Postural Orthostatic Tachycardia and Mast Cell Activation Syndromes

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www.gidoctor.net
Disclosures

• Speakers bureau: Salix, Allergan, Romark

Syndromes don’t get no respect
POTS and MCAS
Systemic - not Somatic
Dx after 16 yrs

19 MD’s

25 Years a Slave ... of Autoantibodies
Age 18 – Flushing and rash in response to food & odors
Age 20 - Bloating, constipation, rotten egg flatus
Age 23 - Gen. weakness and painful depend. edema
Ages 23-43 - Orthostatic lightheadedness & tachycardia, syncope, body pain, no sweating
   
   Ages 34-36 - Dx hypothyroid, thrombocytopenia

Ages 37-43 - Disabled: orthostatic Sx, fatigue, brain fog, body pain, vertigo, tinnitus, dry mouth, HA, altered visual acuity, hand and leg edema, cyanosis, urination 7/night, pressure-induced angioedema - no sleep or rest
Early satiety – liquid diet
Straining - syncope with efforts >3 min

Dx by Mayo – failed 12 meds/diet/stockings...
Naltrexone, IVIg, and Rifaximin

Week Number and Treatment Timeline

1mg LDN

2mg LDN

3mg LDN

4.5mg LDN
Novel Rx for POTS and MCAS

Novel Rx for POTS and MCAS

- Low dose naltrexone
  - Rebound increase in endorphins
  - Reduce T and B cell activity
  - Reduce cytokines
- Block Toll receptor on microglia
- IVIg
  - Bind Fc portion of antibodies
- Rifaximin
  - Antibiotic treatment of SIBO

Common Symptoms – Thinking Inside the GI Box

Symptoms
- GERD
- Dysphagia
- Nausea
- Abdominal pain
- Anal outlet disorder

Comorbidities
- Fatigue

Diagnosis to explain all?
My Own Blindness

- 55 y.o. WF with 20 yrs gastroparesis and severe migraines; ROS: light-headed & weak

- W/U and Rx – abnl GES - temp. G-tube
  Seen by many GI’s and Neurologists
  Failed all medications

- POTS w/u: + tilt table; insurance denied IVIg

- 1 mo Prednisone
  – no sx for 1st time in 20 yrs
  (LDN started)
My Own Blindness

- 34 y.o. WF w 17 yrs epi pain, GERD, diarrhea, SIBO; >250 ER visits; referred to 4 universities

- W/U and Rx – every GI test known
  CCK and 9 sphincterotomies
  Every Rx for gastroparesis

- POTS w/u: + tilt table

- Monthly IVIg
  – no Sx for 1 yr (LDN issue owing to pain meds for migraines)
• Prevalence 1 – 3 million
• Tilt table test – primary diagnostic test
  – Postural increase 30 bpm w/i 10 min
• Autonomic dysfunction
• Incr. risk suicide: 624 pt vs. 139 cntrls (p<0.001)
POTS – sympathetic overdrive

Sympathetic System

- Dilates pupils
- Inhibits salivation
- Relaxes bronchi
- Accelerates heartbeat
- Inhibits peristalsis and secretion
- Stimulates glucose production and release
- Secretion of adrenaline and noradrenaline
- Inhibits bladder contraction
POTS: Sympathetic Dysfx

- CV sympathetic system affected by autoantibodies or neurologic imbalance that trigger sympathetic receptors and result in severe postural tachycardia
- Many GI Sx – mimics GI disorders and syndromes

Deb 2015, Li 2014, Vernino 2016
Active Cardiac POTS Auto-antibodies

Muscarinic acetylcholine autoantibodies

Alpha-1, beta-1 and -2 adrenergic and acetylcholine autoantibodies

Li et al. J Am Heart Assoc. 2014
POTS: Systemic disease

- Esophagus – GERD, dysphagia
- Stomach – gastroparesis, rapid gastric emptying
- Small intestine dysmotility (SIBO – 1st case series)
- CNS – headaches, migraines, brain fog, anxiety, depression
- Urinary tract - inability to empty the bladder
- Ocular – inability to accommodate
- Salivary glands – dry mouth (also can be d/t Sjogren’s syndrome)
- Skin – flushing, rashes, swelling
- Extremities – pain, swelling, vasospasm

Benaroch 2012
Weinstock 2017
POTS Sx (50% percentile)

- Postural lightheadedness
- Palpitations
- Syncope
- Headache
- Blurry visions
- Memory problems
POTS: Causes and Triggers

- Ehlers-Danlos syndrome after Pregnancy
- Traumatic brain injury
- Electrical injury
- Lyme disease
- HPV vaccine (Gardasil)
- MALS – median arcuate ligament syndrome

Kanjwal -09,10,11, Blitshteyn 2014, Brinth 2015
### POTS & GI Symptoms - Mayo

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>39%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9%</td>
</tr>
<tr>
<td>Abd. discomfort</td>
<td>15%</td>
</tr>
<tr>
<td>Bloating</td>
<td>24%</td>
</tr>
<tr>
<td>Constipation</td>
<td>15%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
</tr>
</tbody>
</table>

N = 163 patients, 87% female

Loavenbruck et al. Neurogastroenterol Motil. 2015
POTS & GI Symptoms - Stanford

• Esophageal - 67% dysmotility
• Gastric emptying study - 60% delayed
• GD manometry
  – 93% signs of neuropathy
  – Bursts of uncoordinated phasic activity:
    59% fasting and 42% postprandial
  – 67% low contractility in postprandial state
• SB imaging – 7/12 abnormal loops and A/F levels

POTS Associated Conditions

- MCAS (frequent)
- Ehlers-Danlos syndrome
- Chronic fatigue syndrome
- Fibromyalgia
- Diabetes mellitus
- Lupus
- Chiari malformation
- Multiple sclerosis
- Celiac disease
- Mitochondrial diseases
- Amyloidosis
- Sarcoidosis

www.dysautonomiainternational.org
Ehlers-Danlos Syndrome

**Point each for:**
- Palms to floor - 1
- Thumbs to wrist - 2
- Pinky back 90° - 2
- Elbows hyperextend - 2
- Knees hyperextend - 2

*Positive if ≥ 4*
Ehlers-Danlos Syndrome

N=39 POTS w 7 EDS (18%) N=70 pts w autonomic diseases w/o POTS w 3 EDS (4%) (p=0.0329) OR 4.9

N=35 EDS pts at tilt, 48.6% pts showed orthostatic tachycardia, 31.4% orthostatic intolerance

Wallman 2014. Castori. 2017
MCAS: Mast Cell Activation Syndrome

- Reported in 2010
- KIT mutation
- MC in GI, skin, bone marrow
- Multiple triggers

Involves skin, GI, CV, GU, resp, and neuro systems
MCAS – Mast Cell Activation

• Prevalence 1% – 17% population
• Increase in number of clonal MC C-Kit (CD117) mutation – multiple types of KIT mutations
  – Bone marrow, intestine, skin, etc.
• Array of typical symptoms
• Additional testing
  – Serum typtase - limited value
    • Only good during attack
    • Only if trypsase is the key mediator
  – 24 urine tests – hist., PG, nor-epi
    • Only good if each is key mediator
    • Expensive, poor insurance coverage

Afrin 2015.
MCAS: Causes and Pathophysiology

- Abnormal microbiome
- T-cell interactions
- 200 mediators (www.Cells-Talk.com):
  - Histamine
  - Heparin
  - Typtase
  - Proinflammatory cytokines
  - Proteases
  - Vascular permeability/dilators
  - Leukotrienes
  - Platelet aggregation factor ...
MCAS Sx (50% percentile)

- Fatigue
- Muscle pain
- Pre-syncope/syncope
- Headaches
- Itching/urticaria
- Nausea
- Chills
- Edema
- Eye irritation
- Dyspnea
- Heartburn
MCAS: Systemic disease

- Esophagus – GERD, dysphagia
- Stomach – gastroparesis, rapid gastric emptying
- Colon – diarrhea, constipation
- CNS – headaches, migraines, brain fog, panic attacks, anxiety, depression
- CVS - tachycardia
- Urinary tract – pain and frequency (IC)
- Ocular – conjunctivitis
- Salivary glands – swelling
- Skin – flushing, rashes, swelling
- Extremities – pain, swelling, vasospasm
- Constitutional – fatigue, fever, wt. loss/gain
MCAS Sx – 17 overlap w POTS Sx

- Fatigue
- Insomnia
- Flushing
- Poor healing
- Sinusitis
- Tachycardia
- Syncope
- Weight gain or loss
- Dental deterioration
- Cough
- Panic attacks
- Anxiety
- Multiple drug reactions
- Chemical sensitivity
- Depression
- Tremor
- Heat
MCAS Sx (continued)

- Muscle pain
- Lightheaded
- Headaches
- Itching
- Numbness or tingling
- Nausea and/or vomiting
- Chills
- Edema in different places
- Eye irritation
- Shortness of breath
- Easy bruising /bleeding

- Brain fog
- Rashes
- Throat irritation
- Fast or irregular heartbeats
- Environmental allergies
- Fever
- Chest pain
- Acid reflux
- Difficulty swallowing
- Abdominal pain
- Diarrhea
- Constipation
Basic POTS and MCAS Therapy

**POTS cardiac Rx** - acetylcholinesterase inhib., alpha-1-adrenoreceptor agonism, angiotensin II type 1 receptor blockade, beta-adrenoreceptor antagonism, antidiuretic hormone, erythropoietin, f-channel inhibition, growth hormone release inhibiting factor, methylphenidate, mineralocorticoids, octreotide, SSRI antidepressants, Vit C. Exercise, high-sodium diet, rapid fluid intake, IV hydration, and support stockings

**POTS GI Rx** – recent reports of immune Rx

**MCAS** – Cromolyn, H1/H2 blockers, montelukast, Vit C, etc.

POTS - Immune and SIBO Rx

- IVIg
- IVIg with immunomodulators
- Plasmapheresis combined with prednisone and immunomodulators
- IVIg with Mycophenolate (50 cases)
- Low dose naltrexone
- Antibiotic Rx for SIBO


Weinstock, Brook, Myers, Goodman. manuscript submitted
Immunotherapy for Autoimmune GI Dysmotility

- N=23 w GI dysmotility by testing (6 hr nuclear scintigraphy, G-D manometry and Indium CL3 colon transit). Autonomic testing: abnl in 88%.
- Serologic evidence (16) or personal/FHx autoimmune
- 13 AB tested incl. nicotinic Ach, VGKC, GAD65
- 3 had pos ANNA-1 and Cancer was found
- Slow transit – gastric 11, SB 12, colon 11

Flanagan et al. Neurogastroenterol Motil. 2014
Immunotherapy for Autoimmune GI Dysmotility

- Rx 6 – 12 wks: IVIG 0.4 gm/kg (16), Methylprednisolone 1000 mg/d/3 then weekly (5) or both (2)

- 74% improved Sx and testing, 21% Sx only, and 17% testing only

Flanagan et al. Neurogastroenterol Motil. 2014
11 responders continued therapy long-term

- IVIg 7
- Mycophenolate 4
- Azathioprine 4
- Prednisone 2
- Cyclophosphamide 1
POTS & SIBO

N = 27 (26F, 27% MCAS, 42% EDS)
Sx – Pain 96%, Bloat 92%, Nausea 85%, Constipation 73%, Diarrhea 58%, GERD 58%
Abnormal LBT in 19/27 (69%)

Antibiotic Rx
  helped GI Sx in 10/15
  helped POTS Sx in 4/15

Low dose naltrexone
  helped GI Sx in 7/11
  helped other POTS/MCAS in 5/11 –
    1 POTS, 2 both, 2 MCAS
Summary

• POTS and MCAS – complex disorders – think about it w/ multiple, refractory symptoms

• GI motility system
  – Highly complex interactions
  – Multiple neurohormonal components

• Potential uses for LDN, IVIg, immunomodulators, and antibiotics
  – Augmenting endorphins for motility
  – Reducing neuro-inflammatory receptors
  – Reduce autoantibodies and T-cell/MC activity
  – Decrease SIBO