Gut and Migraine
Case 1

- 21 year old female
  - Episodic migraine / IBS
  - Progressed to daily headache age 20
  - failed 3 different preventatives
  - Triggers
    - None
  - College student / child care provider
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 Pathways

(Goadsby, 2000)
Trigeminal Nucleus Caudalis

- Greater occipital nerve complex
- Trigeminal ganglion
- Trigeminal nucleus caudalis
Enteric Nervous System

- Derived from neural crest cells
- Secretes familiar neurotransmitters
  - Acetylcholine
  - Dopamine
  - Serotonin
  - CGRP
- Precursor cells migrate along vagus nerve
  - Differentiate in the gut
- Up to 600 million neurons!
  Rivaling spinal cord

Helicobacter Pylori and Migraine

- Meta analysis of 5 case control studies
- N=903    H. Pylori infection 39%

- Prevalence of H. pylori infection was significantly greater in migraineurs than in controls
  - 44.97% vs 33.26%
  - OR = 1.92, 95% CI: 1.05-3.51, P = .001

IBS and Migraine

National Health Insurance Research Database (NHIRD) – Taiwan

- 14,117 newly diagnosed migraine
- 56,468 controls

IBS incidence 1.95 fold higher in migraine
- 3.36 fold increase in <30 years old
  (95% confidence interval 2.44-4.63)

Migraine and Nausea

- 73% of migraineurs have associated nausea
- 29% note associated vomiting.
- 49.5% of episodic migraine patients associated high-frequency nausea with their headaches

Functional imaging of nausea

- Phasic activity of the brain preceding nausea
  - Amygdala
  - Putamen
  - Dorsal pons / locus coeruleus

Functional imaging of sustained nausea

- Correlation between anterior insula and midcingulate cortex

Neuroinflammation

- Activated nociceptors release CGRP and substance P
- NO also released

Mast cell degranulation
- Vaso dilation
- NGF, CGRP, NO, substance P
- Mast cell degranulation
- Serotonin
- Proinflammatory cytokines
  - TNF-α, IL-1, IL-6
  - Substance P

CGRP, NO, substance P

CGRP receptor

Substance P receptor

Nociceptor

CGRP receptor

Mast Cell

CGRP

Substance P

NO
### Alterations in glial or neuronal functions

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<tr>
<th>Barrier-inducing</th>
<th>Barrier-disrupting</th>
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<tr>
<td>Glucocorticoids</td>
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<td>cAMP-inducing mediators (VIP)</td>
<td>Purine nucleotides (ADP, ATP and AMP) and adenosine</td>
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<td>Growth factors (TGF, basic FGF)</td>
<td>Free radicals and nitric oxide</td>
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<tr>
<td>Neurotrophins (GDNF)</td>
<td>Platelet-activating factor, leukotrienes and prostaglandins</td>
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<td>Adrenomedullin and noradrenergic mediators</td>
<td>Arachidonic acid and phospholipase A2</td>
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<td>Bradykinin</td>
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<td>S-nitrosothiols (GSNO)</td>
<td>Histamine</td>
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<td>Secreted extracellular matrix components</td>
<td>Glutamate</td>
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<td>Collagen IV, fibronectin, laminin</td>
<td>Serotonin</td>
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<tr>
<td>Regulators of membrane P-glycoprotein and toll-like receptors</td>
<td>Complement-derived peptide C3a-desArg</td>
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<td>Scharff</td>
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<td>Cheese</td>
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<tr>
<td>Citrus Fruit</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol</td>
<td>35%</td>
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</table>

Mechanisms Through Which Diet Can Provoke Migraine

- Hypoglycemia
- Biogenic Amines
- Fasting
- Nitric Oxide
- Activation of Glutamate Receptors
- Omega-3 Fatty Acids
- IgG Response
- IgE Response
Increasing obesity in America

1995 CDC

2010 CDC

- No Data
- <10%
- 10% - 14%
- 15% - 19%
- 20% - 24%
- 25% - 29%
- >30%

Embodys, and the world it has made. Fast food has proven to be a revolutionary force in American life; I am interested in it both as a commodity and as a metaphor.”

- Eric Schlosser
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
Case 2

- 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.
141 participants enrolled with migraine with aura

- Dietary folate consumption, serum folate levels and MTHFR gene mutations collected from all participants

- An inverse correlation was noted between dietary folate equivalents ($R^2=0.201$, $p=0.045$) and serum folate acid ($R^2=0.255$, $P=0.036$)

- For with the CC variant of the MTHFR gene an inverse correlation was also noted between folic acid consumption and headache frequency ($R^2=0.106$; $p=0.029$)
Diet and Migraine

BIOGENIC AMINES
Biogenic Amines

- Includes histamine, tyramine and phenylethylamine
  - Synthesized by decarboxylation of free AA in microbial, vegetable or animal metabolisms
  - Can also be produced by fermentation during storage or decay
  - Found in yeast extracts, fish, chocolate, alcoholic drinks, and fermented products, such as cheese, soy products, sauerkraut, and processed meat
- Challenge studies have been conducted with all of the above biogenic amines, but conclusive evidence linking them to migraine is lacking

Jansen S. Ann Allergy Immunol 2003; 91: 233-40
Histamine Intolerance Test

Symptoms 30 Minutes After Challenge

- Baseline
- Antihistamine

# with symptoms

- Flushing
- Sneezing
- Headache
- Itching
- Weariness

Wantke, Allergy Proc 1994; 15: 27-32
Diet and Migraine
MONOSODIUM GLUTAMATE
Monosodium Glutamate

- M.S.G.
  - Sodium salt of glutamic acid
  - Flavor enhancer
  - Unique taste “umami”
  - Other Names
    - natural flavor, partially hydrogenated vegetable protein, glutamate

- MSG symptom complex
  - Burning, paresthesias, facial pressure, headache, nausea, palpitations, bronchospasm

Kwok R. NEJM 1968; 278: 796
M.S.G. Complex Syndrome

* P< 0.05

Diet and Migraine

ALLERGIC AND IMMUNOLOGICAL MECHANISMS
Food Allergy

- Food allergens can be identified by skin prick testing or RAST.

- Studies suggest that 66-93% of patients positive for a food allergy respond to diet with a reduction in migraine frequency.
  
  - Some of them underwent double-blind placebo controlled food challenge.
    
    - 65% had a migraine to exposure to one or more food allergens.

Mansfield L. Ann Allergy 1985; 55: 126-129
# 0075 IgG4 Food Antibodies (90 Antigens)

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<thead>
<tr>
<th>Category</th>
<th>Item</th>
<th>Score</th>
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**Methodology:** ELISA

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<td>900+</td>
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Georgia Lab Lic. Code #007-007
CLIA ID 1102035945
New York Clinical Lab PFT-578
Florida Clinical Lab Lic. #800008124

Testing Performed by Genova Diagnostics-Methodists
3425 Corporate Way Duluth, GA 30096

Page 2
<table>
<thead>
<tr>
<th>Dairy/Meat/Poultry</th>
<th>Results (ng/mL)</th>
<th>Response Class</th>
<th>Results (ng/mL)</th>
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<td>Beef</td>
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| Apricot                | <10             |                | Navy Bean       | 120            | Mild +2

Class Definitions:
- Class 1: 41 - 80
- Class 2: 81 - 150
- Class 3: 151 - 500
- Class 4: 501 - 900
- Class 5: 900+
IGG Food Sensitivity Testing

• Foods may trigger migraine

• Challenge to identify which food may trigger migraine

• Accepted diagnostic tool
  • Celiac Disease
  • Asthma
  • Eosinophilic Esophagitis

Pasquel J & Orterino A. Cephalalgia 2010;30:777-81
Foods Associated with CNS Inflammation

What are the top foods to consider eliminating for chronic migraine?

1. Gluten
2. Egg
3. Dairy
4. Corn
5. Caffeine
IgG Antibody Based Elimination Diet

Percent Improvement Compared with Baseline

Provocation Diet vs Elimination Diet

*P<0.05 vs baseline

Alpay K. Cephalalgia 2010; 30: 829-835,
Does IgG elevation represent a food allergy?
IgG Elimination Diet

- 65 patients
- Not placebo controlled
- Used IgG testing to identify possible food triggers
- 43/65 patients substantial improvement / complete remission

IgG-based Elimination Diet in migraine plus IBS

- 21 subjects with both IBS and migraine
- Double blind, randomized, controlled, cross over trial
- Diets
  - Usual diet
  - Elimination diet
  - Provocation diet

Elimination diet effect on headache
- ↓ Attack count
  - (4.8 [2.1] vs 2.7 [2.0]; P < .001)
- ↓ Mean attack duration
  - (1.8 [0.5] vs 1.1 [0.8] days; P < .01)
- ↓ Attack severity
  - (vas 8.5 [1.4] vs vas 6.6 [3.3]; P < .001)
- ↓ Acute medication use
  - (4.0 [1.5] vs 1.9 [1.8]; P < .001)
- ↓ pain-bloating severity
- ↑ quality of life

Cost of testing

- IgG food sensitivity testing
  - $1,200 (pt. pays $100)

- MRI Brain
  - $3,500

- Onabotulinum toxin A
  - $17,000 annual
  - 1970s = $40 /vial
Diet and Migraine

GLUTEN ENTEROPATHY
Celiac Sprue

- Enteropathy induced by exposure to gluten
- Characterized by villous atrophy, mucosal inflammation and crypt hyperplasia on small bowel biopsy

Clinical manifestations
- Diarrhea, abdominal bloating/pain, unexplained iron deficiency, LFT abnormalities, neurological manifestations

Treatment
- Gluten Free Diet (GFD): 70% improve within 2 weeks;
Diagnosis and Treatment

- **Serological testing**
  - Tissue transglutaminases (TTG IgA, IgG)
    - IgA important for enteropathy
  - IgA testing
    - Deficiency will produce false negative testing
  - Deamminated gliadin peptide (DGP IgG)

- **HLA genotyping**
  - HLA DQ2 and DQ8 are highly sensitive, but poorly specific
  - Small bowel biopsy is gold standard for enteropathy
Celiac Disease and autonomic dysfunction

- 25 subjects with CED
  - Neurologically asymptomatic
- 30 Controls

- HR variability
  - Rest
  - Sympathetic stimulation
  - Parasympathetic stimulation

- CED more likely to have
  - 36% had HRV with sympathetic dominance
  - 20% had HRV with parasympathetic dominance

Migraine comorbid with Celiac Disease and Gluten Sensitivity

- Chronic headache reported by
  - 30% of Celiac disease
  - 56% of Gluten sensitivity
  - 23% of Irritable bowel syndrome
  - 14% of controls

- Migraine reported by
  - 21% Celiac Disease
  - 40% of Gluten sensitivity

*all significantly higher than controls

Neurological Manifestations

Migraine/Headache
- CS prevalence 4% in migraine patients vs. 1% in controls
- HA Frequency ↓ GFD
- OR 3.79 for migraine in sprue
- Association with WM lesions

Ataxia
- TTG IgG more common than IgA
- < 10% have GI sxs
- 33% have + biopsy
- 60% SM neuropathy

Peripheral Neuropathy
- 23% prevalence with CS
- Sensory motor axonal neuropathy

Gabrieli M. Am J Gastroenterol 2003; 98: 625-29
Diet and Migraine

COMPREHENSIVE DIETS
Nutritional intervention for migraine

- 36 week cross over study
- 16 week treatment periods
  - Placebo
  - Diet modification
    - Low fat vegan x 4 weeks
    - Trigger elimination then reintroduction
- Significant decrease in headache
  - ↓ severity of worst pain (P=.030)
  - ↓ number of headaches (P=.04)
  - ↓ acute medication use (19% less)
- Significant health improvements
  - ↓ Weight (reduced 3.6 kg during diet)
  - ↓ total cholesterol (reduced 14 mg/dl)

Low Fat Diets

- 54 participants recorded headache frequency, severity and duration during run-in and low fat diet (<20 gms/day)

Results

- median headache frequency (6 vs. 1; p<0.05) and severity (2.9 vs. 0.5) was reduced during low fat diet phase as compared to lead-in month

Zuzana B. J Women’s Health Gen Based Med 1999; 8: 623-630
Ketogenic Diet

Ketogenic Diet

Dietary N-3 & N-6 Fatty Acids

Ramsden C. Pain 2013; 154: 2441-51
High Omega 3/Low Omega 6 (H3/L6) vs. Low Omega 6 (L6) Diet

Decrease from Baseline

- HIT-6
  - P < 0.001

- Headache Days/Month
  - P = 0.02

- Headache Hrs/Day
  - P = 0.01
Probiotic Therapy?

- Difficult to know how to direct patients
- Conflicting data
- Basic recommendation
  - Multi specie
  - Multi billion count
- Variable Diet might be best option
Boswellia Serrata

- Ayurvedic treatment
- ↓Prostaglandin synthesis
  - Lipoxygenase (LOX) inhibitor
- Similar to indomethacin

- 375mg bid – 750mg bid
- Gliacin formulated specially for headache populations

Quercetin

- Bioflavanoid compound
- Mast cell stabilizer
- Reduces inflammatory markers
  - Interleukin 6
  - Histidine decarboxylase
  - Tryptase

- Dose - Quercetin 500mg twice a day
- Beneficial for migraine patients with inflammatory / hypersensitivity symptoms?

Approach to Dietary Management

Diet

- Identification of Dietary Triggers
  - Food Diary
  - Patient History
  - IgG Food Testing
  - Allergy Testing

- Specific Diet
  - N3/N6 Diet
  - Low Fat Diet
  - Ketogenic Diet?
Case 1: Followup

- Underwent IgG food Testing
  - High IgG levels to dairy & egg.
  - Advised to follow dairy / egg elimination
  - Placed on cetirizine 20mg qhs
  - Daily headache resolved.
  - Rare episodic migraine.
  - IBS improved.
- Plan reintroduction of foods in 3 months.
Conclusions

- Dietary triggers are commonly reported by patients with migraine.
- Mechanisms through which dietary triggers might precipitate migraine headache are varied.
- IgG testing may help identify foods that promote migraine escalation.
- New diets offer promise for the treatment of patients with chronic headache/migraine.