THE GRINCH SYNDROME
POSTURAL ORTHOSTATIC TACHYCARDIA (POTS) IN ADOLESCENCE

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"But I think that the most likely reason of all... may have been that his heart was two sizes too small!"

Dr. Seuss: Grinch that Stole Christmas, 1966

CONFLICT OF INTEREST – NONE
DISCLOSURE - NONE
OBJECTIVES

1. Identify the symptoms associated with autonomic dysfunction.
2. List symptoms through case study.
3. Correlate treatment modalities with presenting symptoms.

Case Study #1.
14yr old female presents for WCC with history of:

a. Intermittent headaches – some relief from NSAIDS
b. Nausea on a daily basis, no vomiting
c. Fatigue - difficult to get out of bed in am and naps in afternoon
d. Palpitations - heart races w/ or w/out exertion
e. Severe dizziness with changing position
f. Pre-syncope symptoms
g. Sore throat
h. Weight loss
i. Depressed affect
j. Chest pain
k. Concussion during field hockey

DIFFERENTIAL – (WHAT RABBIT WHOLE 1ª?)

- Neurology
  - Migraine
  - Chronic fatigue
  - Fibromyalgia
- Cyclic vomiting
- Gastrointestinal
  - Crohns
  - IBD
- Viral - Dehydration
- Orthostatic hypotension
- Dysrhythmia
- “Overanxious parents”
VITAL SIGNS:
Orthostatics:
BP: supine- 82/64  HRT Rate: 72 bpm
    sitting- 96/74            92 bpm
    standing- 100/76         100 bpm
    standing 5 minutes 115/76 132 bpm
Hrt Rate: regular, no murmur, quiet pre-cordium
Increases significantly with changing of position.
BMI: 18.4   21%
Wt: 50.8kg  35%
Resp: 20 breaths   lung fields clear

POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME
"Orthostatic intolerance with symptoms of palpitation,
fatigue, lightheadedness, exercise intolerance, nausea,
diminished concentration, syncope or near-syncope
on standing that diminishes with recumbence".
(Grath: Circulation,2008)

"Day to day symptoms of orthostatic intolerance
associated with excessive upright tachycardia but not
hypotension. Heart rate increase of >30bpm (40bpmin
young) or exceeding 120 bpm (adult). Symptoms
concurrent with excessive tachycardia. No symptoms,
no POTS".
(Stewart: Expert Rev Cardiovas. Ther, 2012)
DEMOGRAPHICS
Typically female (1:4) ages 12-40yrs
Mostly Caucasian
Acute or sub acute onset
History of prior infection with virus (mono)
Hyperflexive- long extremities – dancer type bodies.
Diagnosis often delayed by 2yrs or more
500,000 in US alone
Unknown etiology –
?? Autonomic dysfunction
?? Autoimmune Basis (Hongliang et al., JAHA, 2014)
?? Cardiac Origins (Hongliang et al., JAHA, 2014)
Multisystem condition with heterogeneous clinical features

NORMAL ORTHOSTATIC RESPONSE
• Standing decreases venous return to heart (500-800 ml in adult)
• Transient fall in BP after standing up
• Decrease of BP inversely related to initial vascular tone
• Compensatory increase in HR, delay of 10-15 sec before onset of active compensatory sympathetic responses and BP fall= initial orthostatic hypotension.
• Within 30-60sec BP is restored
• Sympathetic arterial tone contributes to resting vasoconstriction that affects BP recover
• once hemodynamic stability is established, blood volume continues to be reduced with ongoing standing.
• Avoid by invoking skeletal muscle pump by moving around.
ORTHOSTATIC INTOLERANCE (OI)

- Inability to remain upright
- Deviation regulation of HR, BP, and cerebral blood flow (CBF)
- Increased sympatho-excitation.
- Typical S&S:
  - LOC, lightheadedness, dizziness, vertigo, pallor, fatigue, tachycardia, bradycardia, hypotension, headache, weakness, abdominal pain, vomiting, palpitations, anxiety, diaphoresis, tremors, exercise intolerance.

**POTS is a common form of orthostatic intolerance**

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SYMPTOMS OF OI & SYMPATHETIC OVERACTIVATION

**Orthostatic Symptoms**
- Dizziness and lightheadedness
- Near syncope
- Blurred vision
- Blackout or “whiteout” vision
- Weakness of legs
- Poor concentration
- Headache
- Nausea

**Sympathetic Overactivation**
- Palpitations
- Chest pain
- Migraine
- Tremulousness
- Anxiety
- Pallor
- Excessive sweating

Jarjour, 2013: Seminar in Pediatric Neurology
**FREQUENT NON-ORTHOSTATIC SYMPTOMS**

- Chronic fatigue 79%
- Nausea 60%
- Sleep disorders 56%
- Sweating disorders 49%
- Migraine 46%
- Cognitive dysfunction 44%
- Abdominal pain 42%
- Chronic daily headaches 30%
- Vomiting 26%
- Weight loss 26%

*Jarjour, 2013: Seminar in Pediatric Neurology*

**DIAGNOSTIC CRITERIA FOR POTS**

No consensus to date on diagnostic criteria

No gold standard diagnostic testing

**A. Chronic Orthostatic Intolerance:**

Chronic, frequent daily or near daily symptoms for > 3 months

**B. Excessive postural tachycardia:**

Excessive and sustained Δ/ or absolute HR within 10 min of standing > 30 bpm

or absolute HR > 120 bpm (13–19 yrs old)

> 35 bpm or > 40 bpm or absolute HR > 130 bpm (6–12 yrs old)

**C. Absence of significant orthostatic hypotension:**

Either no or only modest ΔH (≤ 20mmHg systolic BP change)

**D. Absence of reversible cause, i.e. medication**
CLASSIFICATIONS & CLINICAL FEATURES

Primary Form

Partial dysautonomic
- Most frequent
- Suffer mild form of peripheral autonomic neuropathy
- Inability of peripheral vasculature to maintain adequate vascular resistance in face of gravitational pull
- Greater than normal pooling in dependent areas
- Compensatory increase in HR and contractility to maintain cerebral perfusion.

Partial

- Increase dependent on skeletal muscle pump.
- More upright more venous pooling
- 5:1 female to male ratio
- Symptoms begin after viral illness or trauma
- Felt to be autonomic disorder.

Grubb: Circulation. 2008

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- Suffer mild form of peripheral autonomic neuropathy
- Inability of peripheral vasculature to maintain adequate vascular resistance in face of gravitational pull
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Hyperadrenergic
- Less frequent form
- Gradual and progressive emergence of symptoms
- Significant tremors, anxiety, cold, and sweaty extremities with standing
- >50% migraines
- Orthostatic hypotension + orthostatic tachycardia.

- Significant elevated serum norepinephrine levels (>600ng/mL)
- Strong family history
- ?? Genetic Mutation
- Altered norepinephrine reuptake in synaptic cleft.

Causes: norepinephrine transporter deficiency, pheochromocytoma, mast cell activation disorders and baro-reflex failure, trauma or irradiation to neck

HYPOVOLEMIC AND DECONDITIONED

- Reduced plasma volume
- Venous pooling in legs and micturition bed (below diaphragm) results in modest increase in HR to increase CO.
- May have postural swelling and edema.
- Chronic fatigue & fibromyalgia type symptoms
- Decreased exercise tolerance

- Deconditioning J/t POTS vs Symptoms POTN cause deconditioning.
- Preceding viral illness, trauma, or surgery followed by decrease activity.
- Indirect marker low concentration of urinary NA+ (24HR NA <100mEq).
- Low Fe+ stores- mild anemia
- Hypo-vitamin D.
Secondary Form

- Variety of conditions that produce a state of peripheral autonomic deinnervation or vascular unresponsiveness.
- Relative sparing of cardiac innervation
- Most frequent cause Diabetes Mellitus.
- Also seen with amyloidosis, sarcoidosis, chemotherapy, and heavy metal poisoning.
- Present with pure autonomic failuyre
- Multi-system atrophy
- May be form of paraneoplastic syndrome seen with adenocarcinoma of the lungs, breast, ovary, and pancreas. (not seen in adolescents)

CLINICAL AND DIAGNOSTIC EVALUATION

1. Careful and detailed history
   - Acute or gradual onset
   - Events associated w/ i.e. trauma, surgery, illness
   - Worsens/improves symptoms
   - Family history
   - Nonprescription medication
   - Nutritional & fluid intake.
   - Menstrual history.
   - Psychosocial stressors
   - School history

   Assessment usually normal
   - BP @ immediately, 2, 5, & 10 minutes standing
   - ?? Tilt table test
   - CBC, CMP, serum Ferritin, CRP, BUN, Creat., glucose, 25-hydroxy vita D, TSH & T4, metanephrines, and EKG.
   - Neuroimaging – rare

   No Gold standard testing

TREATMENTS

- Most important is diagnosis and elimination of secondary cause
- Treatment for children based on researched treatment for adults
- Few RTC or non RTC – most case studies
- Must include family dynamics – can they handle challenges in treatment
- Multi-disciplinary approach
- Various methods of treatment:
  non-pharmacological vs pharmacological.
NON-PHARMACOLOGIC TREATMENT

Adequate Hydration (64-80oz Non-caffeinated)
Salt (1-5g/d)
Reconditioning PT
Compression stocking Physical counter maneuvers
Adequate Nutrition Fe+ supplement
Good sleep habits, NO caffeine, Raise HOB decrease dizziness

PHARMACOLOGICAL TREATMENT

α-receptor blockers
ACE inhibitors
β-blockers
Calcium Channel blockers
Diuretics
Ethanol
Ganglionic blocking agents
Hydralazine
MAO-inhibitors
Nitrates
Opinates
Phenothiazines
Sildenafil
Tricyclic antidepressants

Cause or Worsen Orthostatic Intolerance
No Drug is presently approved by FDA for treatment of POTS in children.

(Grubb: Circulation. 2008)
DIZZINESS
Florinef (Fludrocortisone acetate) – synthetic mineralocorticoid

- **Dose:** 0.1 – 0.2mg daily
- **S.E.:** Hypertension, Headaches, hypokalemia

Midodrine – α-1 adrenergic agonist

- **Dose:** 2.5–15mg TID or q.4hrs.
- **S.E.:** supine HTN, chills, urinary frequency

Pyridostigmine – cholinesterase inhibitor – increase standing BP w/out worsening supine BP

- **Dose:** 30mg BID
- **S.E.:** abdominal cramps, diarrhea, excessive cholinergic activity

SSRI: Celexa, Lexapro, WellbutrinXL, Lactose root.

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**Pyridostigmine in Treatment of POTS**

- Total Pt Screened: 300
- Eligible Pt: 208
- Number of patient who could not afford Pyridostigmine: 5
- Number of patient who received Pyridostigmine through dose titration: 200
- Number of patients continuing Pyridostigmine through dose titration: 168
- Number of patient developing GI adverse effects: 39
- Number of pt who discontinued medication due to adverse effects: 35
- Number of patient who received Pyridostigmine: 203

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**HEMODYNAMIC EFFECTS OF PYRIDOSTIGMINE**

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting heart rate</td>
<td>77 ± 14</td>
<td>76 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Standing heart rate</td>
<td>94 ± 19</td>
<td>82 ± 16</td>
<td>0.003</td>
</tr>
<tr>
<td>Sitting systolic BP</td>
<td>114 ± 17</td>
<td>115 ± 16</td>
<td>NS</td>
</tr>
<tr>
<td>Standing systolic BP</td>
<td>106 ± 19</td>
<td>109 ± 19</td>
<td>NS</td>
</tr>
<tr>
<td>Sitting diastolic BP</td>
<td>75 ± 11</td>
<td>75 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Standing diastolic BP</td>
<td>71 ± 11</td>
<td>74 ± 12</td>
<td>0.02</td>
</tr>
</tbody>
</table>

SIDE EFFECTS

GI symptoms:
- Severe abdominal cramps
- Severe nausea
- Severe diarrhea
- Bloating
- No history of IBS

Tremors, twitching, hyperhidrosis
Urinary urgency
Hypertension
Chest pain.

FATIGUE/BRAIN FOG

Stimulants
- Ritalin 2.5-5mg BID to 30mg/dose
- Ritalin LA 10-60mg q AM
- Adderall XR 5-60mg q AM
- Focalin XR 5-60mg q AM
- Vyvanse 10-70mg q AM
- Strattera 10-100mg q AM
- Daytrana 10-30mg 1 patch q AM

HEADACHE

- Periactin: 4-8mg BID-TID
- Metroprolol XL: 12.5-100mg HS
- Verapamil SR: 120-240mg HS
- Amitriptyline: 25mg HS
**NAUSEA**

- Zofran 4-8mg TID PRN
- Meclzine 12.5-25mg BID
- Scopolamine 1.5mg patch q.3days

**DEPRESSION**

**SSRI**
- Fluoxetine
- Sertraline (Zoloft)
- Paroxetine (Paxil)
- Citalopram (Celexa)
- Escitopram (Lexapro)
- Bupropion (Wellbutrin)

**PARENTS AND FAMILY**
ACTUALLY SENTENCES FOUND IN PATIENTS CHARTS

1. Patient stated has been constipated for most of her life... until she got divorced.
2. The patient has been depressed since she started seeing me in 1993.
3. Discharge status: Alive but without my permission.
4. Since she can't get pregnant with her husband, I thought you might like to work her up. Between you and me we ought to be able to get this patient pregnant.
5. The patient refused autopsy
6. The patient has no previous history of suicide
7. The lab test indicated abnormal liver function.
8. She is numb from her toes down.
9. Occasional, constant, infrequent headaches
10. Rectal examination revealed a normal size thyroid.

Reference


