Dysautonomia: POTS & PANs

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Will discuss off-label use of medications for dysautonomia

Overview
- Anatomy and function of the ANS
- Autonomic symptoms
- Clinical autonomic testing
- Case examples

Autonomic Nervous System
- An automatic system to maintain homeostasis
- Control involuntary functions (temperature, blood pressure, heart rate, digestion)
- Motor (effector) systems controlling smooth muscle and secretory glands
- React to visceral sensory (afferent) input
- Three functional components (sympathetic, parasympathetic and enteric systems)
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Baroreceptor Reflex

- Vagus

- Baroreceptor reflex

- Decreased pressure

- BP restored

- ↑ cardiac output

- ↑ peripheral resistance

- Autonomic Symptoms

- Syncope

- Weakness or lightheadedness on standing

- Impotence

- Constipation

- Urinary incontinence or retention

- Diminished or increased sweating (heat intolerance)

- Exercise intolerance, fatigue

- Palpitations and tachycardia

- Nausea and vomiting

- Anorexia, bloating or fullness after eating

- Dry eyes and dry mouth

- NOTE: pain is not an autonomic symptom
Autonomic failure

**Sympathetic:**
- Orthostatic hypotension (fainting)
- Anhidrosis (dry skin, heat intolerance)

**Parasympathetic:**
- Impaired pupil light response
- Decreased salivation, lacrimation
- Impotence, bladder dysfunction

**Enteric:**
- Constipation, gastroparesis, diarrhea, nausea/vomiting, abd pain/bloating

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**Orthostatic Hypotension**

**Definition of OH**
(1995 Consensus committee of AAS/AAN)
- Decrease of SBP $\geq$ 20 mmHg OR
- Decrease of DBP of $\geq$ 10 mmHg
within 3 minutes of standing

**Potential causes**
- autonomic disorders
- low blood volume
- vasodilation (alcohol, medications)

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**Autonomic testing**

- **Bedside testing**
  - Pupil light reflex
  - Supine & Standing Blood pressure and heart rate

- **Cardiovascular Lab (HR and BP)**
  - Heart rate variability (deep breathing)
  - Valsalva response
  - Response to head-up tilt
  - Plasma catecholamines

- **Sudomotor/thermoregulatory (sweating)**
  - Quantitative sudomotor axon reflex
  - Thermoregulatory sweat test
**Respiratory sinus arrhythmia**
- Heart rate varies with the breathing cycle (especially slow deep breathing)
- HR increases with inhalation
- Decrease with exhalation.
- Interaction of cardiac and pulmonary centers
- Mainly mediated by parasympathetic (vagus)

**HR response to deep breathing**

![ECG graphs showing HR response to deep breathing](image)

**Response to Valsalva**
- **Phase I**
- **Phase II**
- **Phase III**
- **Phase IV**
Tilt table test

Orthostatic intolerance
“T’m dizzy when I stand up”

Vertigo    Imbalance    Lightheaded (presyncope)    Woozy??

Orthostatic hypotension    POTS    Episodic Syncope

Case 1
22 yo thin, healthy woman had “flu-like” illness and then developed:
- Palpitations, fatigue, nausea
- Lightheaded with prolonged standing
- Exercise intolerance (previously an avid runner)

- General medical exam and ECG – normal
- Supine BP 120/70  HR 70
- Standing (5 min) 125/75  HR 130 (sick and dizzy)

Diagnosis: Postural tachycardia syndrome (aka POTS)
POTS
• Symptomatic orthostatic HR increase of ≥ 30 bpm (or HR > 120) without orthostatic hypotension
• True syncope (LOC) is uncommon
• Exclude medication effects or other cause
• A heterogenous spectrum of disorders
• Estimated 500,000 US patients (~ 25% disabled)
• 5:1 female predominance
• Onset after viral prodrome, surgery or trauma
• Associated symptoms: chronic nausea, acrocyanosis, headache, chronic fatigue, ptosis, blurry vision, confusion

Joint hypermobility
• With or without a firm diagnosis of EDS
• ? Increased vascular compliance (pooling)
• ? Impaired muscle pump

Other apparent risk factors:
• Low body mass (thin endurance athletes)
• Mitral valve prolapse, irritable bowel syndrome, migraine, anxiety
• Bed rest (after illness)
• History of autoimmune or endocrine disorders

POTS Classification scheme
• Neuropathic POTS
  – Mild peripheral autonomic neuropathy (?autoimmune)
  – Gravitational blood pooling in legs (cool, blue feet)
  – Relative vascular hypovolemia → increased HR
  – Autonomic tests may show distal sweating or cardiovagal dysfunction

• Hyperadrenergic POTS
  – Inappropriate excess sympathetic response to posture
  – Tremor, nausea, sweating, headache when upright
  – Often have orthostatic hypertension along with ↑HR
  – Standing plasma norepinephrine > 600 ng/ml
Secondary POTS

- Severe deconditioning (bed rest)
  - Prolonged weightlessness (astronauts)
- Chronic hypovolemia
  - Anorexia, diuretics, endocrine disorders, stimulants
- Severe anemia
- Syndrome of inappropriate sinus tachycardia (IST)
  - Orthostatic intolerance, but also supine HR >100
  - May also occur as post-viral syndrome
- Other cardiovascular causes
  - PSVT, heart failure

POTS Evaluation

- Thorough history & medication review
- Physical exam, ECG, basic lab work
- 10 min stand test (or full autonomic testing)
- Investigate and correct any secondary causes
  - Cardiac, Rheumatology, Endocrine if indicated
  - Eliminate vasodilators, anticholinergics, stimulants
- Supine and standing catecholamines
  - If suspected hyperadrenergic

POTS Management

1. Reconditioning
2. Aerobic Exercise
3. Gentle resistance training

Exercise is critical but must be done correctly with regular encouragement

- 20-30 min 3-4x/week
- Limit intensity to avoid fatigue
- Heart rate monitor (70% max)
- Start with supine exercise
- Move to seated activity
- No running or treadmill
- Very slow increments
- Trainers often push too fast
POTS Management

4. Volume expansion
   - Hydration > 2L water per day
   - Liberal salt intake (except hyperadrenergic)
   - iv fluid bolus is a last resort

5. Elevated head of bed

6. Compression garments

7. Medications (short term if possible)
   - Fludrocortisone
   - Pyridostigmine, Midodrine
   - SSRI/SNRI (venlafaxine)
   - Hyperadrenergic – clonidine, carvedilol, phenobarbital

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POTS Management

- This is a common condition
- Most cases can be managed by a primary physician
- Most patients will improve
- The patient must be motivated and dedicated
  - Limited data suggest 90% will improve (unless there is 2º cause)
  - Recovery takes months and may take 2-5 years
  - Outside of research studies, compliance with exercise program is often poor
  - If there is secondary gain, management is challenging

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Case 2

- 40 yo obese woman presents with excessive sweating, lightheadedness, and burning discomfort in feet
- Also has N/V, 60 min after eating
- Nerve conduction and EMG are normal
- Neuro exam: Reduced reflexes, Loss of sensation to pin up to ankles. Feet are dry
- Lab work shows fasting glucose of 140

Diagnosis: Small fiber sensory and autonomic neuropathy (diabetes or glucose intolerance)
Autonomic testing

- Loss of distal sweat (QSART) responses
- Impaired heart rate variability
- Impaired BP response to Valsalva

Supine  150/90, HR 70
70° tilt, 1’ 140/85, HR 70
70° tilt, 3’ 120/75, HR 72
70° tilt, 5’ 115/72, HR 73 (lightheaded)

Peripheral autonomic neuropathy (PAN)

Peripheral autonomic neuropathy

- Small fiber neuropathies
  - Autonomic and pain axons are C fibers
  - Not evaluated by nerve conduction study
  - Can evaluate with autonomic testing or skin biopsy

Diabetic PAN
- 35% of patients have autonomic deficits
- Impotence, constipation, gastroparesis, OH
- Compensatory hyperhidrosis of head and chest
- Severe autonomic neuropathy (5%) associated with higher mortality & complication rates

Case 3

- 56 yo woman has onset over 2 weeks of nausea and vomiting after meals, severe constipation, dry mouth, trouble passing urine and dimming of vision upon standing
- She is healthy except for 25 py smoking
- Neuro exam - normal except slow pupil light reaction
- Nerve conduction and EMG are normal
- Supine BP 114/74  HR 64
- Standing 74/60  HR 64

Diagnosis: Acute autoimmune (or paraneoplastic) autonomic ganglionopathy
**Autoimmune Autonomic Ganglionopathy**

- Age ~55 (22-82 years), 65% women
- Subacute onset (but sometimes more insidious)
- Severe OH and GI symptoms prominent (70%)
- Urinary retention, sluggish pupils in more severe cases
- Idiopathic cases have ganglionic AChR antibody
- May improve with immunotherapy (PLEX, steroids)
- Paraneoplastic cases (thymoma, lung cancer) may have other antibody markers (such as anti-Hu, VGCC Ab)

Suarez et al., 1994; Klein et al., 2003; Vernino et al., 2001

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**Case 4**

- 70 yo woman with Parkinson disease
- Tolerating levodopa well for 5 years
- Gradually developed lightheadedness and falling (syncope) occurring after meals
- Supine BP 180/84 HR 54
- Standing (3 min) 74/60 HR 64
- Autonomic testing: adrenergic autonomic failure

Diagnosis: Parkinson disease \ autonomic failure

Symptomatic OH in 18% of PD. Early autonomic failure (\ bladder) could suggest MSA

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**Autonomic Failure**

- Neurodegenerative disorders
  - α-synucleinopathies (PAF, PD, MSA, DLB)
  - Affect central and peripheral autonomic pathways

- Peripheral autonomic neuropathy/ganglionopathy
  - Diabetes
  - Autoimmune conditions (e.g. Sjogren, paraneoplastic)
  - Amyloidosis
  - Toxins (e.g. chemotherapy, amiodarone)
  - Inherited autonomic neuropathy (rare)
Neurogenic Orthostatic Hypotension

- Lightheadedness, dizzy, fainting
- Other symptoms with standing: weakness, fatigue, confusion, leg buckling, graying vision, “coat hanger” neck pain, dyspnea, chest pain
- Postprandial hypotension
- Supine hypertension
- “reverse dipping” – BP high at night and low in AM
- Symptoms of hypotension may lessen over time resulting in syncope with little or no warning.

Management of neurogenic OH

Goal: Relieve symptoms – not necessary to normalize BP
1. Address the underlying cause if possible
2. Review medications (bladder, diuretics, PDEi)
3. Increase fluid (>2L per day) and salt
4. Recognize and avoid activities that worsen OH
   - Large meals, alcohol
   - Heat, hot showers or hot bev.
5. Elevate head of bed by 10-20° (6-9 inches)
6. Utilize physical countermaneuvers
7. Regular exercise (recumbent)
8. Fitted compression garments

Elevate HOB

- Reduce nocturnal diuresis
- Reduce supine nocturnal hypertension
Countermaneuvers

- Can briefly raise BP by 10 mmHg
- Leg crossing
- Buttock clenching
- Squat
- Hand grip

Water drinking

- 400-500 ml of tap water raises BP
- This is a sympathetic autonomic reflex
- Minimal effect in normal subjects
- Can help alleviate morning OH

The Pressor Response to Water Drinking in Humans.
Jordan et al. Circulation 2000

Medications for OH

**Sympathomimetics**
- midodrine
- droxidopa (dihydroxyphenylserine)
- Ephedrine, DHE

**Anti-diuretics**
- fludrocortisone
- desmopressin

**Others**
- caffeine
- Indomethacin
- erythropoetin
- methylphenidate

(all other drugs are off label)

**Dosages**
- midodrine: 2.5 – 10mg tid before meals
- droxidopa (dihydroxyphenylserine): 300-600mg tid
- Ephedrine, DHE: 5-15mg tid

**SE:** itching, hypertension

- norepinephrine precursor
- Approved in Europe and Japan
- Effective in several clinical trials
- Recently approved by FDA

**Anti-diuretics**
- fludrocortisone: 0.1 to 0.2mg daily
- desmopressin: 0.1 to 0.2mg at HS

**SE:** hyokalemia, edema
- Vasopressin analogue, DDAVP
- Reduces nocturnal diuresis

(all other drugs are off label)
Supine hypertension

- Patients with autonomic failure can have supine BP > 210/120
- Elevate head of bed
- No pressor medications after 5pm
- Reduce water intake before bed
- Snack or small glass of wine at bedtime
- If necessary, short-acting antihypertensive at bedtime (e.g. captopril, hydralazine)

Summary

- Autonomic disorders are common
- Careful history and med review is critical
- Most can be diagnosed and treated by any physician
- Autonomic testing and neurological assessment is appropriate for more complex cases
- Dysautonomia may be first sign of a progressive neurological disorder
- Symptoms are treatable (even when cause is not)

Continuum (Dec 2007) – Autonomic Disorders
Broca’s Area (TNS Jan 2014) – Autonomic Testing
Postural Tachycardia Syndrome (Circulation 2008)