with sexual abuse, physical abuse, witnessed domestic violence</td>
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<tr>
<td>cross-sectional survey</td>
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<tr>
<td>Tietjen et al, 2017</td>
<td>14,356 young adults, nationally representative sample</td>
<td>Migraine</td>
<td>Emotional, physical, sexual abuse</td>
<td>Migraine associated with emotional abuse</td>
</tr>
<tr>
<td>Add Health</td>
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<td></td>
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<tr>
<td>cross-sectional survey</td>
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</tbody>
</table>
Early life stress is associated with migraine comorbidities
Migraine Comorbidities

- Vascular/Metabolic
  - Stroke
  - MI/Angina
  - Hypertension
  - POTS
  - Hyperlipidemia
  - Obesity
  - Diabetes mellitus
  - Hypothyroidism

- Psychiatric
  - Depression
  - Anxiety
  - Bipolar
  - PTSD

- Pain Conditions
  - Irritable bowel syndrome
  - Fibromyalgia
  - Chronic Fatigue Syndrome
  - Osteoarthritis
  - Endometriosis
  - Interstitial cystitis
  - Musculoskeletal sx

- Other
  - Asthma
  - Sleep apnea/Snoring
  - GERD
Comorbidity constellations in a migraine clinic population

N = 1348

Cluster 1
n=231
Relative absence of comorbid conditions

Cluster 2
n=669
Pain conditions
- Irritable bowel syndrome
- Chronic fatigue syndrome
- Fibromyalgia
- Interstitial cystitis
- Endometriosis
- Uterine fibroids
- Arthritis

Cluster 3
n=448
Metabolic and psychiatric conditions
- Hypertension
- Diabetes
- Hyperlipidemia
- Depression
- Anxiety
## Comorbidity Constellations

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Women)</td>
<td>93%</td>
<td>84%</td>
<td>83%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>36</td>
<td>42</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>83 %</td>
<td>90%</td>
<td>91%</td>
<td>0.005</td>
</tr>
<tr>
<td>Chronic Frequency (%)</td>
<td>26%</td>
<td>34%</td>
<td>38%</td>
<td>&lt;0.009</td>
</tr>
<tr>
<td>HIT 6 scores</td>
<td>48</td>
<td>58</td>
<td>58</td>
<td>&lt;0.001</td>
</tr>
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</table>
## Comorbidity Constellations

<table>
<thead>
<tr>
<th>Childhood Maltreatment</th>
<th>Group 1 Ref</th>
<th>Group 2 OR (95% CI)</th>
<th>Group 3 OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Abuse</td>
<td>1.00</td>
<td>1.90 (1.35-2.92)</td>
<td>2.32 (1.54-3.65)</td>
</tr>
<tr>
<td>Sexual Abuse</td>
<td>1.00</td>
<td>1.72 (1.29-2.52)</td>
<td>1.84 (1.22-2.66)</td>
</tr>
<tr>
<td>Emotional Abuse</td>
<td>1.00</td>
<td>2.88 (1.99-4.17)</td>
<td>3.20 (2.18-4.70)</td>
</tr>
<tr>
<td>Physical Neglect</td>
<td>1.00</td>
<td>2.44 (1.56-3.90)</td>
<td>2.70 (1.61-4.38)</td>
</tr>
<tr>
<td>Emotional Neglect</td>
<td>1.00</td>
<td>1.58 (1.12-2.23)</td>
<td>2.36 (1.64-3.38)</td>
</tr>
</tbody>
</table>
Potential mechanisms of the link of early life stress and migraine and its comorbidities
Shared Pathogenesis

LIFE SPAN

X Migraine FM, IBS, CFS Depression Stroke

X may be:
1) Genes
2) Environment
3) Gene-environment interactions
Genes Associated with Migraine

- Vascular Function
- Oxidative Stress
- Neuronal Function
  - Ion Channel & Homeostasis
  - Pain Sensing
  - Glutamatergic Transmission
- Glutamatergic Transmission
- Ion Channel & Homeostasis
- Pain Sensing
Environment: Role of Toxic Stress

• Toxic stress is the excessive or prolonged activation of the physiologic stress response systems in the absence of the buffering protection afforded by stable, responsive relationships

• Toxic stress early in life has a role disrupting the circuitry and architecture of the developing brain
Environmental links between migraine and comorbidities

Stressful environment effects the following systems:

- Neuroendocrine
- Endocannabinoid
- Serotonergic
- Oxytonergic
- Inflammatory
Neuroendocrine system

**Acute stress**: fight-or-flight response-- hypothalamic signaling of catecholamine release from adrenal medulla via the sympathetic nervous system

**Chronic Stress**: loss of negative feedback control, leads to long-term changes in HPA regulation and persistent alterations in stress responsivity.
CRHR1 SNPs
Alter stress reactivity via pituitary and amygdala CRHR1s

Stressful and Traumatic Life Events

Note: Experience of chronic stress/trauma may lead to stress-system blunting

NR3C1, NR3C2, FKBP5 SNPs
Alter efficacy of negative feedback via MR/GRs

Amygdala (↑ Volume)

Positive Feedback

HPA Axis Activation

Cortisol Release

Negative Feedback

Hippocampal (↓ Volume)
Neurobiological consequences of Stress

The brain under stress: structural remodeling

Prefrontal cortex
Atrophy

Hippocampus atrophy

Amygdala

Hippocampus

Amygdala, hypertrophy and later atrophy

Figure 4. Brain regions that are involved in perception and response to stress, and which show structural remodeling as a result of stress.

McEwen BS. Dialogues Clin Neurosci. 2006;8:367-381
Structural brain changes

- Chronic stress → glucocorticoids → dendritic remodeling of limbic system structures, especially hippocampus (atrophy) and amygdala (hypertrophy)
  - Brain regions show unique sensitive periods to effects of stress
- Structural changes in the limbic system lead to dysregulation of the HPA-axis
Functional brain changes

**Emotional abuse** predicted on fMRI

- resting state functional connectivity between the right amygdala and pregenual anterior cingulate cortex,
- anxiety after acute stress

**Migraine** showed resting-state connectivity between the amygdala, PFC and ACC and the periaqueductal gray matter

*Abnormal neural circuitry may be a link between abuse and migraine*
Maternal Separation Reduces CSD Threshold in Rodent Model

$P = .0008$

- Threshold (V)

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Separated</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Separated</td>
<td>9</td>
<td>7</td>
</tr>
</tbody>
</table>

- P = 0.0008
Environmental links between migraine and comorbidities

Stressful environment effects the following systems:

- Neuroendocrine
- Endocannabinoid
- Serotonergic
- Oxytonergic
- Inflammatory
Inflammatory system

- Inflammation implicated in the pathophysiology of depression and migraine
- Inflammatory cytokines activate the HPA axis
- HPA axis modulates inflammation and immunoreactivity
- Cytokines disrupt neural function
  - excitation of NMDA receptor
  - Increase in glutamate
  - change GABAergic neurotransmission from inhibitory to excitatory
- Inflammatory marker levels elevated in adults abused as children
Childhood maltreatment is associated with biomarkers of inflammation

Persons maltreated as children, showed a graded increased risk of immune (elevated CRP) and metabolic consequences at age 32 years old. This risk was independent of adulthood stress, health, and health behaviors. Danese A. et.al. PNAS;2007;104:1319-1324
Relationship of ACE and Vascular Biomarkers

The ACE score correlated with:

- NOx, $r=-0.31$, $p=.001$
- vWF activity, $r=0.21$, $p=.009$
- F1.2, $r=0.36$, $p=.001$
- tPA Ag, $r=0.28$, $p=.004$
- hsCRP, $r=0.98$, $p=.0001$
- TGFbeta1, $r=0.28$, $p=.003$
- TNF alpha, $r=0.20$, $p=.03$
- IL-6, $r=0.22$, $p=.03$
- Adiponectin, $r=-0.29$, $p=.003$
- BMI, $r=0.43$, $p=.0001$
Stressful Experiences

- Stressful experiences program stress hormone systems to have exaggerated and prolonged response to subsequent stressors.
- Stressful experiences affect gene expression (epigenetics), myelination, neuronal morphology, neurogenesis, and synaptogenesis.
- The impact on developing brain depends on timing, vulnerability of specific brain regions, and genetic factors.
Epigenetic mechanisms link environment to gene expression

- Epigenetics: processes that govern expression of genes through alterations unrelated to the DNA sequence
  - Chronic stress can influence epigenetic patterns of 2000 genes

- Epigenetic mechanisms—stable throughout the lifespan and across generations
  - DNA methylation
  - Gene regulation by microRNAs.
  - Post-translational histone modifications
Diagnostic and Treatment Implications of the early life stress-migraine link
Clinical Implications

Within a clinic population, migraineurs with a history of abuse are more likely to experience

- comorbidity constellations, including pain, vascular conditions, depression and anxiety
- headache chronification
- headache-related disability increase
- quality of life decrease
Clinical Implications

- History of abuse identifies population at risk for present and future abuse
Abuse in childhood predicts abuse in adulthood

More than half of those individuals reporting physical and sexual abuse in adulthood were exposed to early emotional abuse and neglect.
Clinical Implications

- Identifies increased risk of developing other comorbid conditions linked to abuse, usually after onset of migraine
<table>
<thead>
<tr>
<th>Condition</th>
<th>n (%)</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>1234 (92)</td>
<td>19.39</td>
</tr>
<tr>
<td>Asthma</td>
<td>286 (18.5)</td>
<td>19.57</td>
</tr>
<tr>
<td>Interstitial cystitis</td>
<td>41 (3)</td>
<td>24.33</td>
</tr>
<tr>
<td>CFS</td>
<td>60 (4)</td>
<td>25.42</td>
</tr>
<tr>
<td>POTS</td>
<td>20 (1)</td>
<td>26.38</td>
</tr>
<tr>
<td>Depression</td>
<td>586 (38)</td>
<td>27.04</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>133 (9)</td>
<td>27.19</td>
</tr>
<tr>
<td>IBS</td>
<td>197 (13)</td>
<td>27.37</td>
</tr>
<tr>
<td>Raynaud's</td>
<td>52 (3)</td>
<td>27.51</td>
</tr>
<tr>
<td>Anxiety</td>
<td>446 (29)</td>
<td>29.06</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>194 (12.5)</td>
<td>29.19</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>189 (12)</td>
<td>32.35</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>100 (7)</td>
<td>35.69</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>44 (3)</td>
<td>36.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>58 (4)</td>
<td>36.28</td>
</tr>
<tr>
<td>Arthritis</td>
<td>385 (25)</td>
<td>36.99</td>
</tr>
<tr>
<td>Uterine fibroid</td>
<td>167 (11)</td>
<td>37.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>273 (18)</td>
<td>37.88</td>
</tr>
<tr>
<td>MI/Angina</td>
<td>25 (2)</td>
<td>42.53</td>
</tr>
</tbody>
</table>

* Number (percent) with available information. Values plotted are the mean age at onset of conditions and error bars represent the 95% confidence intervals (CI). The two vertical dotted-lines correspond to the 95% CI for age at migraine onset. CFS: Chronic fatigue syndrome, POTS: Postural orthostatic tachycardia syndrome, IBS: Irritable bowel syndrome, TIA: Transient ischemic attack, MI: Myocardial infarction.

Tietjen GE et al. Cephalagia 2009;29:95
Temporal relationship of comorbid conditions with onset of migraine

Tietjen GE et al. Cephalagia 2009;29:95
Treatment Strategies

- Cognitive Behavioral Therapies
- Aerobic Exercise
- Histone deacetylase (HDAC) inhibitors
Aerobic Exercise

• Enhances endorphins
• Decreases inflammation
• Increases serotonergic activation and neurogenesis
• In rodents-- exercise reverses early life stress-related HPA axis dysfunction
• In migraine--
  • systematic review (9 studies): exercise has at least modest benefit in frequency and intensity
Histone deacetylase (HDAC) inhibitors

- Valproic acid and topiramate (FDA-approved for migraine), as well as 2-pyrrolidinone-n-butyric acid, a major metabolite of levetiracetam, are all HDAC inhibitors.
- HDAC inhibition is proposed mechanism for valproate’s effectiveness in treating bipolar disorder.
- Unknown:
  - Is HDAC inhibition key mechanism in migraine treatment?
  - Would HDAC inhibition be effective in migraineurs with a history of childhood abuse?
Neuroplasticity — the brain’s ability to form new neural connections and be influenced by the environment — is greatest in childhood and adolescence.

With HDAC inhibitors the harmful effects of early life experiences on gene expression are potentially reversible much later in life. This is also very good news for humans, since early life stress is a strong risk factor for many psychiatric illnesses, like mood and anxiety disorders as well as certain personality disorders.
CSD threshold in Maternal Separation rats normalizes with HDAC inhibitor
Summary

• Childhood maltreatment & abuse is prevalent and it is an important social determinant of health
  • It is associated with migraine and its comorbidities

• Migraines associated with abuse are more likely to be chronic, disabling and with a decreased quality of life
Summary

• Early life stress affects a number of physiological systems (neuroendocrine, inflammation/immunity, autonomic nervous system, metabolic)

• Early life stress is associated with changes brain structur and function by affecting myelination, neuronal morphology, neurogenesis, and synaptogenesis

• Epigenetics translates the environment into pathology
Summary

• Clinical implications of childhood maltreatment
  • Abuse in childhood predicts future abuse, more severe migraine, higher likelihood of developing migraine comorbidities

• Treatment implications of childhood maltreatment
  • Targeting systems impacted by abuse, or reversing epigenetic changes caused by abuse may reveal new therapies for migraine and its comorbidities