DYSAUTONOMIA & MAST CELL DISEASE

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The Mast Cell Disease Society Webinar
OVERVIEW

- Dysautonomia overview
- POTS overview
- POTS & MCAS Research
- Potential Mechanisms
- Questions
WHAT IS DYSAUTONOMIA?

- Not a specific diagnosis
- General term for “dysfunction of the autonomic nervous system”
  - structural (damaged/missing nerves)
  - functional (nerves intact, but not working properly)
  - sometimes both
Chronic Migraine
Neurocardiogenic Syncope
Fibromyalgia
Complex Regional Pain Syndrome
POTS/OI
Interstitial Cystitis
Currently idiopathic

Known Pathology

Central
Peripheral
Pure Autonomic Failure
Small Fiber Neuropathies

Multiple System Atrophy
Parkinson’s/Lewy Body Dementias

Metabolic
Inflammatory
Genetic

Diabetes
Immune
Mitochondrial

Dysautonomias

Neurocardiogenic Syncope
Chronic Fatigue Syndrome
Interstitial Cystitis
Chronic Migraine

### Dysautonomia Cheat Sheet
#### Disorders of Orthostatic Tolerance

<table>
<thead>
<tr>
<th>neurogenic orthostatic hypotension</th>
<th>postural orthostatic tachycardia syndrome</th>
<th>orthostatic Intolerance</th>
<th>vasovagal syncope</th>
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<tbody>
<tr>
<td>gradual, sustained ↓sBP≥20 or ↓dBP≥10 w/in first 3 minutes of standing; not due to meds/blood loss/deconditioning/dehydration</td>
<td>sustained ↑HR≥30 w/in first 10 min. upright; no OH; must have symptoms on standing; symptoms lasting ≥3 months; not due to meds/blood loss/deconditioning/dehydration</td>
<td>chronic lightheadedness &amp; other symptoms upon standing due to blood flow problem that does not meet the OH or POTS criteria; not due to meds/blood loss/deconditioning/dehydration</td>
<td>sudden ↓HR, followed by sudden ↓BP; often results in a faint</td>
</tr>
<tr>
<td>patients often don’t report symptoms</td>
<td>patients report many symptoms</td>
<td>patients report many symptoms</td>
<td>some feel it coming, some don’t</td>
</tr>
<tr>
<td>severe autonomic neuropathy (MSA, Parkinson’s, diabetes)</td>
<td>some have mild-moderate autonomic neuropathy</td>
<td>some have mild-moderate autonomic neuropathy</td>
<td>not associated with neuropathy</td>
</tr>
<tr>
<td>rare</td>
<td>common</td>
<td>common</td>
<td>very common</td>
</tr>
</tbody>
</table>

These three conditions are mutually exclusive.

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Can occur alone or with any of the other disorders.

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more severe autonomic impairment

less severe autonomic impairment
RECOGNIZING AUTONOMIC DYSFUNCTION

- Orthostatic intolerance
  - Lightheadedness/fainting
  - Fatigue
  - Exercise Intolerance
  - Shortness of breath
  - Chest pains
  - Coat hanger pain
  - Blood pooling in limbs
  - Brain fog
- GI dysmotility
- Pupil dysfunction
- Bladder dysfunction
- Gallbladder dysfunction
- Dry eyes/mouth
- Other mucosal dryness
- Abnormal sweating
- Temperature sensitivity
- Facial/upper trunk flushing
- Acrocyanotic legs
- Erectile dysfunction in males
Modulates immune function
AUTONOMIC REGULATION OF IMMUNE FUNCTION

- COMPLICATED!

- General concept...

Sympathetic  \[\uparrow\]  Inflammation  \[\uparrow\]

Parasympathetic  \[\uparrow\]  Inflammation  \[\downarrow\]
WHAT IS POTS?

- Chronic autonomic nervous system disorder associated with orthostatic intolerance, but entire ANS impaired
- Most common diagnosis seen in autonomic clinics
- 1-3M Americans
- ~90% female, Caucasian
- Peak age of onset: 14
41% of POTS patients report onset w/in 3 months of a specific event:

- infection (41%)
- surgery (12%)
- pregnancy (9%)
- accident (6%)
- concussion (4%)
POTS: DIAGNOSTIC CRITERIA

- HR increase of ≥30bpm from supine to standing within 10 minutes (≥40bpm for ages 12-19)
- In the absence of orthostatic hypotension (defined as ≥20/10mmHg drop within 3 min. of standing)
- Symptoms of orthostatic intolerance lasting ≥6 months
- Symptoms exacerbated by standing and improved with recumbency
- Absence of other overt causes of orthostatic symptoms or tachycardia
TILT TESTING

POTS

Control

Heart Rate (bpm)

Blood Pressure (mmHg)

Tilt Angle (deg)

SR Raj, Indian Pacing Electrophysiol J. 2006;6:84-99
POTS SIGNS & SYMPTOMS

- Orthostatic tachycardia
- Palpitations
- Shortness of breath
- Lightheadedness/pre-syncope
- GI motility (33% too fast, 33% too slow)
- Nausea
- Sicca (>65%)
- Bladder dysfunction (17%)
- Exercise intolerance
- Sensitivity to heat/cold
- Sensitivity to light/sounds
- Migraines
- Orthostatic headaches
- Profound fatigue
- Weakness (normal EMG)
- Tremulousness
- Dependent acrocyanosis
- Flushing
- Increased allergies & sensitivities
- and more....
PURPLE POTS LEGS

- Acrocyanotic legs after a few minutes of standing
- Prolonged blanching/delayed capillary refill
ORTHOSTATIC PAIN

COAT HANGER PAIN

Suboccipital and paracervical pain that worsens in the upright position is common in orthostatic disorders and is believed to be caused by poor blood flow to the muscles of the upper back and neck.

www.dysautonomiainternational.org
POTS “SUBTYPES” ARE NOT DISTINCT DIAGNOSES

- Neuropathic
- Hypovolemic
- Hyperadrenergic
- Autoimmune

Other terms used:
- low flow
- high flow
- developmental
deconditioning

Not to scale...
SMALL FIBER NEUROPATHY IN POTS

- ~55% with evidence of sudomotor neuropathy

- Sensory small fiber neuropathy too – pain, numbness, burning, sensory overload

- Vasomotor neuropathy in POTS (coming soon!)

- These nerves communicate with mast cells and other immune cells
Quantitative sensory testing (QST) – standardized non-invasive assessment to screen for small fiber neuropathy

QST correlates to reduced IENFD in POTS
- 56% of POTS patients with reduced IENFD
- QST thresholds of nonpainful stimuli and thermal pain were increased
- small fiber impairment in both hands and feet

Billig SCI, Schauermann JC, Rolke R, Katona I, Schulz AB, Maier A. Quantitative sensory testing predicts histological small fiber neuropathy in postural tachycardia syndrome. Neurology: Clinical Practice October 2020 vol. 10 no. 5 428-434
Adrenergic & other GPCR antibodies present in >65% of POTS patients
- Research in progress to determine significance

Case reports/series on POTS and...
- Antiphospholipid syndrome
- Bechet’s
- Multiple sclerosis
- Juvenile RA
- Still’s disease
- Ankylosing spondylitis
- Lupus
- Celiac
- Crohn’s
- Sjogren’s
- Hashimoto’s
- UCTD
POTS patients often feel worse after large meals or carbohydrate rich meals.

ANS plays a key role in maintaining glucose homoeostasis.

\[ \text{SNS} \uparrow \rightarrow \text{insulin} \downarrow \rightarrow \text{blood glucose} \uparrow \]
New Vanderbilt research...

POTS patients vs controls – 75g oral glucose

- POTS patients have:
  - significantly increased standing HR after glucose
  - increased C peptide and insulin compared to controls
  - blood glucose was NOT reduced in most POTS patients, despite increased insulin
  - suggesting insulin resistance

POTS IS NOT A “TEENAGE SYNDROME”

47% developed POTS after age 18

Peak age of onset: 14

N=4723
EVERYONE DOESN’T “GROW OUT OF IT”

Outcomes in Adolescent POTS

- Symptoms completely resolved: 19.2%
- Symptoms persist, severity better: 51.2%
- Remitting and relapsing: 15.7%
- Symptoms persist, severity same: 8.7%
- Symptoms persist, severity worse: 3.5%
- Not reported: 1.7%

N=172

EVERYONE DOESN’T “GROW OUT OF IT”

- 172 Mayo Clinic pediatric POTS patients
- Seen between 2013-2010
- Mean duration from diagnosis to survey: 5.4 years
- Mean age at time of survey: 21.8
- 84% female
- Mean physical component score significantly lower than norm (36.6 vs 50)
- Mean mental composite score normal (50.1 vs 50)
- Males much more likely to improve
- Patients with persistent symptoms had more physical than mental health concerns
POTS: NON-PHARMA TREATMENT

- 10g salt daily (3876mg sodium)
- 2-3L of hydrating fluids daily (avoid sugary drinks)
- Medical compression stockings
- Abdominal binders
- Recumbent exercises
- Good sleep habits
- Healthy diet
- Cooling vests
- Avoid heat, prolonged standing, hot showers, alcohol
- Educating patient on the physiological cause of symptoms can help patient learn to manage symptoms
SALT IS NOT EVIL
- Insurance typically covers with prescription for OH
- 20-30mmHg strength
- Full length stockings work best
- Open-toe is easier to get on, and works with flip-flops
- Fun colors/prints now
- Athletic leggings for males
Avoid orthostatic stress during exercise until patient builds up exercise tolerance, can take MONTHS/YEARS.

- Rowing, recumbent bike, swimming, floor/core
- Start SLOW and LOW
Vasoconstrictors
- Midodrine
- Octreotide
- Droxidopa (Northera)
- Phenylephrine (Sudafed PE)

Blood volume expansion
- Fludrocortisone
- Desmopressin
- EPO
- IV Saline

Beta blockers
- Ivabradine
- Mestinon

Immunotherapy???
If mast cell dysfunction is present:
- H1/H2 blockers
- Cromolyn (Gastrocrom)
- Omalizumab (Xolair)
- Ketotifen
- Quercitin
- Vitamin C

No FDA approved treatment for POTS.
POTS IN MCAS

- CANADIAN STUDY - 30 MCAS PATIENTS
  - 23% HAD POTS
  - 6% HAD MCAS/POTS/EDS

Peter Vadas, Juan Guzman, Laura McGillis, Nimish Mittal, Scott Walsh, Cosegregation of postural orthostatic tachycardia syndrome, hypermobile Ehlers-Danlos syndrome, and mast cell activation syndrome, Annals of Allergy, Asthma & Immunology, Volume 125, Issue 6, 2020, Pages 719-720,
POSSIBLE MECHANISMS OF MCAS IN DYSAUTONOMIA

1) Excessive sympathetic tone sets off mast cells
2) Antibodies found in POTS & OH set off mast cells
3) Genetic risk factors

Many other mechanisms we haven’t studied yet!
First paper on POTS/MCAS

Vanderbilt, 2005

POTS/MCAS patients are hyperadrenergic

MCAS reactions triggered by:
- prolonged standing
- exercise
- premenstrual
- meals
- sex

EXCESSIVE SYMPATHETIC TONE

- First paper on POTS/MCAS
- Vanderbilt, 2005
- POTS/MCAS patients are hyperadrenergic
- MCAS reactions triggered by:
  - prolonged standing
  - exercise
  - premenstrual
  - meals
  - sex

These are all things that increase sympathetic nervous system activity!

Numerous studies documenting G-protein coupled receptor (GPCR) antibodies in a majority of POTS patients:
- alpha-adrenergic
- beta-adrenergic
- muscarinic
- angiotensin
- nociceptive

Same antibodies also reported in OH, hypertension, pre-eclampsia, Chagas, Sjogren’s, CRPS, myocarditis, cardiomyopathy
Autoantibodies against G-Protein-Coupled Receptors Modulate Heart Mast Cells

Ludmila Okruhlicova\textsuperscript{1,2,4}, Rosemarie Morwinski\textsuperscript{2}, Wolfgang Schulze\textsuperscript{2}, Sabine Bartel\textsuperscript{2}, Peter Weismann\textsuperscript{3}, Narcisa Tribulova\textsuperscript{1} and Gerd Wallukat\textsuperscript{2}

- **What antibodies?**
  - alpha\textsubscript{1}-adrenergic receptor antibodies
  - angiotensin II Type 1 antibodies

- **What type of tissue was studied?**
  - rat cardiomyocytes (heart muscle cells)

- **What happened?**
  - the antibodies increased mast cell maturation
  - the antibodies increased mast cell degranulation

SOME RASHES IN POTS RESPOND TO ANGIOTENSIN BLOCKERS

- Rash appears during hyperadrenergic POTS flares
- Author described it as “evanescent hyperemia”
- Hyperemia = too much blood in a tissue
- Evanescent = comes and goes quickly

These antibodies contribute to a more hypertensive/hyperadrenergic state in POTS.

Losartan blocks angiotensin II type 1 receptors.

Case report: the rash resolved and POTS symptoms improved after Losartan.
HEREDITARY ALPHA-TRYPTASEMIA

- Extra copies of the alpha-tryptase gene, TPSAB1
- Impacts 4-6% of the population (not rare)
- All with elevated basal serum tryptase >8ng/mL
  - Due to increase tryptase synthesis, not mast cell activation
- ~2/3 have no symptoms
- ~1/3 have symptoms
  - Skin, gastro, autonomic and/or psychiatric
- Can amplify other mast cell diseases
- Can co-inherit with other genes

Quick Links

dysautonomiainternational.org/exercise
dysautonomiainternational.org/salt
dysautonomiainternational.org/stockings
dysautonomiainternational.org/support
vimeo.com/dysautonomia