Recent Advances in Headache Medicine

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What Is Migraine?

- A chronic disorder with episodic attacks
- Integrated mechanisms and complex pathophysiology

During attacks
- Headache
- Several associated symptoms
- Functional disability

In-between attacks
- Enduring predisposition to future attacks
- Anticipatory anxiety
- Changes in brain function, eg,
  - Lack of habituation
  - Reduced nociceptive threshold
Migraine Comorbidity
Disorders highly associated with migraine that occur at a rate significantly greater than chance

Gut Cluster

- Irritable bowel syndrome
- Gastritis
- Peptic ulcer disease
- H. pylori
- GERD
- Colitis
Migraine Comorbidity
Disorders highly associated with migraine that occur at a rate significantly greater than chance

- Asthma
- Hayfever
- Chronic allergic rhinitis
- Gluten sensitivity
- Hypothyroidism
- Female infertility
- Endometriosis

MG food allergy testing
- Accepted diagnostic tool in Celiac Disease
- More likely to have immune response
- Excluding foods may reduce migraine symptoms

Have a seat Kermit. What I'm about to tell you might come as big shock...

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Migraine and Anxiety

• Strong association with migraine
• Possibly more prognostic for progression and intractability
• Autonomic hypersensitivity?
• Associated with the hyperactive migraine state

(Smitherman et al., 2008)
(Aurora et al., 2009)
Persistent Aura without infarction

- Aura symptoms persisting > 1 week
- No infarction on imaging
- Usually migraine aura history
- More common in later life
- Hypercoagulopathy associated
- Relatively resistant to treatments
  - Acetazolamide
  - Valproic Acid
  - Lamotrigine
Cortical Spreading Depression

Endothelial Dysfunction

- **Von Willebrand factor**
  - Procoagulant promoting platelet adherence
  - Independent risk factor for stroke
  - Increase in plasma vWF noted in migraineurs
    - Interical (between attacks)
    - Ictal (during attacks)

- **Elevated prothrombin levels**
  - Found in 50% of migraineurs with aura
  - No significant elevation in migraineurs w/o aura

(Tietgen et al., 2001)
(Folsum et al., 1999)
Homocysteine and Folate metabolism

- Subtle ↑ homocysteine in migraine with aura
- Significantly elevated in atypical aura?
- MTHFR C677T Polymorphism
  - Folate metabolism deficiency
  - Methyl Tetra Hydro Folate?
Migraine with Aura, Cervicalgia and Vitamin B-12

- 26 y/o female
- ICHD II - migraine with aura
  With daily cervicalgia
- Serum vitamin B-12 133 pg/ml
- MRI - c spine without gad.
  - Subtle hyperintensities on T2 weighted imaging
    - Sagital imaging
    - Axial imaging (not shown)
- Resolved after B-12 tx.
Vitamin B-12 levels in Migraineurs

- Sample (n=167) = 431 pg/ml
- Migraine with aura (n=70) = 419 pg/ml
- Migraine without aura (n=97) 441 pg/ml

- B12 < 300 pg/ml 19.7%
  - Migraine with aura = 28.6%
  - Migraine without aura = 13.4%

- B12 < 200 pg/ml = 3.0%
  - 100% migraine with aura
Cortical Spreading Depression

(Brennan et al., 2007)
Glial Calcium Waves and Spreading Depression

Glial Calcium Waves

• Observed in conjunction with electrophysiological spreading depression in brain slices

• Can be dissociated from Cortical Spreading Depression

• Related but Distinct phenomena
  – Independent mechanisms of propagation

(Basarsky et al., 1998)
(Peters et al., 2003)
Endorphins

• Produced in Pituitary and Hypothalamus
• Released in Exercise, excitement, Sex
  – “Runners High”
• Mu opioid receptor active
• Exogenous opioids cause down regulation of endorphins
Dynorphin

- Upregulated in pain and opioid exposure
- Expressed in neurons
- Expressed in Immune system
  - Macrophages
  - Lymphocytes
  - Possible role in Allodynia, hyperalgesia
Neurogenic inflammation

Dynorphin mediated Glial Cell Modulation may be related to Neurogenic Inflammation

Histamine
Serotonin
Cytokines
Leukotrienes (LTC₄)
Prostaglandins (PGD₂, PGI₂)

Dynorphin / Proceptin Associated with Prolonged Pain Modulation
NMDA and Glial Cell activation

- Glutamate activates post synaptic AMPA receptor
- Enhanced NMDA receptor expels Magnesium and promotes Ca++ influx
- Results in long term propagation
- Possible therapeutic targets
  - Magnesium
  - Memantine

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Adiponectin

- Metabolic protein hormone
  - Glucose
  - Fatty acid metabolism
  - Inflammation
- Secreted from adipose tissue
- Regulates feeding cycle in hypothalamus

(Peterlin, 2009)
Preventive Medication

Antiepileptics
- Topiramate
- Pregabalin
- Valproic Acid
- Gabapentin
- Zonisimide
- Carbamazepine
- Oxcarbazepine

Beta Blockers
- Propranolol
- Nadolol
- Atenolol
- Metoprolol
- Timolol

TriCyclics
- Nortriptyline
- Amitriptyline
- Doxepin

Ca Channel Blockers
- Verapamil
- Nimodipine
- Diltiazem

SNRIs
- Venlafaxine
- Duloxetine

SSRIs
- Fluoxetine
- Sertralazine
- Paroxetine
- Escitalopram

Muscle Relaxants
- Tizanidine
- Lioresal
- Clonazepam

Others
- Phelanzine
- Tranlycypromine
- Methergine
- Lithium
- Cyclophedantine
- Hydroxyzine
- Clonidine

Muscle Relaxants
- Tizanidine
- Lioresal
- Clonazepam

Vitamins
- Magnesium
- CoQ10
- Butterbur
- Feverfew
- Vitamin B

NSAIDs
- Indomethacin
- Celecoxib
- Naproxen
- Diclofenac

Botulimum Toxin

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Special Considerations
Topiramate

- Typical effective dose
  50mg – 200mg

  However:
  - 15 mg sprinkle caps
  - 1200mg

- May be given Qhs

- Renal Lithiasis

- Effective within 1-2 wks of therapeutic dose

- Side Effects:
  - Parasthesias
    - Electrolyte sports drink
    - Increased H2O intake
  - Cognitive slowing
    - Reduce dose
    - Qhs dosing
  - Mood Change
    - Acute depression – STOP
  - Weight Loss

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Zonisamide

- Similar migraine benefit as topirimate?
- Much less cognitive side effects
- Typical dose is 50-200mg qhs
- Possible weight reduction

Zone Gran
Can Cun, Mexico
Angiotensin Receptor Blockers

- Candesartan best studied
- Typically dosed 4-16mg per day
- Well tolerated
  - No fatigue
  - No weight gain
  - No mood change
Memantine

- NMDA receptor antagonist
- FDA approved for moderate-severe Alzheimer's Dementia
- Effective for multiple centralized pain syndromes – Fibromyalgia – TMD?
- Pregnancy category B
- Minimal adverse events – Dizziness – Confusion – Insomnia

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Lamotrigine

- Modulates firing of presynaptic excitatory amino acids – Glutamate – Aspartate
- Very effective for second bimodal peak of TN
- Very well tolerated
- Slow titration leads to efficacy in >6 weeks
- Boxed warning – Stevens Johnson Syndrome
  - Worse adverse events with generic
  - Altered dosing for use with carbemazepine (tegretol)
    - Hepatic enzymes induced by carbemazepine reduced half life
Peripheral Nerve Stimulation

- Stimulation has an antinociceptive effect at the peripheral nerve and possibly the central pain processing regions
- Peripheral nerve as a gateway to central pain
Various Stimulator Locations

- Motor Cortex
- Supra Orbital
- Sphenopalatine
- Deep Brain
- Auriculotemple
- Occipital
- Cervical Paddle

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**Occipital Nerve Stimulator**

- **Patient Selection**
  - Chronic headache
    - >15 days per month
    - Typically daily
  - Ability to maintain followup appts
    - Stimulator setting adjustments
    - Device Maintenance
      - Battery
      - Leads
  - Stable psychological profile

- **Risks**
  - Lead Migration
  - Lead Fracture
  - Skin Erosion
  - Infection
  - Muscle Spasm

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Neurostimulation

- Occipital nerve stimulator
  - Effective in Cervicogenic HA
  - Effective in refractory Migraine
  - Relatively safe
  - Occipital Nerve Block **NOT** predictive of outcome

- Cervical “Paddle” leads for direct meningeal stimulation

- Neurostimulation
  - Occipital Nerve Stimulation

(Schwedt & Dodick, 2007)
ONSTIM Feasibility Study

(Saper et al., 2010)

Table 4. Percentage change in number of headache days

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>Baseline</th>
<th>3 months</th>
<th>Percentage change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjustable stimulation</td>
<td>28</td>
<td>22.4 ± 6.3</td>
<td>15.7 ± 10.0</td>
<td>27.0 ± 44.8</td>
</tr>
<tr>
<td>Preset stimulation</td>
<td>16</td>
<td>23.4 ± 5.1</td>
<td>21.9 ± 7.8</td>
<td>8.8 ± 28.6</td>
</tr>
<tr>
<td>Medically managed</td>
<td>17</td>
<td>23.7 ± 4.3</td>
<td>22.8 ± 6.3</td>
<td>4.4 ± 19.1</td>
</tr>
<tr>
<td>Ancillary</td>
<td>5</td>
<td>25.3 ± 5.0</td>
<td>16.3 ± 14.3</td>
<td>39.9 ± 51.0</td>
</tr>
</tbody>
</table>

SD = standard deviation.
Conclusions

- Food sensitivities may exacerbate migraine
- Migraine represents an enhanced and high activity brain state
- Many treatment options for your patients