Peripheral Autonomic Disorders

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Peripheral Autonomic Nervous System

- Nerves
- Autonomic Ganglia
- Autonomic Neurons
- Enteric Nervous System

Diagram:
- Preganglionic neurons
- Parasympathetic (ciliary or cardiac ganglia)
- Long parasympathetic preganglionic axons
- Long sympathetic postganglionic axons
- Sympathetic (superior cervical ganglia)
- Heart
- Sweat
- Pupil
- Blood vessels
- Heart
Case 1

• 40 yo obese woman presents with excessive sweating, lightheadedness and burning 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 300

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

- Small fiber neuropathies
  - Postganglionic autonomic fibers are C fibers
  - Pain and temperature axons are C fibers (or Aδ)
  - Not evaluated by nerve conduction study or EMG
  - Evaluate with autonomic testing or skin biopsy
Case 1 - Autonomic testing

- Loss of distal sweat (QSART) responses
- Impaired heart rate variability (cardiovagal)
- 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)
Length-dependent small fiber autonomic & sensory impairment
Small fiber assessment - Skin biopsy

IntraEpidermal Nerve Fiber Density:
10-20 fibers / mm

Assessment of C fibers
- Intraepidermal sensory
- Sympathetic pilomotor
- Sympathetic sudomotor
Diabetic autonomic neuropathy

- **Diabetic PAN**
  - 14-35% with diabetic neuropathy have autonomic deficits
  - Impotence, constipation, gastroparesis, OH
  - 20-30% with GI involvement (nausea, early satiety, diarrhea)
    - Isolated diabetic dysmotility (gastroparesis) can occur
  - Cardiovascular impairment precedes OH
  - Compensatory hyperhidrosis of head and chest
  - Severe autonomic neuropathy (5%) associated with higher mortality & cardiovascular morbidity
  - Pupil may be affected (even in absence of diabetic eye disease)

- **Risk factors for more severe diabetic PAN:**
  - High A1c, type 2, duration of diabetes
  - Hypertension, Smoking, BMI, older age, cholesterol, triglycerides
Differential diagnosis of chronic PAN

• Small fiber neuropathy with prominent autonomic features
  o Diabetes (or pre-diabetes metabolic syndrome)
  o Amyloidosis (TTR, myeloma)
  o Familial dysautonomia (HSAN III) – rare, childhood onset

• Small fiber sensory > autonomic
  o Other HSAN, Fabry, Tangier
  o Sjogren (and other immune-mediated)
  o Infectious (HIV, Leprosy, botulism)
  o Nutritional deficiencies & alcohol
  o Idiopathic

• Aging
  o Reduced BRS, reduction in gut innervation (constipation), sexual dysfunction

• Other restricted peripheral autonomic dysfunction
  o Chronic idiopathic anhidrosis, Adie syndrome, Ross syndrome

• Rare inherited autonomic disorders
  o AAA syndrome
  o Dopamine ß hydroxylase deficiency
  o Hirschsprung
  o Cold-induced sweating
Case 1 – diabetic PAN

- Poorly controlled diabetes Hgb A1C – 12.5%
- Starts insulin with aggressive blood sugar control
- Weight loss and exercise

- Returns in 6 weeks with worse symptoms
- Severe burning pain in hands and feet
- Marked increase in pain and allodynia
- More orthostatic lightheadedness
- Insomnia
- HbA1C – 7.5%
Treatment –induced neuropathy of diabetes (TIND)

• a.k.a. “insulin neuritis”
• Acute pain +/- autonomic within 8 wks of markedly improved glycemic control

• 80% risk if ↓HbA1c > 4% in 3 mo
• 4.3% risk if ↓HbA1c < 2% over 3 mo
Case 2

• 50 yo man with 5 years of orthostatic lightheadedness, alternating constipation/diarrhea, dyspnea on exertion & reduced sensation/sweating in the feet

• Distal small fiber sensory loss, OH, sluggish pupil responses

• NCS - peripheral axonal neuropathy and bilateral CTS

• Normal glucose, A1c, SPEP/IEP. Elevated NT pro-BNP

Diagnosis: Progressive sensory and autonomic neuropathy
Suspicious for a myloid neuropathy

Genetic analysis - Thr60Ala mutation in TTR gene
Amyloidosis

Deposition of protein aggregate fibrils in tissues (muscle, nerve, vessels)
• Small fiber predominant sensory neuropathy
• Autonomic: OH, Hypohidrosis, Bladder and GI dysmotility, Impotence
• Carpal tunnel syndrome in 25%, loss of taste, Cardiomyopathy (or skeletal myopathy)

Acquired amyloidosis
• Paraproteinemia λ light chains: AL type
• κ light chains: Multiple myeloma; MGUS

Familial amyloid polyneuropathy
• Most common type – mutations in transthyretin (autosomal dominant)
• Most common point mutation: Val30Met – autonomic symptoms less common
• Other mutations (including Thr60Ala) – common autonomic symptoms
• Treatment of FAP:
  o Liver transplantation
  o TTR stabilizers (Diflusinal or Tafamidis) – slow neuropathy progression
  o TTR gene silencing drugs (Patisiran or Inotersen)
Case 3

- 60 yo woman has onset over 2 weeks of nausea and vomiting after meals, severe constipation, dry mouth, trouble passing urine & 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 BP 74/60 HR 64

Diagnosis: Subacute autoimmune (or paraneoplastic) autonomic ganglionopathy
Acute/subacute PAN / ganglionopathy

- Autoimmune Autonomic Ganglionopathy (AAG)
- Paraneoplastic autonomic neuronopathy
- Inflammatory sensory and autonomic neuropathy
- Acute cholinergic neuropathy
- Botulism
- Toxic neuropathies
  - Organic solvents
  - Heavy metals
  - Acrylamide
  - Amiodarone
  - Cisplatin, vincristine, taxol
Autoimmune Autonomic Ganglionopathy

- Age ~55 (22-82 years), 65% women
- Marked OH and GI hypomotility (severe constipation) are usual chief complaints (about 70%)
- Urine retention, ↓ pupil constriction in more severe cases
- Neuropathic sx (tingling) in extremities in 25%, normal sensation and NCS
- Severe autonomic failure on autonomic testing
- Low plasma norepinephrine
- 50% have ganglionic AChR antibodies (high titer)
- Orthostatic tachycardia without hypotension is NOT AAG
- AAG is rare!
- May improve with immunotherapy

Suárez et al. Neurology, 1994
Vernino et al. Autonomic Neurosci., 2001
Ganglionic AChR antibodies

Upper limit 0.05 nmol/L
Clinical significance 0.2 nmol/L

McKeon et al. Arch Neurol 2009
Li et al. Muscle Nerve 2015

Vernino et al. NEJM 2000
Paraneoplastic autonomic neur(on)opathy

- With lung cancer (usually SCLC)
  - ANNA-1 (anti-Hu) antibody – less commonly CRMP-5

- Enteric neuropathy
  - Gastroparesis & intestinal hypomotility is very prominent
  - Nausea/vomiting/weight loss may be dismissed by oncologist

- Autonomic ganglionopathy
  - Sympathetic failure also present (OH)
  - Similar to AAG but less pupil/bladder involvement
  - Often have associated sensory neuronopathy (or limbic encephalitis)

- Cancer treatment / immunotherapy – modest benefits
“Seronegative AAG”

- A challenging scenario – several variants
- Subacute onset of GI dysmotility and OH
- Usually less cholinergic (sicca, pupil)
- gAChR and paraneoplastic Abs negative
- Pain and small fiber neuropathy in some cases
  - sensory and autonomic neuropathy
- Some respond to high dose steroids, even if IVIG and PLEX do not work

Iodice et al. Neurol, 2009
Golden et al. JCNMD, 2016
Other immune-mediated autonomic neuropathies

• Autonomic dysfunction with small fiber neuropathies
• Sicca or Sjogren syndrome
  o 20% of SS patients have neuropathy
  o Autonomic symptoms common (with sensory neuropathy)
  o Mixed pattern of autonomic deficits:
    • cholinergic deficits predominate (GI, pupil, anhidrosis, tachycardia)
  o Very rare patients have severe autonomic failure
  o Treatment often ineffective

Wright et al. J Auto Nerv Sys, 1999
Mori et al. Brain, 2005
Birnbaum. Neu`rologist, 2010
Peripheral autonomic disorders

Summary points

• Autonomic fiber involvement in small fiber neuropathies
  o Prominent autonomic features may guide diagnosis

• Autonomic ganglia may be target of autoimmunity
  o Interpret gAChR antibodies with caution

• Enteric autonomic nerves may be involved
  o Neurologists can ask about constipation

• Differentiate subacute from chronic etiologies
  o Some disorders are treatable
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