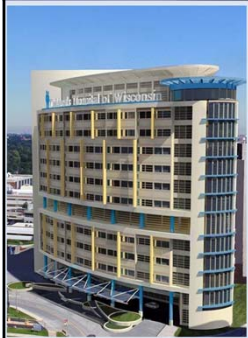


THE AUTONOMIC NERVOUS SYSTEM: A MISSING LINK IN FGID?



Gisela Chelimsky, MD
Professor of Pediatrics
Medical College of
Wisconsin



Disclosures

- ❑ No financial disclosure
- ❑ Many medications discussed are used "off label"

Objectives

- ❑ Understand the relationship of POTS to FGIDs
- ❑ List the comorbidities of FGID
- ❑ Describe the central mechanisms of autonomic and pain modulation
- ❑ Relate pain modulation to autonomic function

Clinical history

- ❑ 17 yr female with a history of H1N1 flu 3 years prior to first visit
- ❑ Hx multiple skin infections that required Atb

Gastrointestinal symptoms

- ❑ Eats and vomits within 5 minutes of eating
 - continue for about an hour until she has emptied her stomach
 - small amounts, bigger than a mouthful
 - not forceful
- ❑ Nausea and epigastric pain
- ❑ Bloating and increased flatus
- ❑ Bowel movements
 - Every 1-2 days to every week; pebbles
- ❑ Weight loss of 15 pounds over past 3 months
- ❑ Upper endoscopy : normal biopsies.

Functional gastrointestinal disorders (FGID)

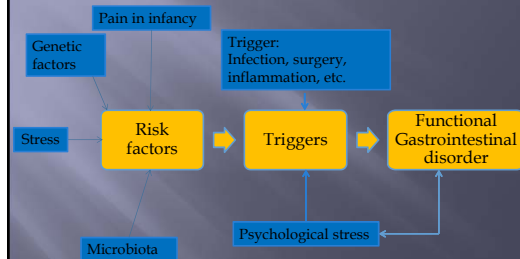
- ❑ Exact prevalence is unknown
- ❑ 6% of middle school students and 15% of high school students fulfilled criteria for IBS (Hyams JS, JPGN 2000)
- ❑ Prevalence of recurrent abdominal pain in childhood: 10-20% (Apley J, Arch Dis Child 1958) (Boey C, J Paediatr Child Health 2000)
- ❑ IBS affects 20% of adults (Gwee KA et al. J Gastroenterol Hepatol 2010)

Functional gastrointestinal disorders (FGID)

- In adults costs of IBS: \$19.2 billion annual indirect costs (e.g. work absenteeism, reduced productivity) and \$1.6 billion direct medical cost

(Mach, T Med Sci Monit, 2004)

Development of FGID

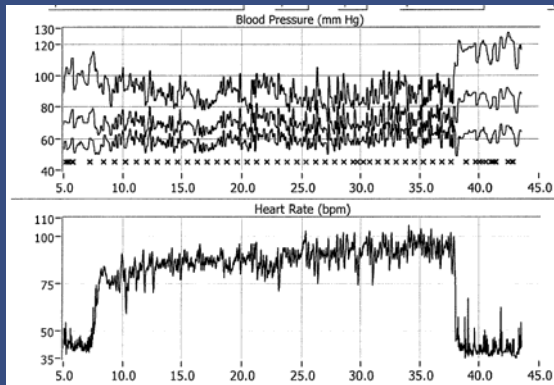


Modified from ROME III, The Functional Gastrointestinal Disorders, 3rd Ed, Drossman, D Editor, 2006

Review of systems

Orthostatic hx

- Fainted episodes: 4 in lifetime
- Always standing – never supine
- Tunnel vision
- Dizzy entire life when standing up, worse past 4-5 months



What is POTS

Sustained HR increase > 40 bpm during upright portion of the tilt without decrease in BP and with associated orthostatic symptoms



Singer W. *The Journal of Pediatrics*. 2012;160(2):222-226

Autonomic Abnormalities in Children with Functional Abdominal Pain: Coincidence or Etiology?

- First case series in pediatrics n = 8
 - 10 to 17 years with 6 females
- **Most of the children with FAP had Postural Tachycardia Syndrome (POTS)**
- Many also had an associated autonomic neuropathy

Chelimsky, G et al. JPGN 2001

Association between FGID and orthostasis

- 24 pediatric patients with FGID
- **Only tilt**
- Presenting symptoms:
 - Abdominal pain 71%
 - Nausea 56%
 - Vomiting 50%
- Results:
 - POTS 4
 - POTS + syncope 8
 - Syncope 12

Sullivan, S et al. JPGN 2005

Association between FGID and orthostasis

- Patients were treated for orthostatic intolerance
- Follow up 18/24
- Resolution of symptoms with fludrocortisone: 4
- Improvement in symptoms:
 - Fludrocortisone: 4
 - Fludrocortisone + sertraline: 4
 - Midodrine: 1

Sullivan, S et al. JPGN 2005

Nausea and Fludrocortisone

- Study of children with nausea and orthostatic intolerance
- Mean age: 14.8 +/-2.8 yrs
- Results of tilt at 45 min:
 - POTS alone = 5
 - Syncope alone =1
 - POTS followed by syncope = 9
 - OH followed by syncope =1
- Symptoms during tilt:
 - Orthostatic symptoms = 14/16
 - **Nausea = 11/16**

Fortunato, JPGN 2014

Results

- Tx fludrocortisone 0.1-0.2 mg for > 4 weeks
- **Significant improvement: Nausea, dizziness, abdominal pain, flushing, and missing school**
- No significant improvement: vomiting, syncope, constipation, and anorexia

Fortunato, JPGN 2014

Review of systems

Headaches

- Daily
- Last from 30 minutes to 5 hours
- Photophobia and phonophobia
- Nausea and vomiting with headaches
- No fainting with headache

Sleep

- ▣ Takes her 2-3 hours to fall asleep
- ▣ Never refreshed even when she can sleep longer
- ▣ Wakes up 2 times per night

Other symptoms

- ▣ Always fatigued
- ▣ Aches and pains in the neck, in the back, in the arms
- ▣ Double jointed
- ▣ No history of depression, anxiety, or traumatic experience

Why so many comorbidities?

FGID's *NOT* limited to GI tract

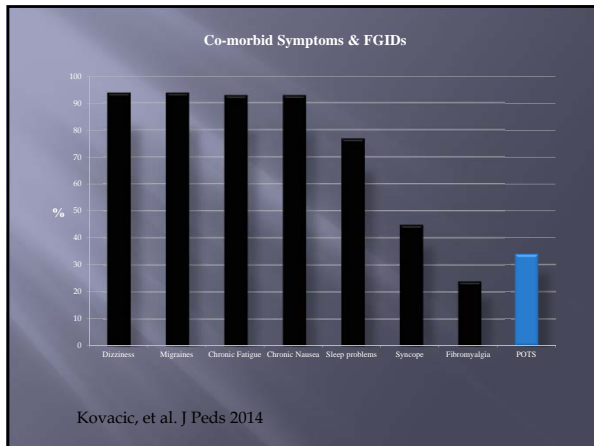
- ▣ 91% of subjects with IBS will have at least 1 comorbidity
- ▣ Patient with IBS report an average of 5 comorbidities
 - 1 psychiatric
 - 4 physical
- ▣ **The medical cost of IBS is mainly secondary to the comorbidities**

Lackner et al. Clinical Gastroenterology and Hepatology 2013;11:1147-1157
Johansson et al. BMC Gastroenterology 2010, 10:31

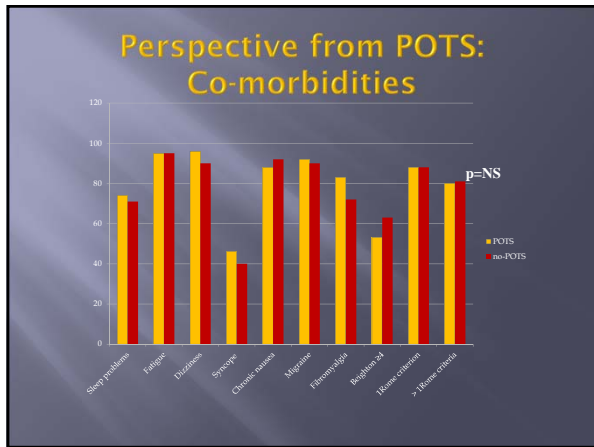
Comorbidities of IBS

- ▣ 16% of IBS subjects have more physical comorbidities than healthy controls
- ▣ Most common comorbidities:
 - **Interstitial cystitis**
 - **Pelvic pain/vulvodynea**
 - **Chronic fatigue**
 - **Dysmenorrhea**
 - **TMJ**

Whitehead et al. Am J Gastroenterol 2007;102:2767-2776

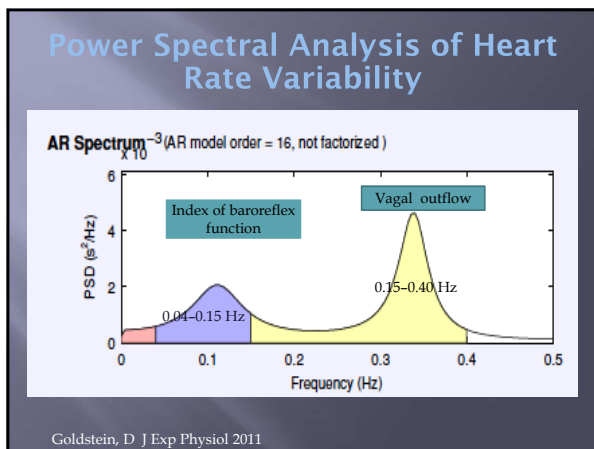


Is all due to POTS?
Is all
“dysautonomia?”



Autonomic function and FGID

- POTS is just one more comorbid problem in FGID
- Perhaps we need a different measurement of autonomic function: HRV?



Vagal tone in adult IBS

- 11 articles , 392 IBS subjects; 263 controls
- HRV during awake and restful state
- IBS
 - Lower HF HRV (Hedges's $g = -0.38$, 95% CI -0.68 to -0.09) than controls ($I^2 = 63.6\%$, $P = 0.003$) = **LESS VAGAL TONE**
 - 7 studies (156 IBS; 152 controls) reported LF/HF, -> increased LF/HF in IBS patients (Hedges's $g = 0.43$, 95% CI $0.13-0.74$) = **MORE SYMPATHETIC TONE**
 - 6 studies reported LF values . No significant difference between IBS and controls (Hedges's $g = 0.19$, 95% CI -0.43 to 0.81)

Liu, Q Journal of Digestive Diseases 2013; 14; 638-646

HRV in IBS: conclusions

- Lower vagal tone (lower HF-HRV)
- Higher sympathetic tone (higher LF/HF ratio)
- Probably the higher sympathetic tone is only due to decrease HF-HRV = ↓vagal tone

Liu, Q *Journal of Digestive Diseases* 2013; 14: 638-646

HRV in pediatric pain disorders

- 104 healthy control children; 48 children with chronic pain ages 8-17 years
- Pain diagnosis:
 - Headaches 58.3%
 - Functional neurovisceral pain disorder (functional bowel, uterine, or bladder disorder) 47.9%
 - Complex regional pain syndrome 8.3%
 - Myofascial pain 35.4%
 - Fibromyalgia 22.9%
 - Joint pain 6.3%
- Multiple pain diagnoses were present in 58.3% of the sample

Evans, S et al. *J Pain Research* 2013

Study design and results

- HRV measured for 5 minutes before and after a painful stimulus

	Control group	Pain group
HF pre-task	59.58 (5.7)	51.59 (17.8)
HF post-task	51.03 (17.9)	52.39 (18.2)
LF/HF pre-task	0.847 (0.57)	1.262 (0.88)
LF/HF post-task	1.379 (1.05)	1.272 (0.91)

Evans, S et al. *J Pain Research* 2013

Conclusions

- Healthy controls have higher vagal tone at baseline
- Pain group has lower vagal tone with higher sympathetic tone at baseline
- In healthy controls, there is an increase in sympathetic tone in response to pain
- The increase in sympathetic tone is not seen in the chronic pain group

Evans, S et al. *J Pain Research* 2013

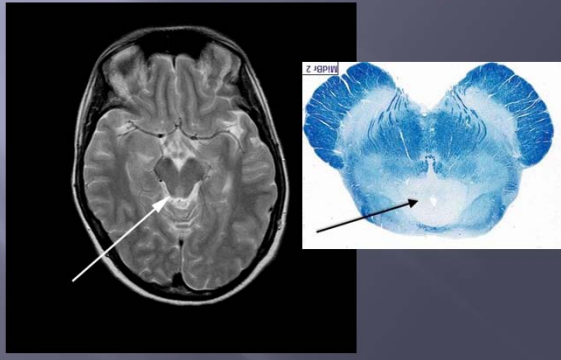
Other studies

- Jarrett et al. (*J Pain* 2012): FAP group 70 girls, 30 boys and HC 44 girls, 18 boys, ages 7-10 yrs
 - No difference in HF HRV or LF/HF ratio
- Sowder, E et al. (*Appl Psychophysiol Biofeedback* 2010). 20 FAP; 10 controls; ages 5-17
 - Significant different in LH/FH ratio

Low vagal tone and chronic pain

- Fibromyalgia (Chalaye P. *Clin J Pain* 2012) (Meeus M. *Semin Arthritis Rheum* 2013)
- Chronic neck and shoulder pain (Shiro, Y. *BMC Musculoskeletal Disord* 2012)
- Chronic back pain (Gockel M. *J Rehabil Med* 2008)

Periaqueductal Gray



PAG: Pain and HRV

- Stimulation of the dorsal PAG did not change HRV
- Stimulation of **ventral PAG**:
 - Did not affect LF HRV
 - **Significant improvement of the HF HRV and therefore ↓ of the LF/HF ratio**
- Stimulation of ventral PAG **reduced the visual analog pain score** from 7.5/10 to 4.3/10 - an 84% reduction in pain ($p < 0.01$)
- Both HF power changes ($p = 0.02$) and LF/HF power ratio ($p = 0.01$) correlated with pain reduction. LF power changes did not

Pereira, Experimental Neurology 2010

Pain Modulation Networks

- Diffuse noxious inhibitory control (DNIC) part of conditioned pain modulation (CPM)
- Counter-irritation phenomenon
- Occurs when pain perception from one nociceptive stimulus is substantially inhibited by a second nociceptive stimulus administered somewhere else in the body
- **Barrier to prevent the spread of pain by providing a tonic inhibitory influence**

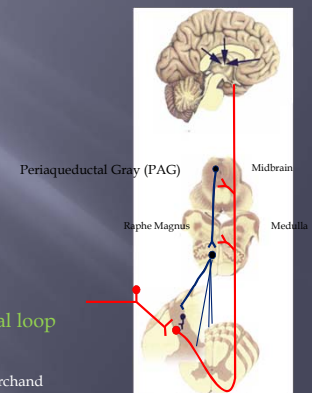
Inhibitory Mechanisms

Descending System

Diffuse
Noxious

Inhibitory
Control

spinal-supraspinal-spinal loop



Picture: Courtesy of Dr. Serge Marchand

Pain modulation and IBS

- Mixed data:
 - **Abnormal CPM**
 - Heyman, S et al. Clin J Pain 2010; Piché, et al. PAIN 2010
 - **Decreased CPM, but not significantly**
 - Jarrett, ME Biol Res Nurs.2014
 - A subgroup has significant abnormalities
 - Chalaye, P Clin J Pain 2012

Conclusions

- **FGID are associated with POTS, but POTS is only one more comorbid disorder**
- POTS may be the cause of dyspepsia symptoms if they develop in the upright position
- **Adults with IBS may have lower vagal tone**
- The role of vagal tone in pediatric FGID still not clear
- **At least some adults with IBS have decreased CPM**
- Perhaps the PAG may play a role in the pathogenesis of a subgroup of FGID

