THE AUTONOMIC NERVOUS SYSTEM: A MISSING LINK IN FGID?

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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)
- 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
  

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**Development of FGID**

- Pain in infancy
- Genetic factors
- Stress
- Triggers
- Functional Gastrointestinal disorder
- Psychological stress
- Microbiota

Modified from ROME III, The Functional Gastrointestinal Disorders, 3rd Ed, Raven, 2006

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**Orthostatic hx**

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

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

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
- Presenting symptoms:
  - Abdominal pain 71%
  - Nausea 56%
  - Vomiting 50%
- Results:
  - POTS
  - POTS + syncope
  - Syncope

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 + sertaline: 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

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
  - FM

Lackner et al. Clinical Gastroenterology and Hepatology 2013;11:1147–1157
Johansson et al. BMC Gastroenterology 2010, 10:31
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 (I² = 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 = \( \downarrow \) 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, bladder, or bladder disorder) 42.9%
  - 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

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>Pain group</th>
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</thead>
<tbody>
<tr>
<td>HF pre-task</td>
<td>59.58 (5.7)</td>
<td>51.59 (17.8)</td>
</tr>
<tr>
<td>HF post-task</td>
<td>51.03 (17.9)</td>
<td>52.59 (18.2)</td>
</tr>
<tr>
<td>LF/HF pre-task</td>
<td>0.847 (0.57)</td>
<td>1.262 (0.88)</td>
</tr>
<tr>
<td>LF/HF post-task</td>
<td>1.379 (1.05)</td>
<td>1.272 (0.91)</td>
</tr>
</tbody>
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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)
Pereira, Experimental Neurology 2010

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

PAG: Pain and HRV

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

Diffuse noxious inhibitory control (DNIC) part of conditioned pain modulation (CPM)
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Barrier to prevent the spread of pain by providing a tonic inhibitory influence

Pain modulation and IBS
- Mixed data:
  - Abnormal CPM
  - Decreased CMP, but not significantly
      - 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 pediatrics 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
THANK YOU!!!