Gut and Migraine

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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

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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

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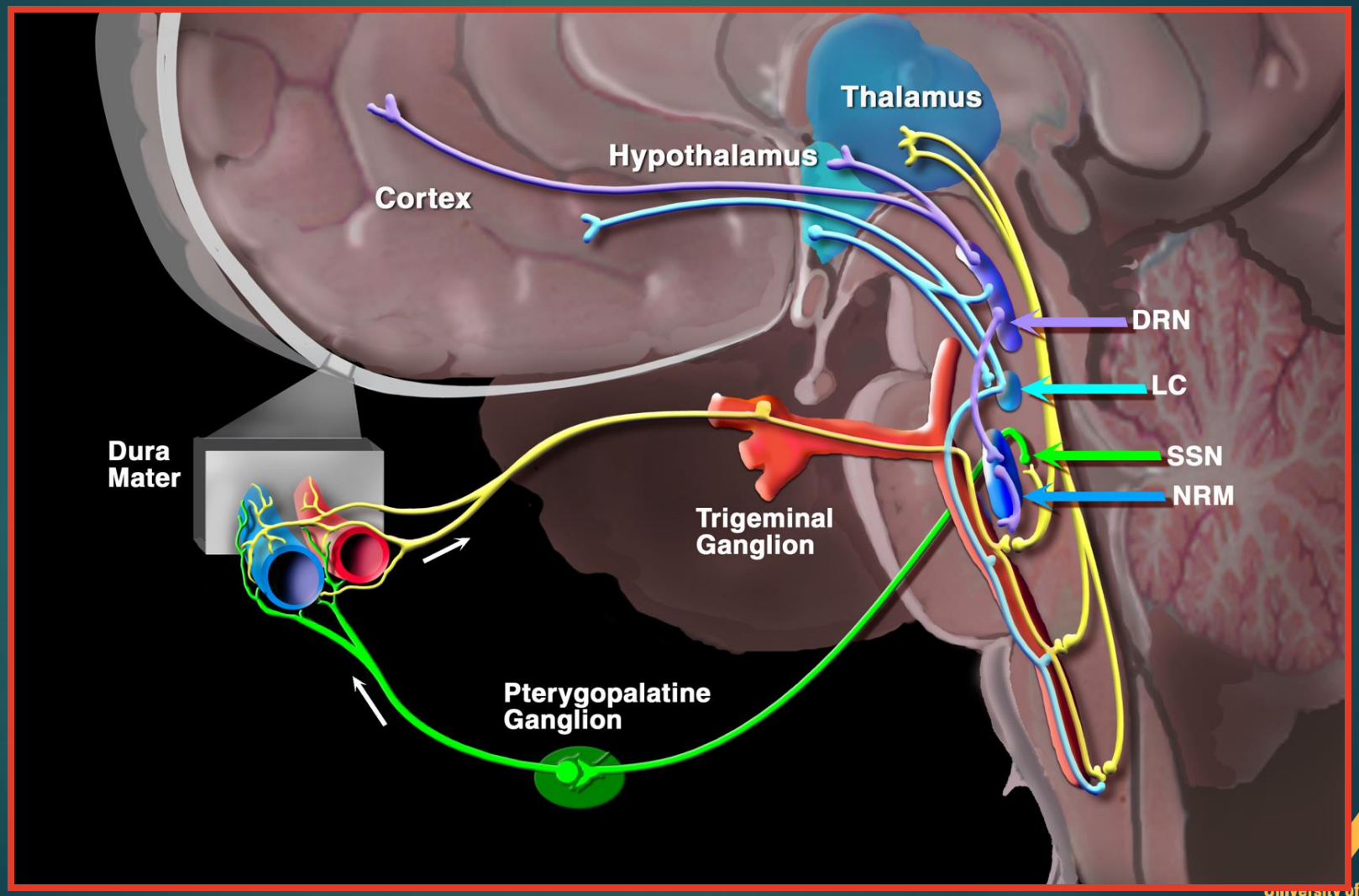
Migraine Pathways



(Goadsby, 2000)

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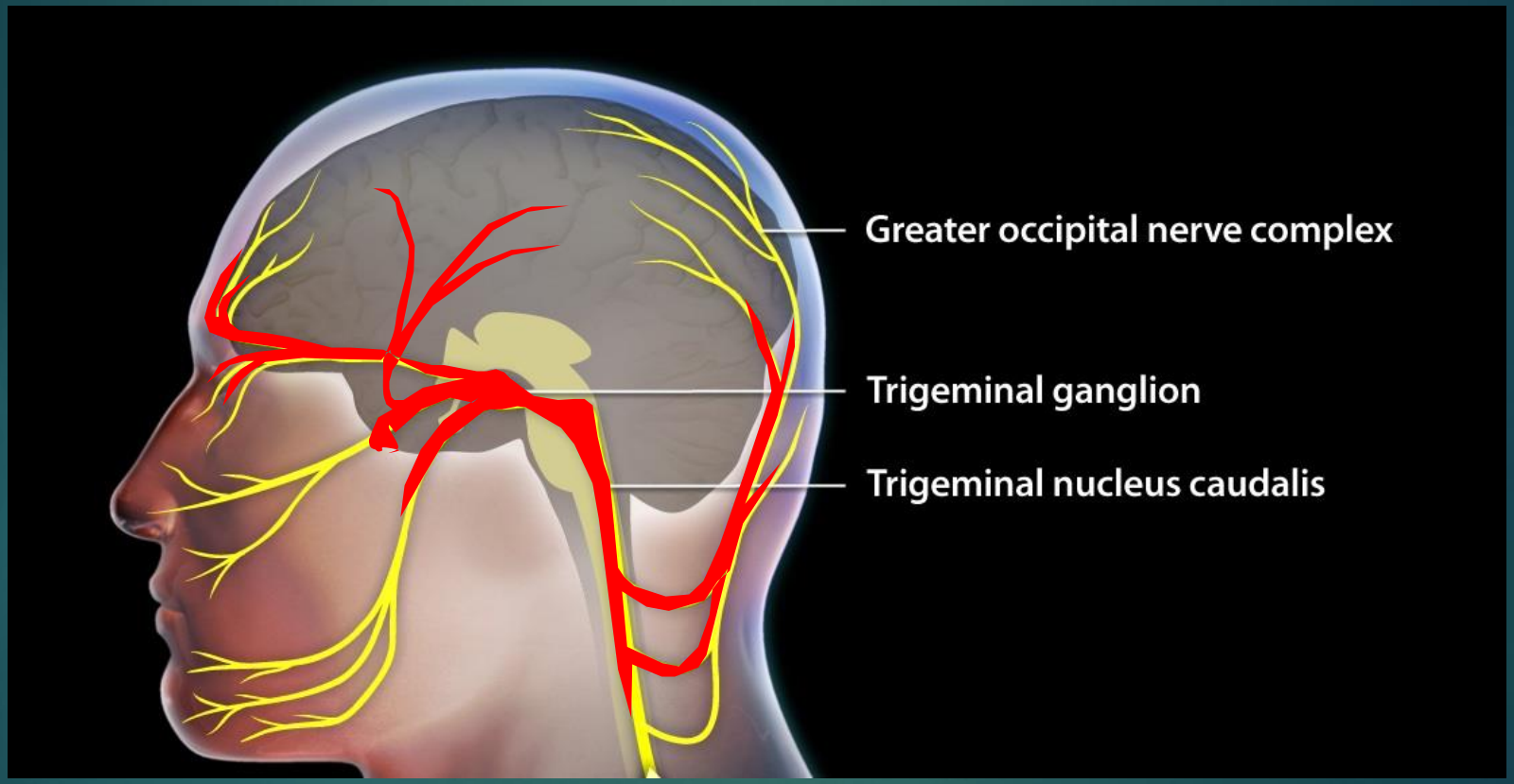
Trigeminal Nucleas Caudalis



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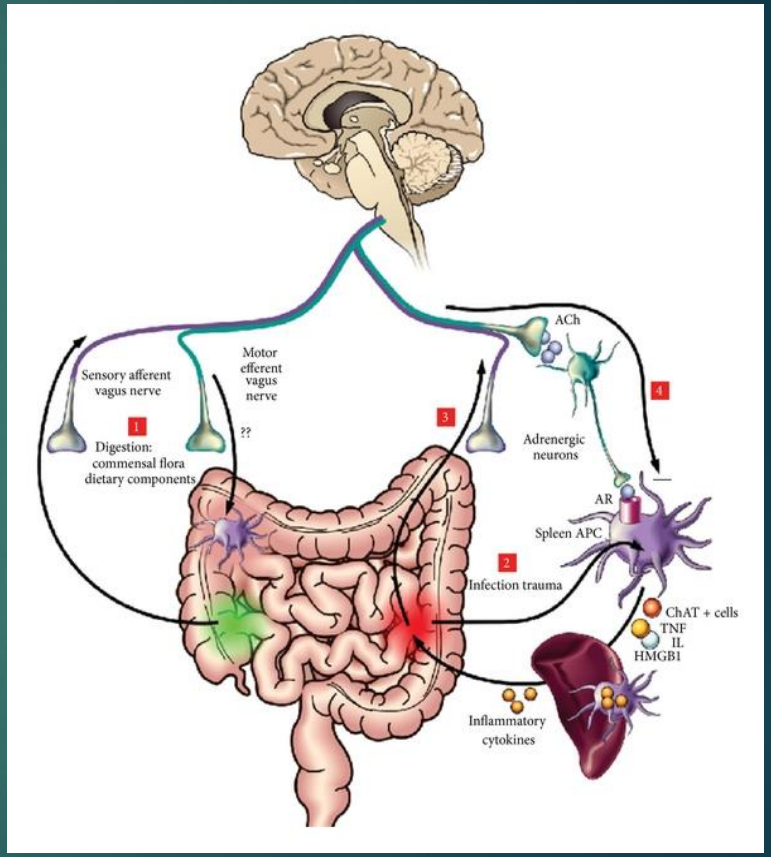
Enteric Nervous System

- 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



Gershon MD, Chalazonitis A, Rothman TP. From neural crest to bowel: development of the enteric nervous system. J Neurobiol. 1993;24:199–214.

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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

Su J, Zhou XY, Zhang GX. Association between *Helicobacter pylori* infection and migraine: A metaanalysis. *World J Gastroenterol*. 2014;20:14965-14972.

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)

Lau CI, Lin CC, Chen WH, et al. Association between migraine and irritable bowel syndrome: A population-based retrospective cohort study. *Eur J Neurol*. 2014;21:1198-1204.

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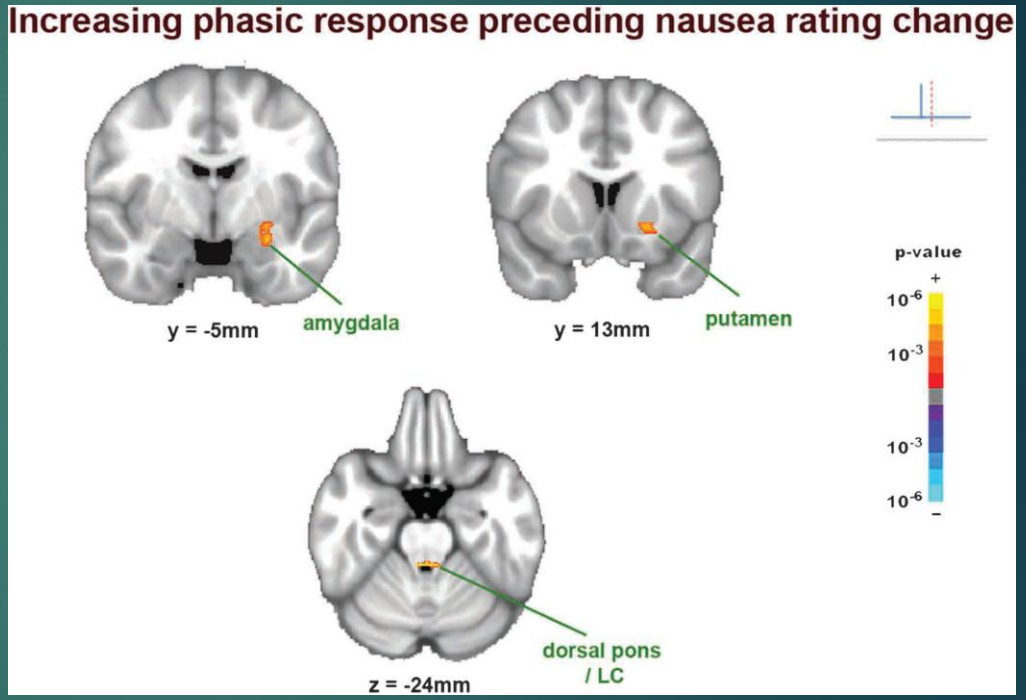
Migraine and Nausea

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

Lipton RB, Buse DC, Saiers J, et al. Frequency and burden of headache-related nausea: results from the American Migraine Prevalence and Prevention (AMPP) Study. Headache. 2013;53:93–103.

Functional imaging of nausea

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



Napadow V, Sheehan J, Kim J, et al. The brain circuitry underlying the temporal evolution of nausea in humans. Cereb Cortex. 2013;23:806–13.

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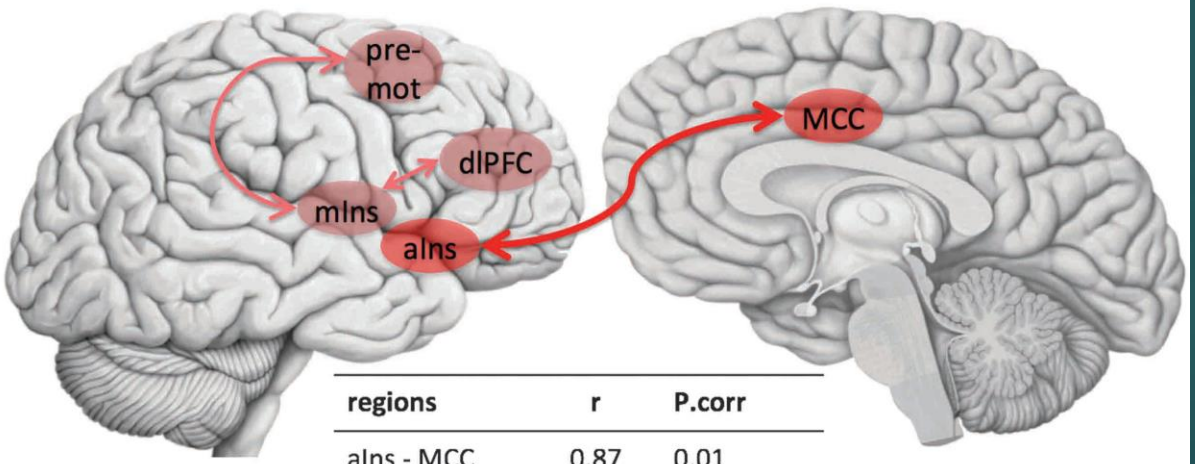
Functional imaging of sustained nausea

- Correlation between anterior insula and midcingulate cortex

Inter-regional correlations for sustained response to strong nausea



regions	r	P.corr
aIns - MCC	0.87	0.01
mIns - dlPFC	0.80	0.10
mIns - premotor	0.81	0.07

Napadow V, Sheehan J, Kim J, et al. The brain circuitry underlying the temporal evolution of nausea in humans. Cereb Cortex. 2013;23:806–13.

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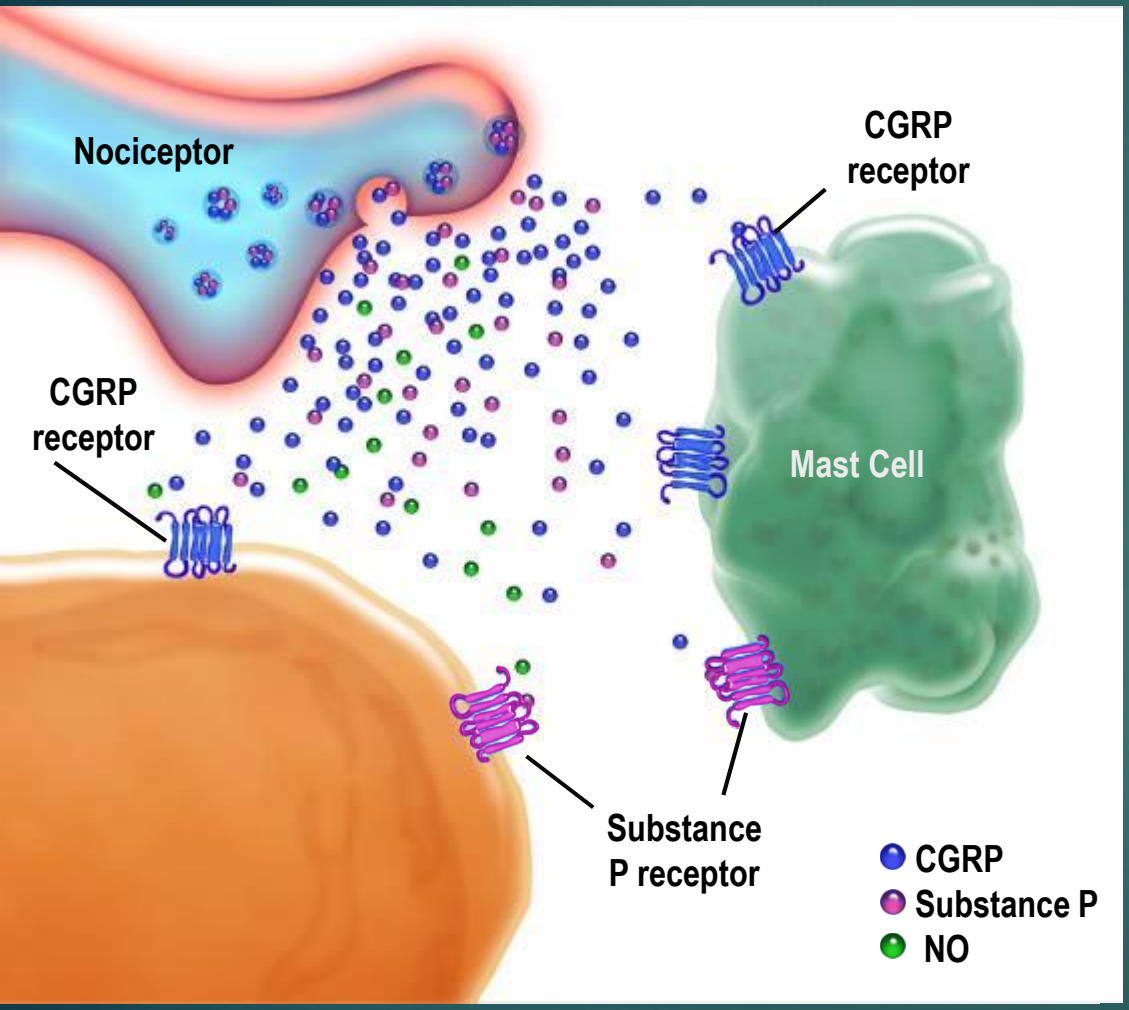
Neuroinflammation



- Activated nociceptors release CGRP and substance P
- CGRP and substance P activate mast cells
- NO also released
- Mast cell degranulation
  - Vasodilation
    - CGRP, NO, substance P
  - NGF
  - Serotonin
    - CGRP, substance P
  - Proinflammatory cytokines
  - Plasma extravasation
    - substance P
    - TNF-α, IL-1, IL-6

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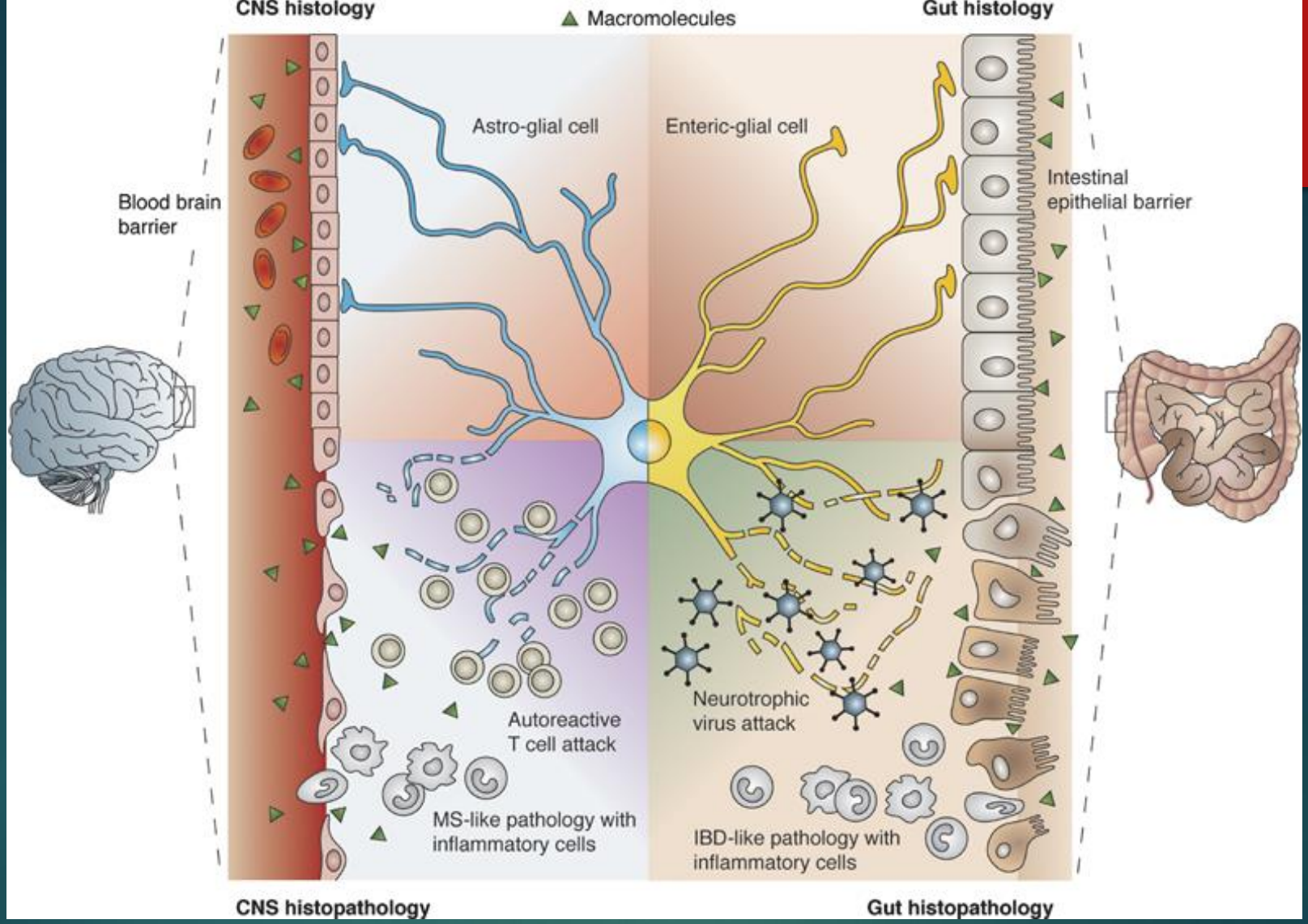

Savidge TC, Sofroniew MV, Neunlist M. Starring roles for astroglia in barrier pathologies of gut and brain. Lab Invest. 2007 Aug;87(8):731-6.

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Alterations in glial or neuronal functions

Barrier-inducing	Barrier-disrupting
Glucocorticoids	Proinflammatory cytokines (TNF-, IL-1, IL-6, MIP)
cAMP inducing mediators (VIP)	Purine nucleotides (ADP, ATP and AMP) and adenosine
Growth factors (TGF, basic FGF)	Free radicals and nitric oxide
Neurotrophins (GDNF)	Platelet-activating factor, leukotrienes and prostaglandins
Adrenomedullin and noradrenergic mediators	Arachidonic acid and phospolipase A2
Endothelin-1 S-nitrosothiols (GSNO)	Bradykinin Histamine
Secreted extracellular matrix components	Glutamate
Collagen IV, fibronectin, laminin	Serotonin
Regulators of membrane P-glycoprotein and toll-like receptors	Complement-derived peptide C3a-desArg

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Prevalence of Dietary Triggers

Triggers	Scharff	Peatfield
Chocolate	22%	19%
Cheese	9%	18%
Citrus Fruit	-	11%
Alcohol	35%	29%

Peatfield, Cephalalgia 1984; 4: 179-83; Scharff L. Headache 1995; 35397-403.

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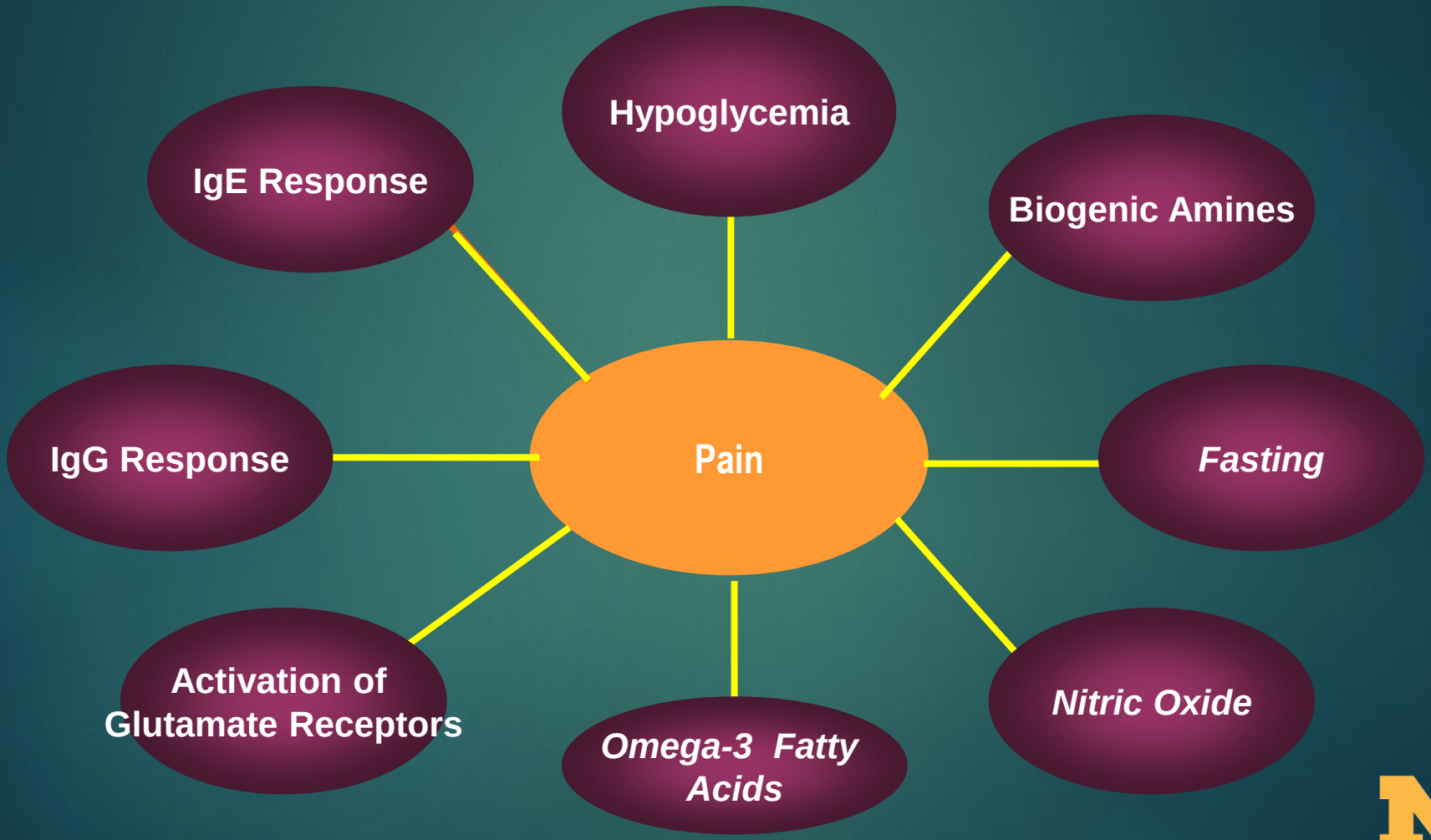
Mechanisms Through Which Diet Can Provoke Migraine



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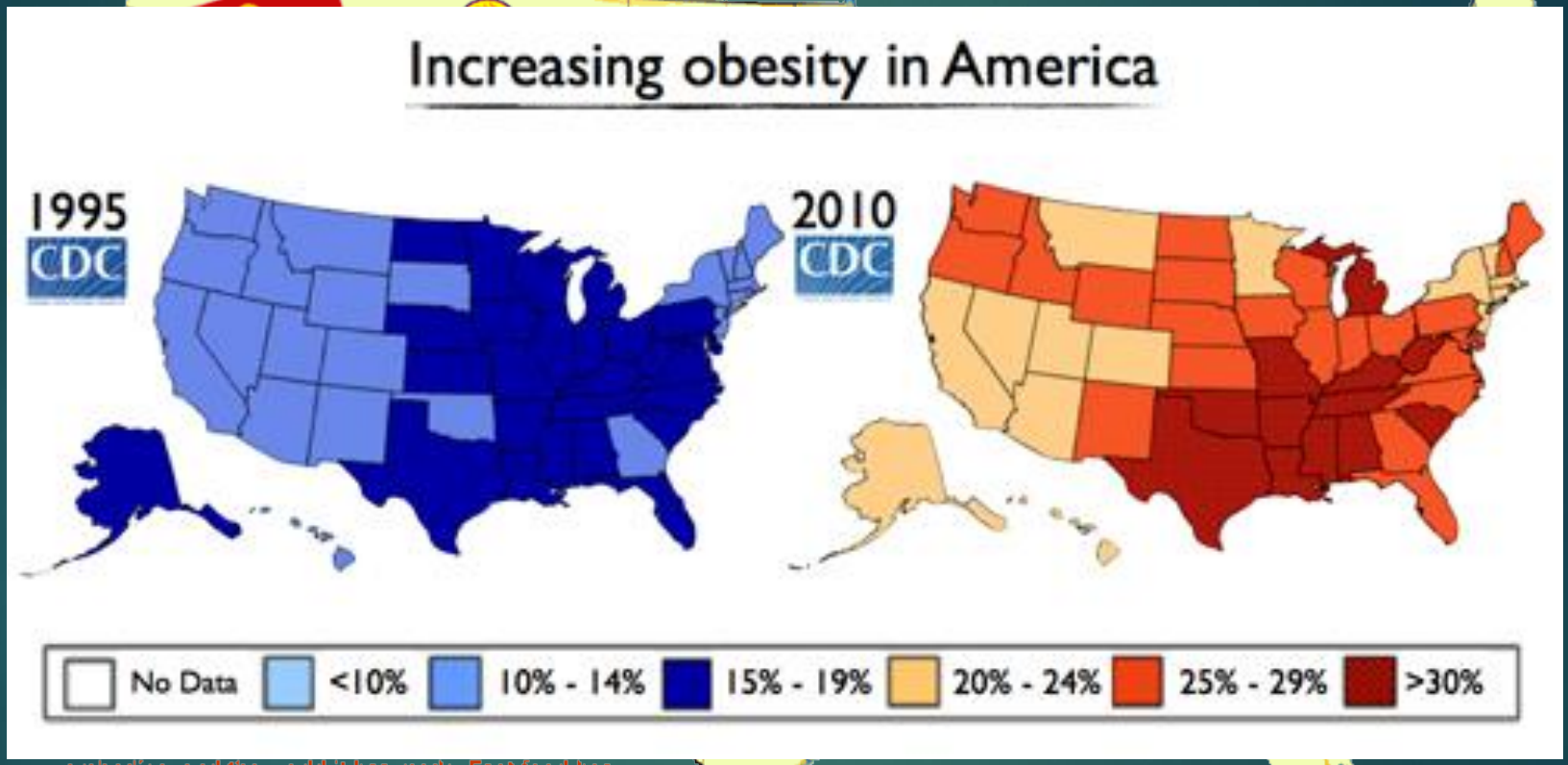

Increasing obesity in America

1995 CDC

2010 CDC

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

embodies, 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

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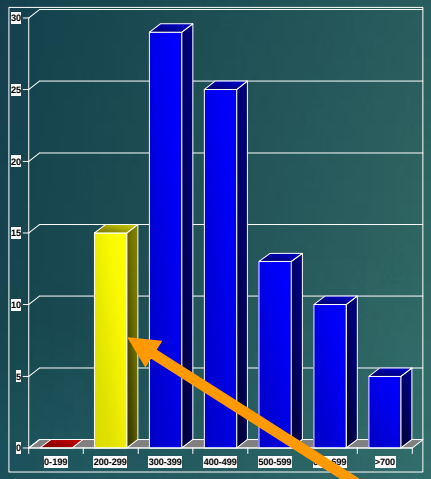
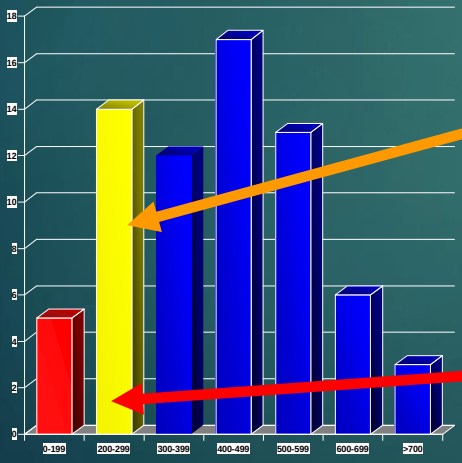
Vitamin B-12 levels in Migraineurs



Mig. Without Aura



Mig. With Aura

- 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

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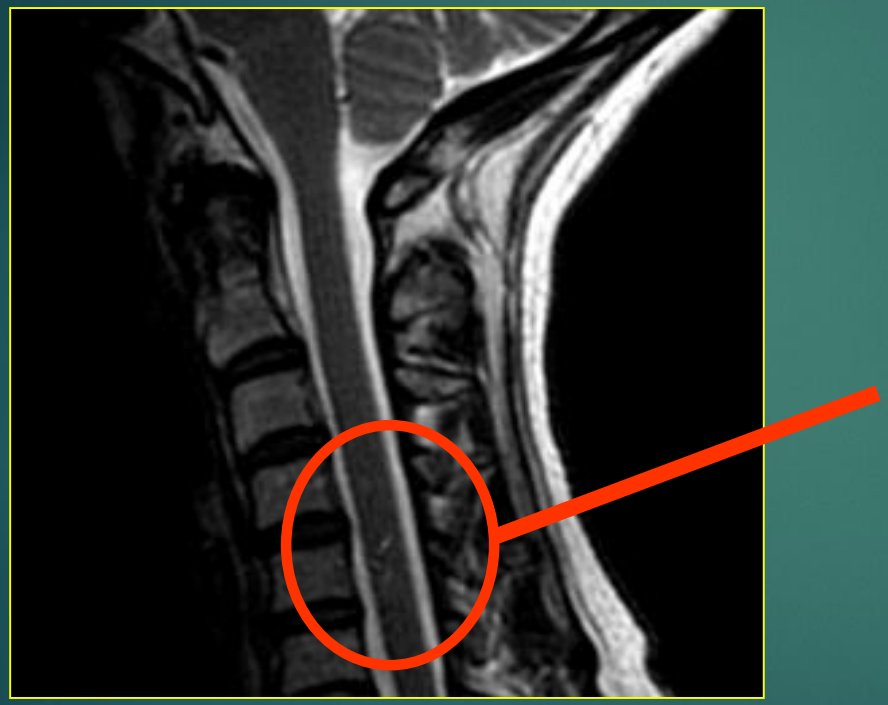
Case 2



- 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.

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Homocysteine

- 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)

Menon. Headache 2015; 15: 301-309

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BIOGENIC AMINES

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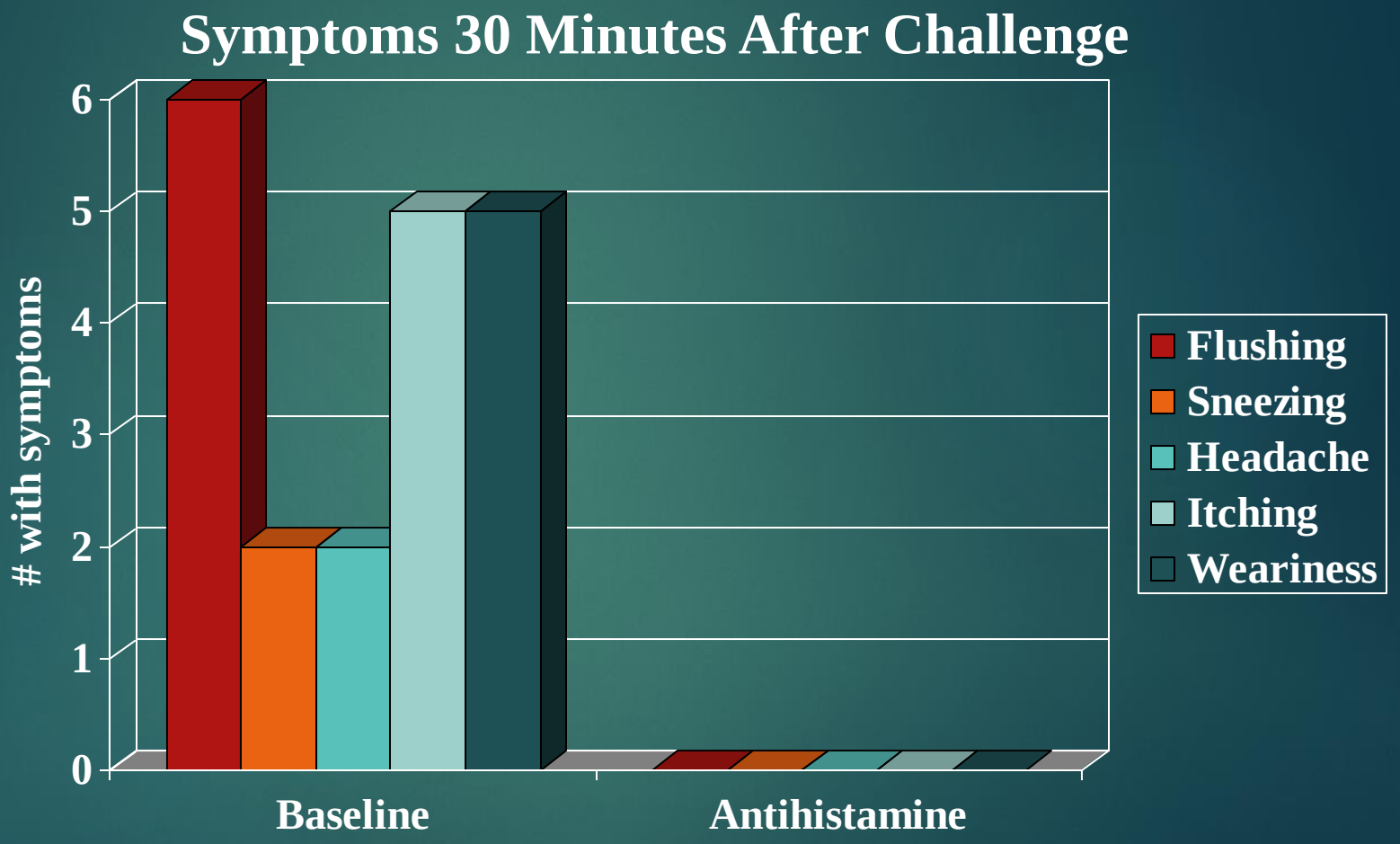
Biogenic Amines

- 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



Wantke, Allergy Proc 1994; 15: 27-32

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Diet and Migraine

MONOSODIUM GLUTAMATE

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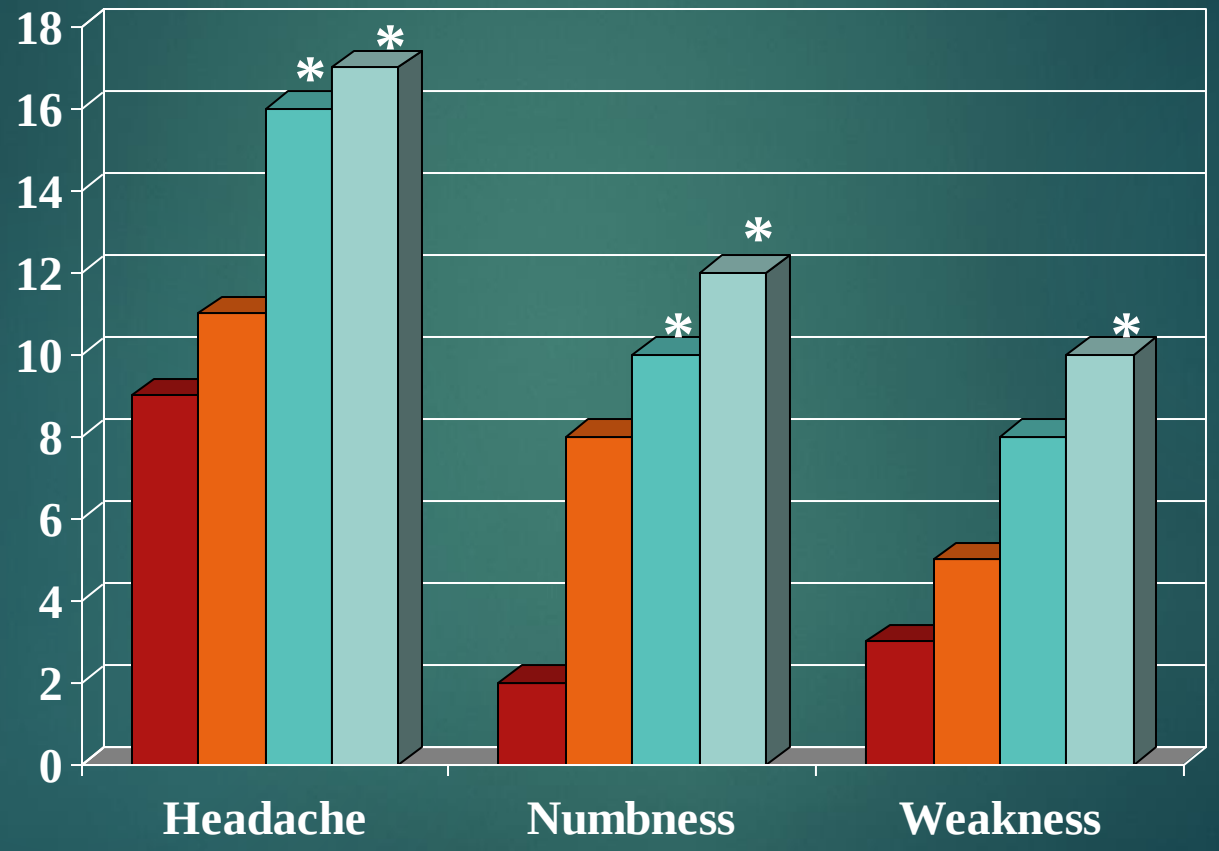
Monosodium Glutamate

- M.S.G.
  - Sodium salt of glutamic acid
  - Flavor enhancer
  - Unique taste "umani"
  - 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

Yang, J Allergy Clin Immunol 1997; 99: 757-62.

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Diet and Migraine

ALLERGIC AND IMMUNOLOGICAL MECHANISMS

Food Allergy

- Food allergens can been 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

Egger K. Lancet 1983; 2: 65-69

Mansfield L. Ann Allergy 1985; 55: 126-129

Suite 100
Ann Arbor, MI 48109-0322

Reprinted:
Comment:

0075 IgG4 Food Antibodies (90 Antigens)

Methodology: ELISA

Pea, Green	9
Peanut	12
Pinto Bean	8
Soybean	9
Miscellaneous	
Aspergillus	20
Black Pepper	10
Chocolate	<10
Cinnamon	<10
Coffee	10
Ginger	16
Malt	11
Tea	<10
Vanilla	<10
Yeast, Baker's	<10
Yeast, Brewer's	<10
Nuts/Seeds	
Almond	20
Cashew	22
Coconut	9
Pecan	9
Pistachio	20
Sesame	<10
Sunflower	14
Walnut	<10
Vegetables	
Asparagus	10
Avocado	<10
Broccoli	8
Cabbage	<10
Carrot	10
Cauliflower	<10
Celery	<10
Cucumber	<10
Garlic	10
Lettuce	<10
Mushroom	10
Mustard Seed	13
Olive	19
Onion	<10
Pepper, Green	<10
Potato	8
Spinach	<10
Sweet Potato	<10
Tomato	<10
Zucchini	<10

Class Definitions:

Class	Cutoffs
Negative	0-40
Class 1	41 - 80
Class 2	81 - 150
Class 3	151 - 500
Class 4	501 - 900
Class 5	900+

0075 IgG4 Food Antibodies (90 Antigens)

Methodology: ELISA

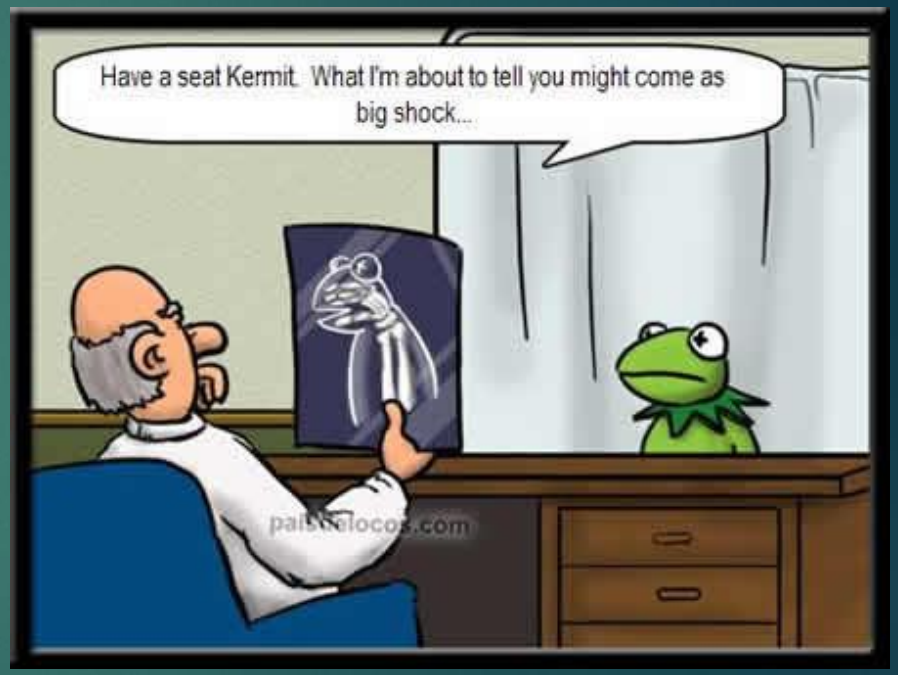
	Results ng/mL	Response	Class
Dairy/Meat/Poultry			
Beef	38		
Casein	37		
Chicken	22		
Egg, White	>2000	Severe	+5
Egg, Yolk	652	Mod	+4
Lamb	24		
Milk	110	Mild	+2
Pork	10		
Turkey	<10		
Fish/Shellfish			
Clam	10		
Codfish	13		
Crab	22		
Flounder	15		
Halibut	16		
Lobster	10		
Mackerel	9		
Oyster	<10		
Salmon	24		
Shrimp	<10		
Trout	9		
Tuna	9		
Fruits			
Apple	9		
Apricot	<10		
Banana	<10		
Blueberry	15		
Cantaloupe	22		
Cranberry	<10		
Grape	13		
Grapefruit	20		
Honeydew	15		
Lemon	12		
Orange	14		
Peach	<10		
Pear	9		
Pineapple	<10		
Strawberry	15		
Watermelon	<10		
Grains			
Barley	<10		
Corn	11		
Oat	16		
Rice	8		
Rye	<10		
Wheat	<10		
Legumes			
Bean, String	<10		
Lentil	18		
Lima Bean	11		
Navy Bean	120	Mild	+2

Class Definitions:

Class	Cutoffs
Negative	0-40
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

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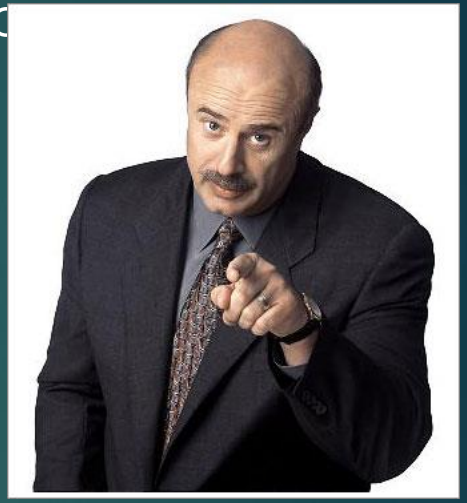
Foods Associated with CNS Inflammation

- What are the top foods to consider eliminating fo chronic migraine?



1.
2.
3.
4.
5.

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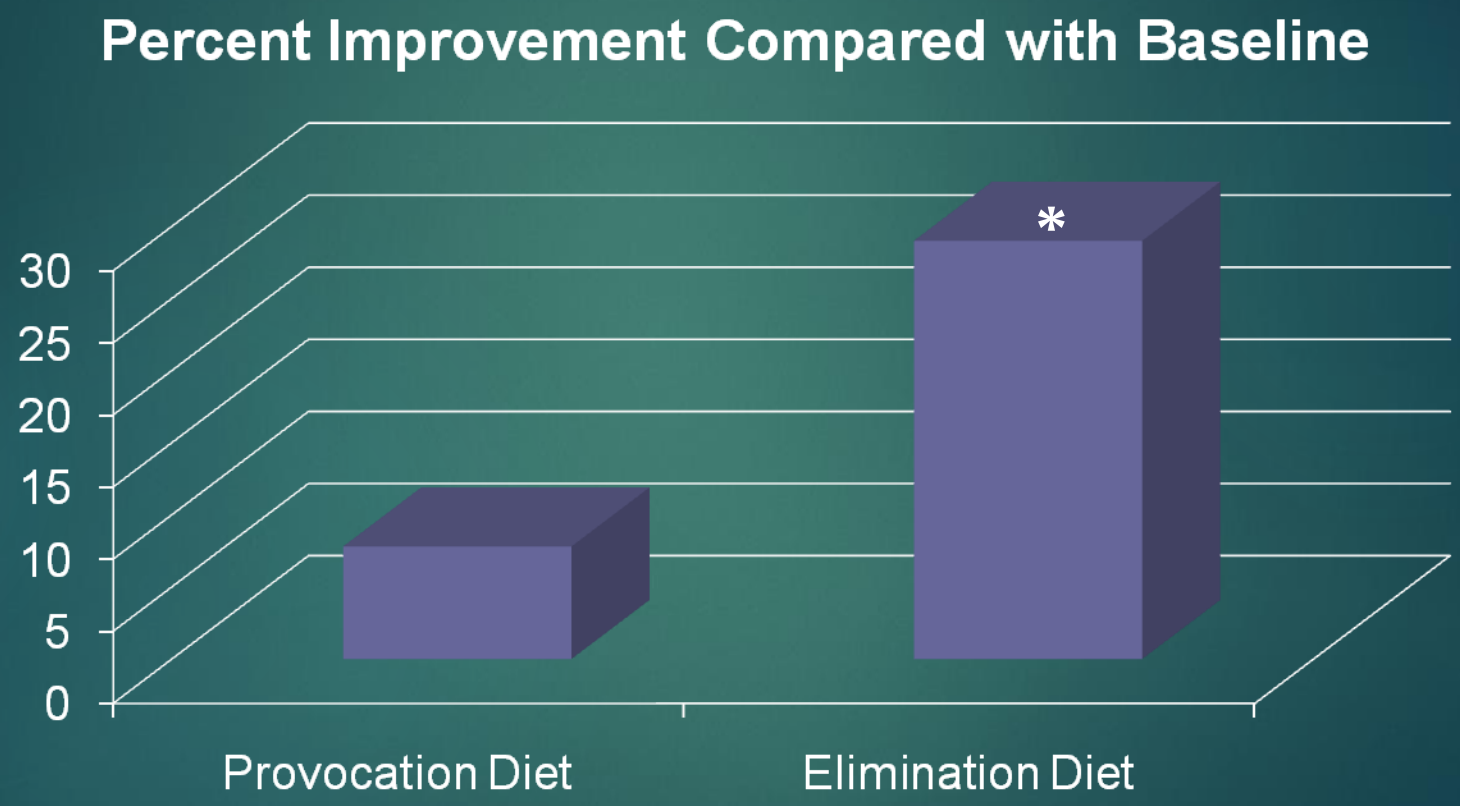
IgG Antibody Based Elimination Diet



*P<0.05 vs baseline

Alpay K. Cephalalgia 2010; 30: 829-835,

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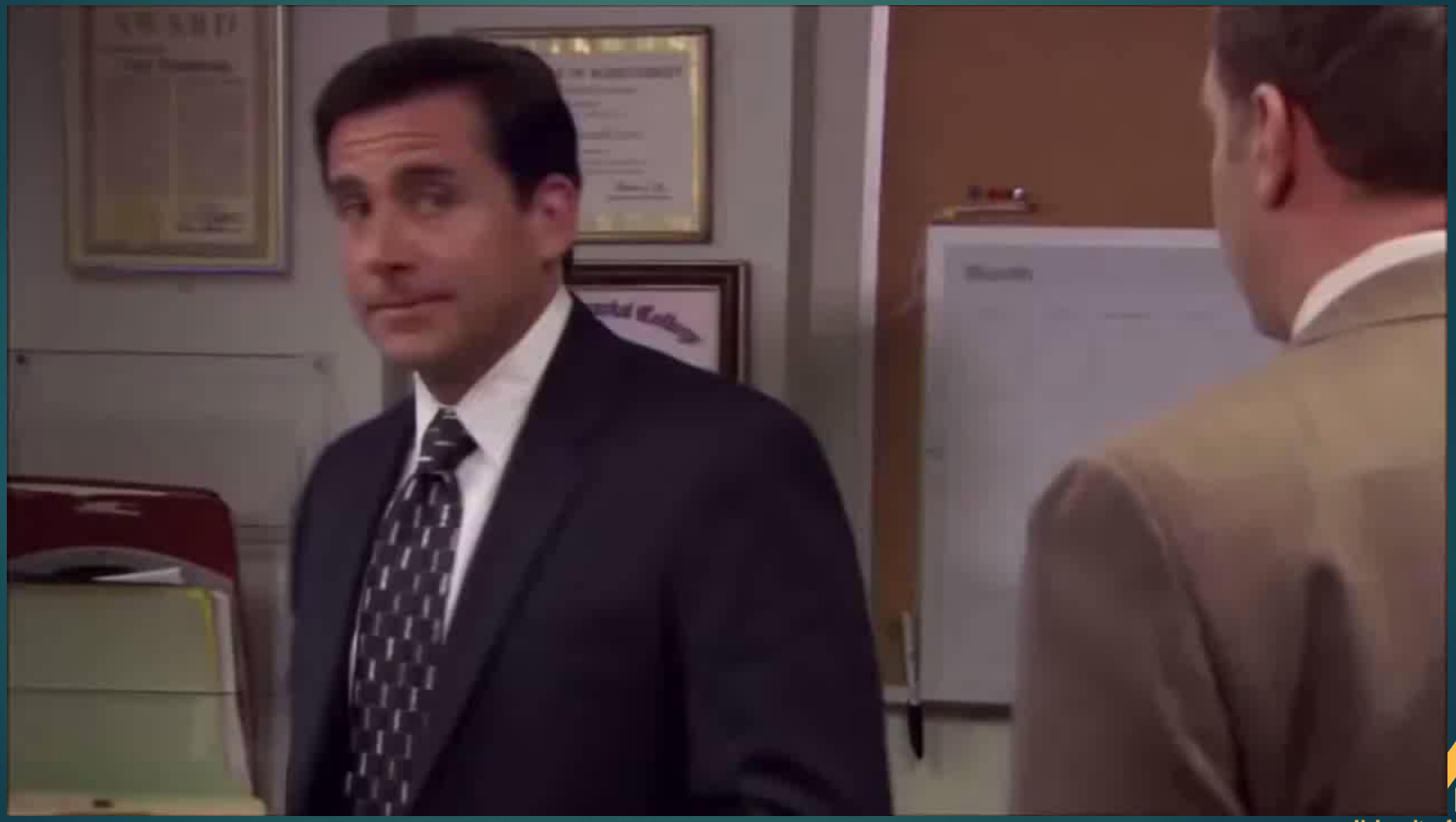
Does IgG elevation represent a food allergy?



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IgG Elimination Diet

- 65 patients
- Not placebo controlled
- Used IgG testing to identify possible food triggers

- 43/65 patients substantial improvement / complete remission

Arroyave Hernández CM, Echavarría Pinto M, Hernández Montiel HL. Food allergy mediated by IgG antibodies associated with migraine in adults. Rev Alerg Mex. 2007;54:162-168.

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

Avdinlar EI, DIkmen PY, Tiftikci A, et al. IgG-based elimination diet in migraine plus irritable bowel syndrome. Headache. 2013;53:514-525.

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

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Celiac Sprue

- Enteropathy induced by exposure to gluten
- Characterized by villous atropy, 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;

Up to Date 2014

Diagnosis and Treatment

- Serological testing
  - Tissue transglutaminases (TTG IgA, IgG)
    - IgA important for enteropathy
  - IgA testing
    - Deficiency will produce false negative testing
  - Deaminated gliadin peptide (DGP IgG)
- HLA genotyping
  - HLA DQ2 and DQ8 are highly sensitive, but poorly specific
- Small bowel biopsy is gold standard for enteropathy

Up to Date 2014

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Celiac Disease and autonomic dysfunction

- 25 subjects with CED
  - Neurologically asymptomatic
- 30 Controls

- HR variability
  - Rest
  - sympathetic stimulation
  - parasympathetic stimulation

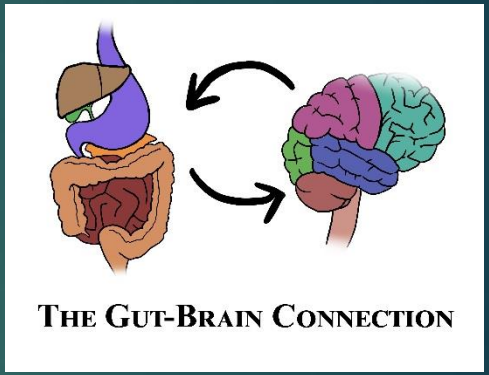
- CED more likely to have

- 36% had HRV with sympathetic dominance
- 20% had HRV with parasympathetic dominance

Przybylska-Felus M, Furgala A, Zwolinska-Wcislo M, Mazur M, et al. Disturbances of autonomic nervous system activity and diminished response to stress in patients with celiac disease. J Physiol Pharmacol. 2014 Dec;65(6):833-41.

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

Dimitrova AK, Ungaro RC, Lebwohl B, et al. Prevalence of migraine in patients with celiac disease and inflammatory bowel disease. Headache. 2013;53:344–55.

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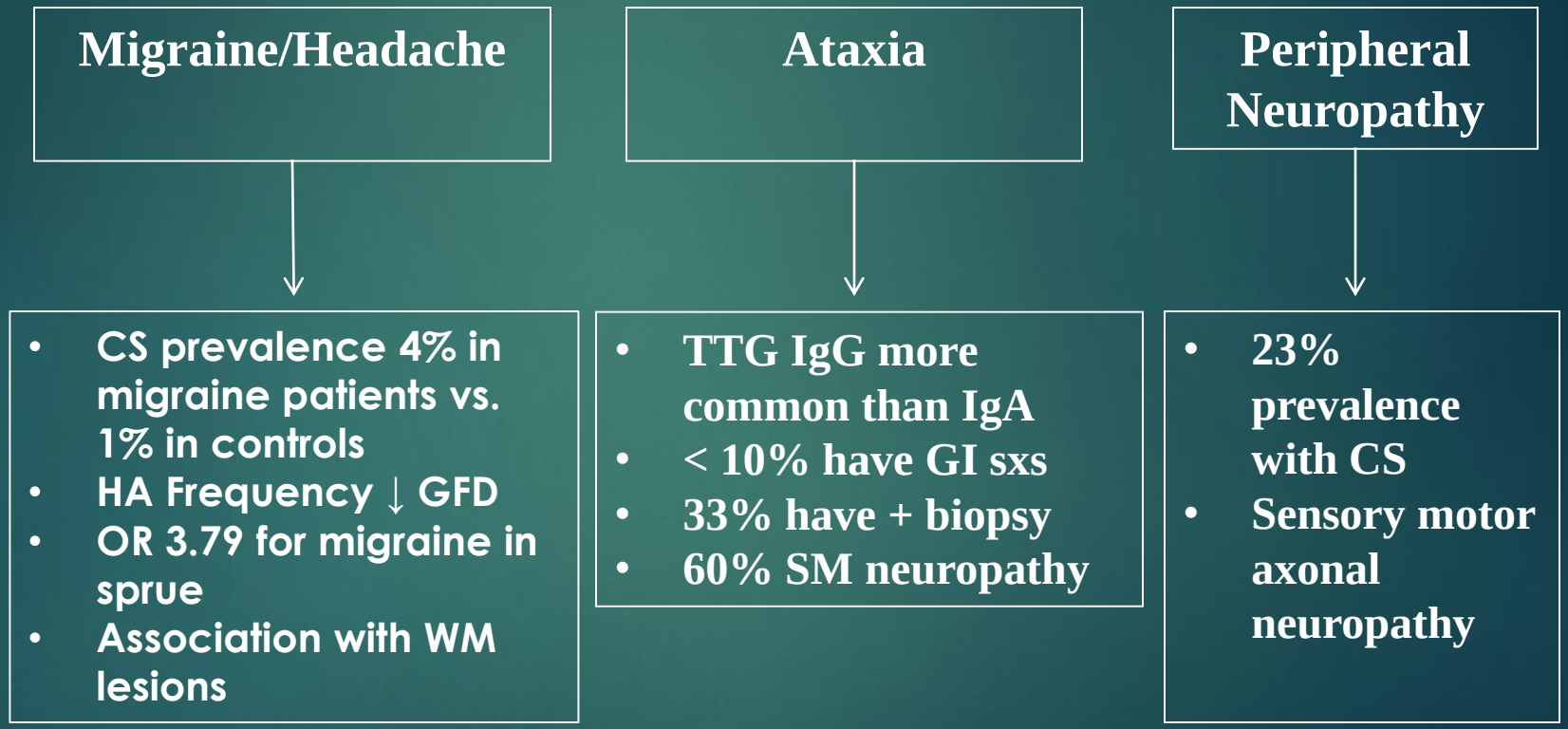
Neurological Manifestations



Hadjivassiliou M. Lancet Neurol 2010; 9: 318-330; Dimitrova A. Headache 2013; 53: 344-35
Gabrieli M. Am J Gastroenterol 2003; 98: 625-29

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Diet and Migraine

COMPREHENSIVE DIETS

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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)

Bunner AE, Agarwal U, Gonzales JF, Valente F, Barnard ND. Nutrition intervention for migraine: A randomized crossover trial. *J Headache Pain*. 2014;Oct 23;15:69.

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

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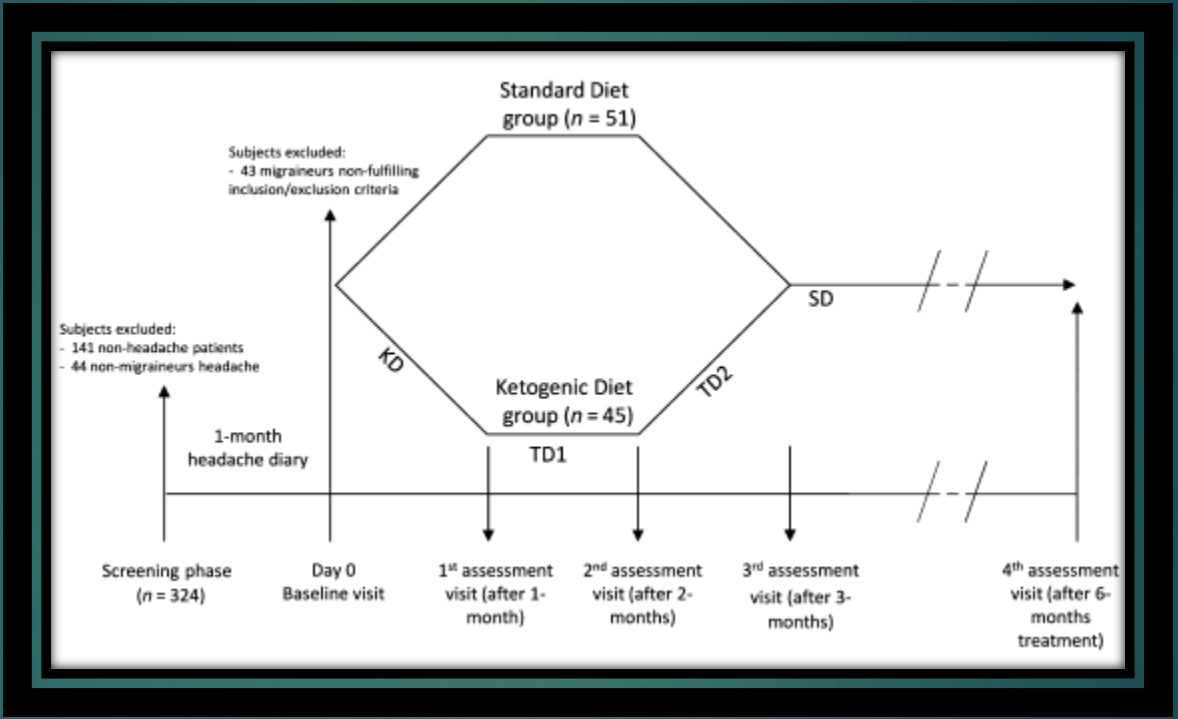
Ketogenic Diet



DiLorenzo C. Eur J Neurol 2015; 22: 170-7

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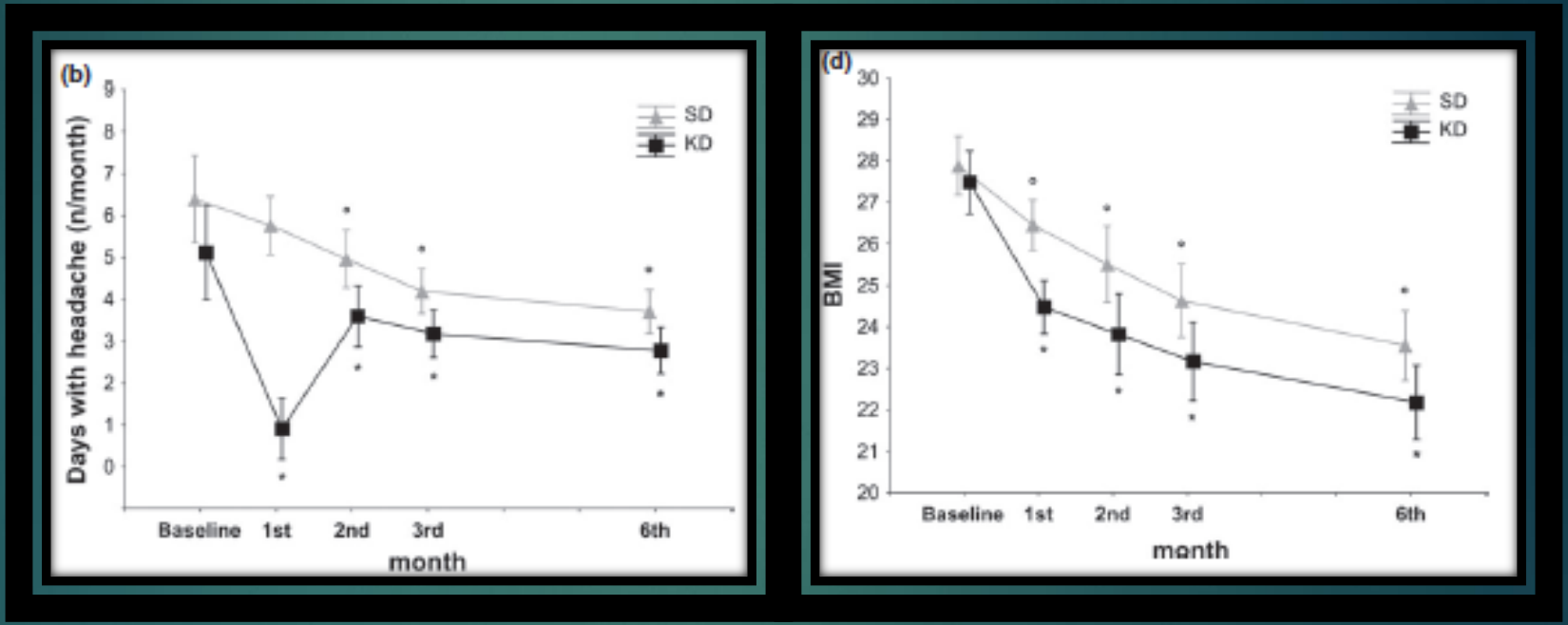
Ketogenic Diet



DiLorenzo C. Eur J Neurol 2015; 22: 170-7

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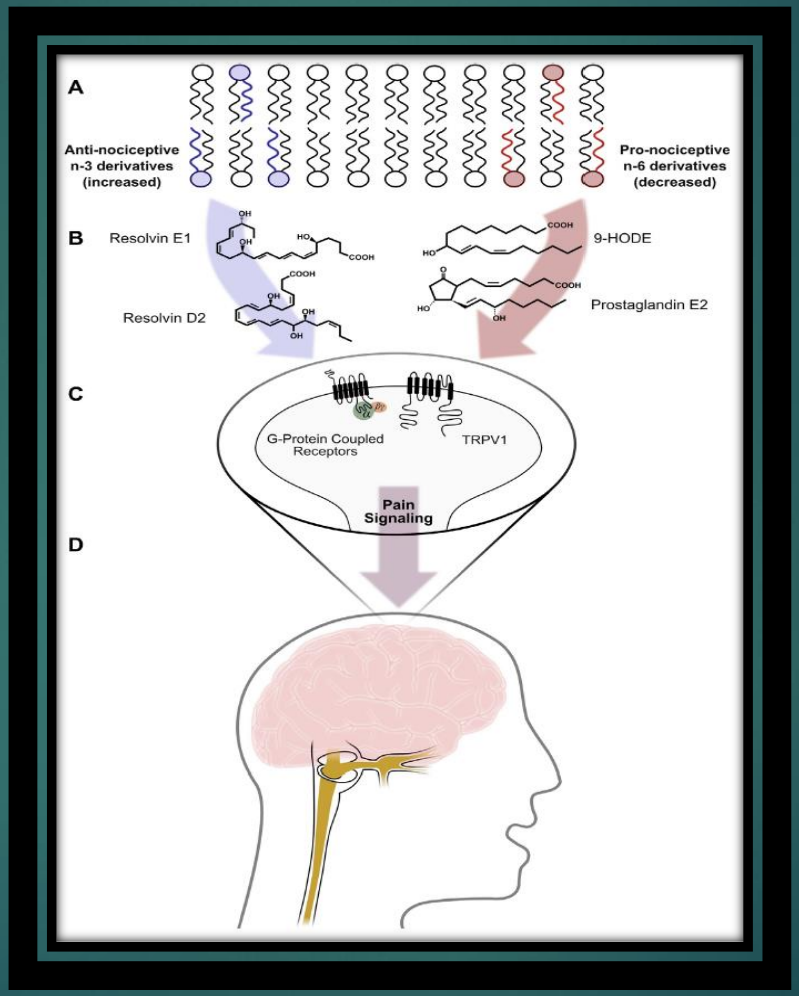
Dietary N-3 & N-6 Fatty Acids



Ramsden C. Pain 2013; 154: 2441-51

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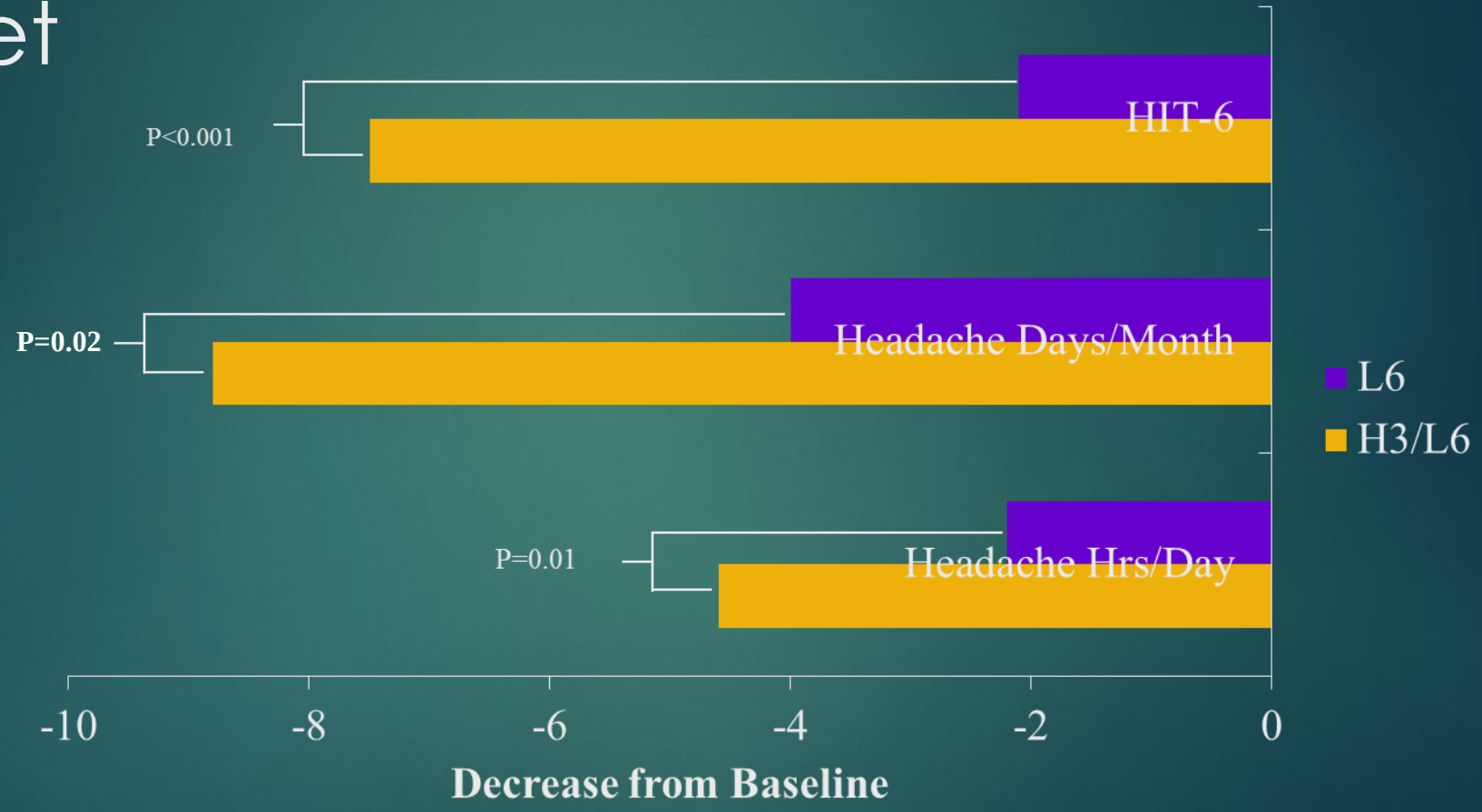
High Omega 3/Low Omega 6 (H3/L6) vs. Low Omega 6 (L6) Diet



Ramsden C. Pain 2013; 154: 2441-51

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Probiotic Therapy?

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

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Boswellia Serrata

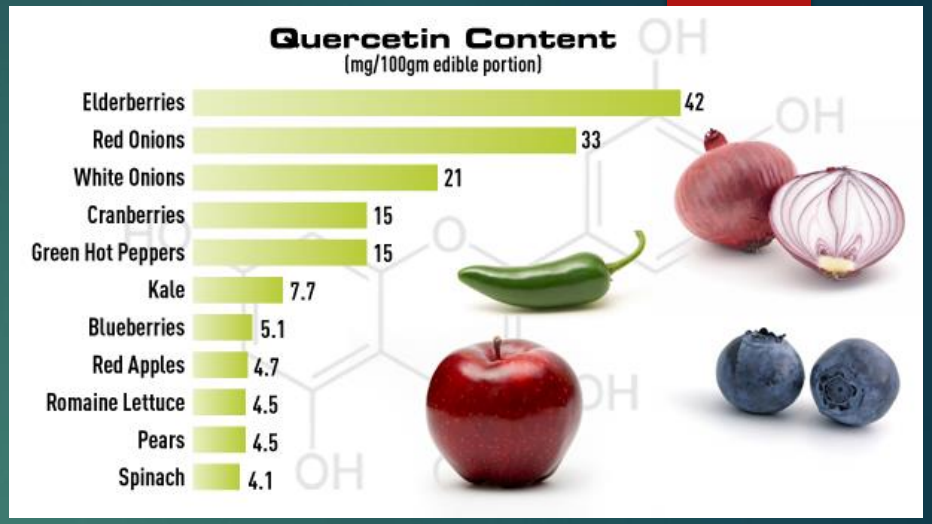
- Ayervedic treatment
- ↓Prostaglandin synthesis
  - Lipoxygenase (LOX) inhibitor
- Similar to indomethacin

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

Gliacin for the Prophylactic Treatment of Migraine: Review of an initial case series. Eross EJ. Headache 2014. 54(8)1418-34.

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?

Kempuraj D, Castellani ML, Petrarca C, et al. Inhibitory effect of quercetin on tryptase and interleukin-6 release, and histidine decarboxylase mRNA transcription by human mast cell-1 cell line. Clin Exp Med. 2006 Dec;6(4):150-6.

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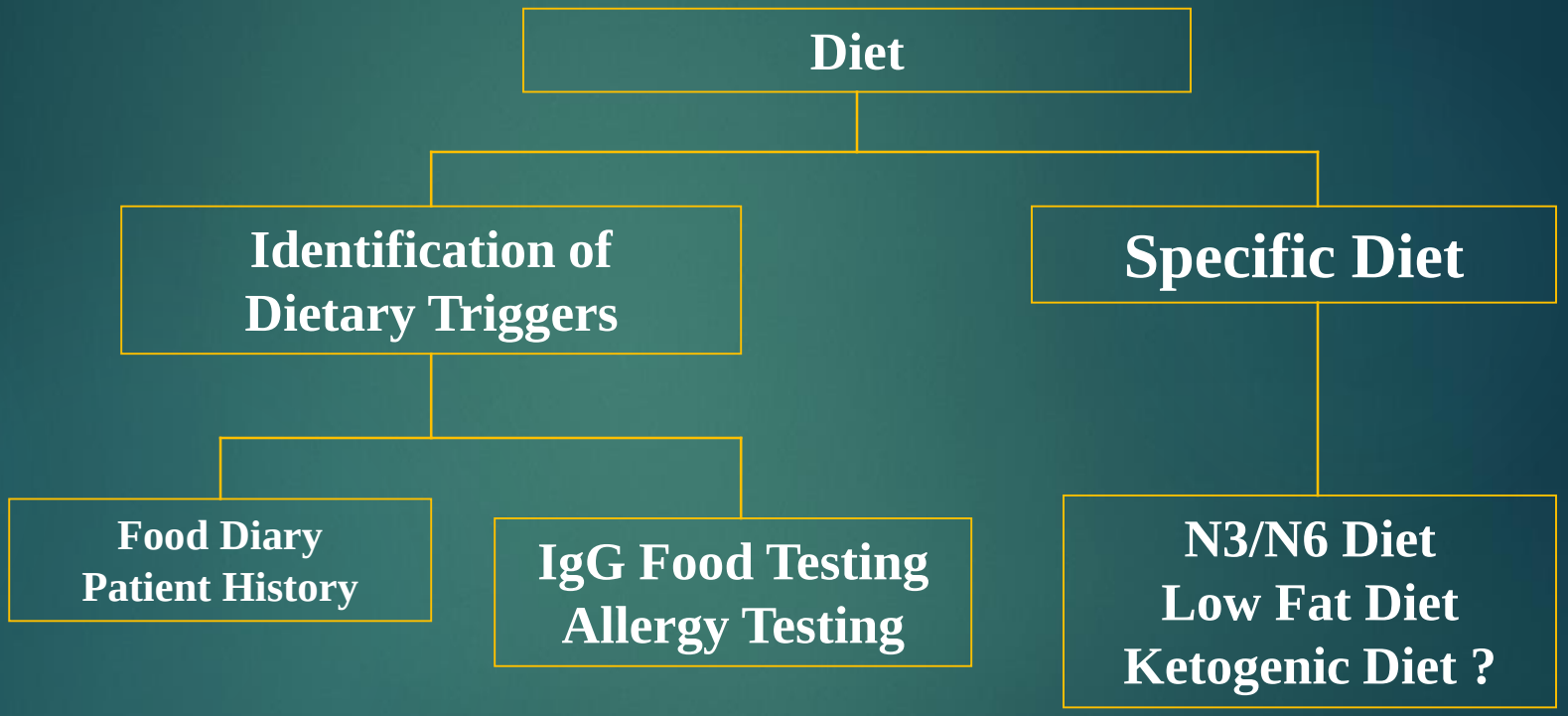
Approach to Dietary Management



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Case 1: Followup

- Underwent IgG food Testing
  - High IgG levels to dairy & egg.
  - Advised to follow dairy / egg elimination
  - Placed on certirizine 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

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