Peripheral Autonomic Disorders

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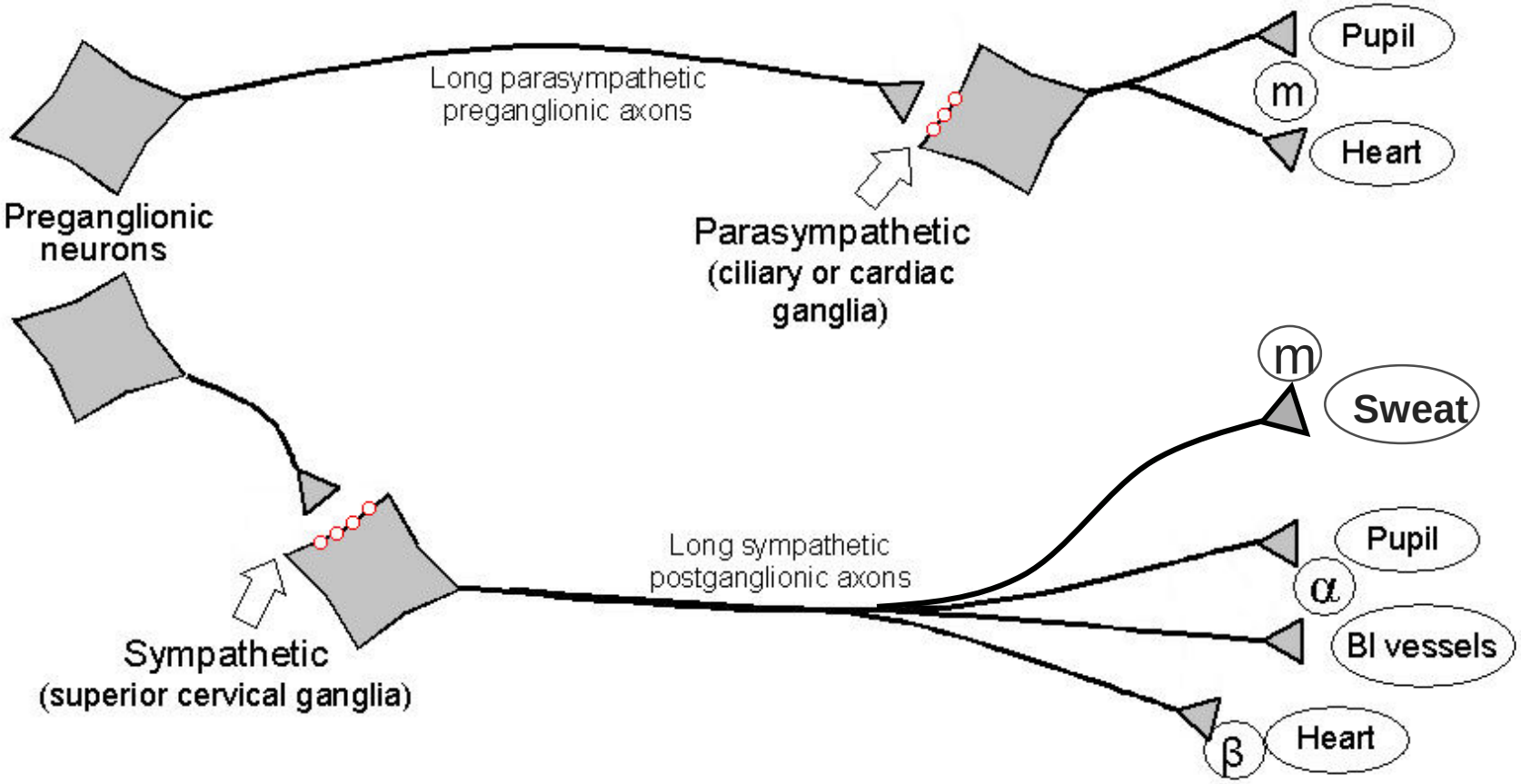
Peripheral Autonomic Nervous System

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



Case 1

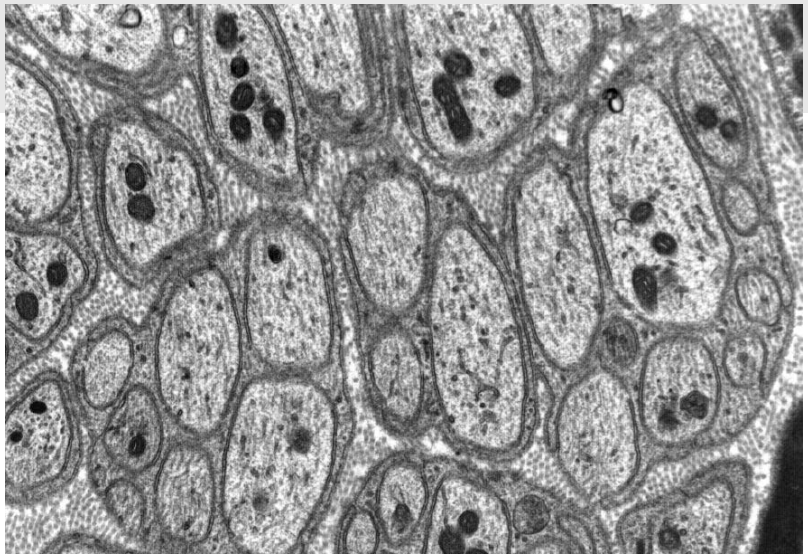
- 40 yo obese woman presents with excessive sweating, lightheadedness and burning feet
- Also has N/V, 60 min after eating
- Nerve conduction and EMG are normal

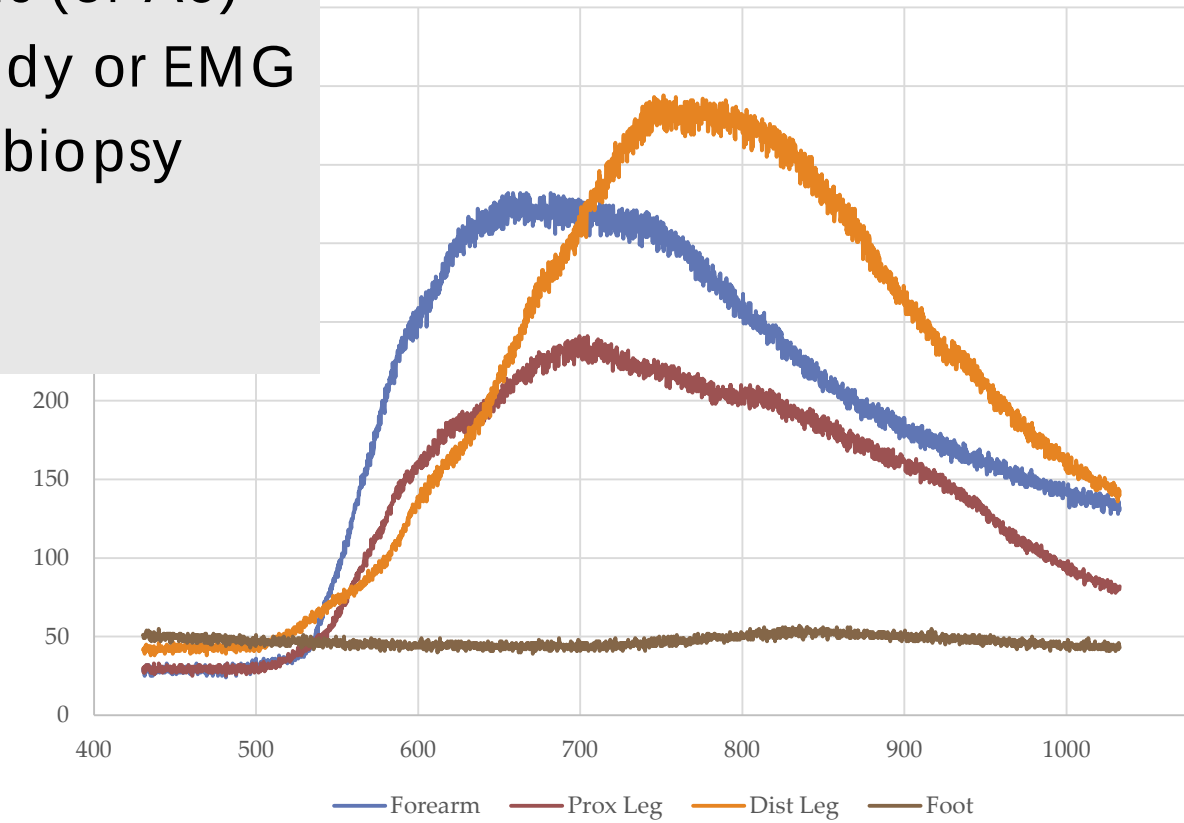
- Neuro exam: Reduced reflexes, Loss of sensation to pin up to ankles. Feet are dry
- Lab work shows fasting glucose of 300

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
70º tilt, 1’	140/85, HR 70
70º tilt, 3’	120/75, HR 72
70º tilt, 5’	115/72, HR 73 (lightheaded)

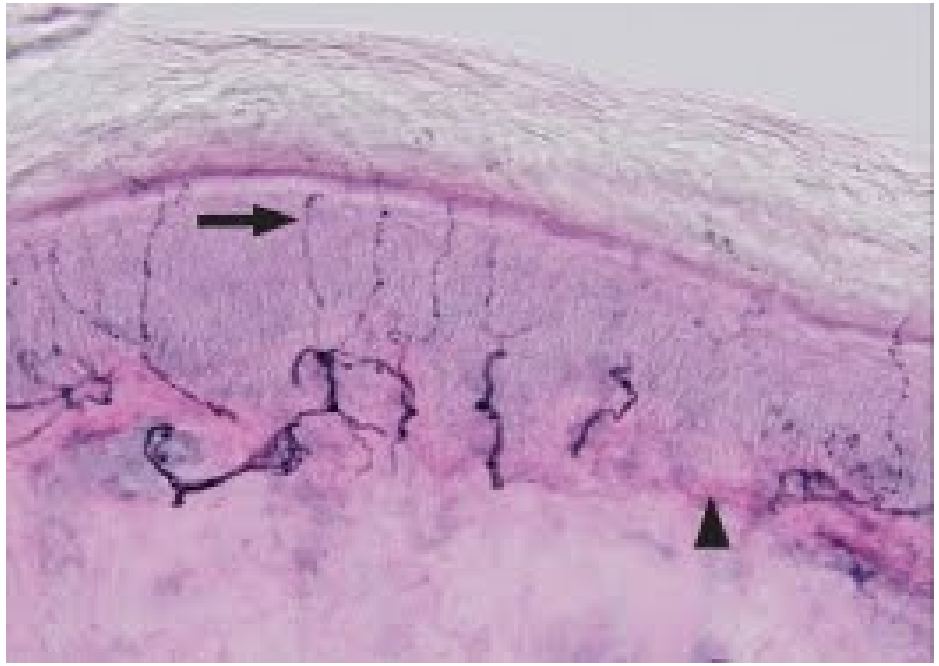
OH

Peripheral autonomic neuropathy (PAN)

Length-dependent small fiber autonomic & sensory impairment

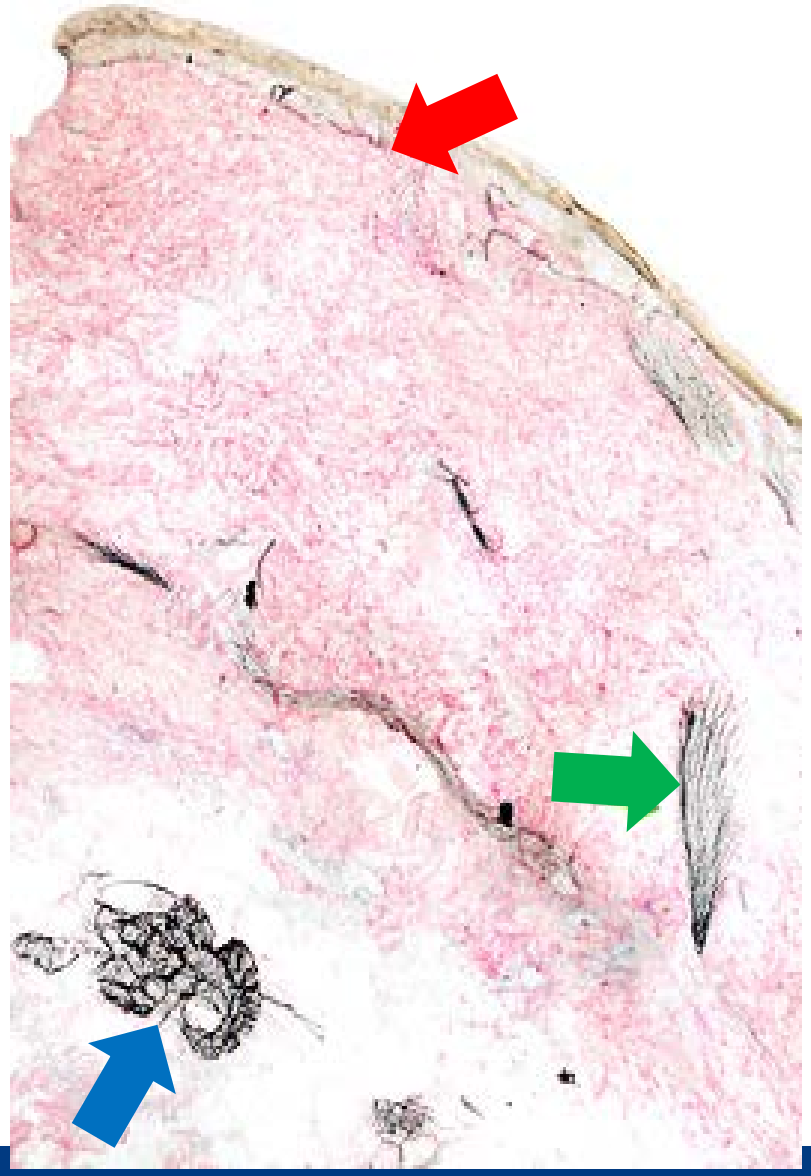
Small fiber assessment - Skin biopsy

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
  - Cardiovagal 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
  - Diabetes (or pre-diabetes metabolic syndrome)
  - Amyloidosis (TTR, myeloma)
  - Familial dysautonomia (HSAN III) – rare, childhood onset
- Small fiber sensory > autonomic
  - Other HSAN, Fabry, Tangier
  - Sjogren (and other immune-mediated)
  - Infectious (HIV, Leprosy, botulism)
  - Nutritional deficiencies & alcohol
  - Idiopathic
- Rare inherited autonomic disorders
  - AAA syndrome
  - Dopamine ß hydroxylase deficiency
  - Hirschsprung
  - Cold-induced sweating
- Aging
  - Reduced BRS, reduction in gut innervation (constipation), sexual dysfunction
- Other restricted peripheral autonomic dysfunction
  - Chronic idiopathic anhidrosis, Adie syndrome, Ross syndrome

Case 1 – diabetic PAN

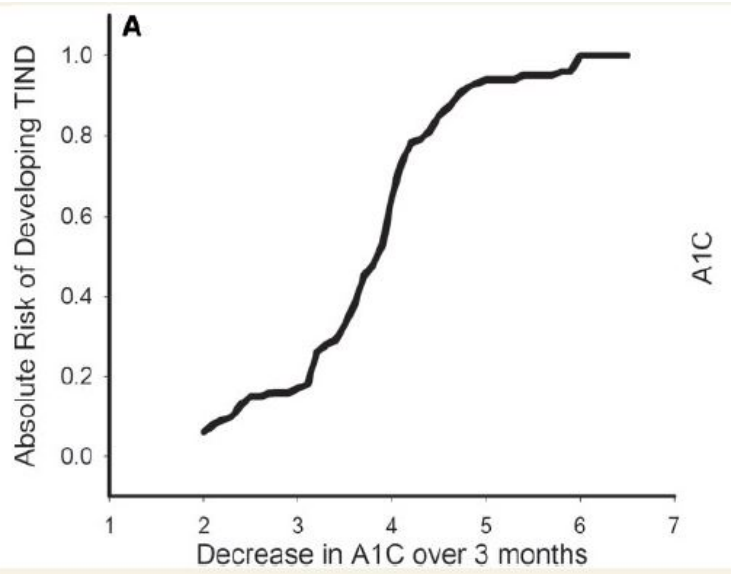
- Poorly controlled diabetes Hgb A1C – 12.5%
- Starts insulin with aggressive blood sugar control
- Weight loss and exercise

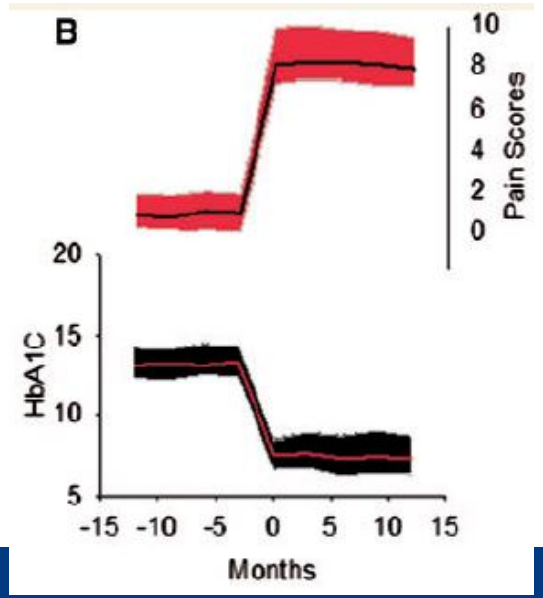
- Returns in 6 weeks with worse symptoms
- Severe burning pain in hands and feet
- Marked increase in pain and allodynia
- More orthostatic lightheadedness
- Insomnia
- HbA1C – 7.5%

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





BRAIN
A JOURNAL OF NEUROLOGY
BRAIN 2015; 138: 43-52

Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes

Christopher H. Gibbons and Roy Freeman

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 amyloid 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:
  - Liver transplantation
  - TTR stabilizers (Diflusinal or Tafamidis) – slow neuropathy progression
  - 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

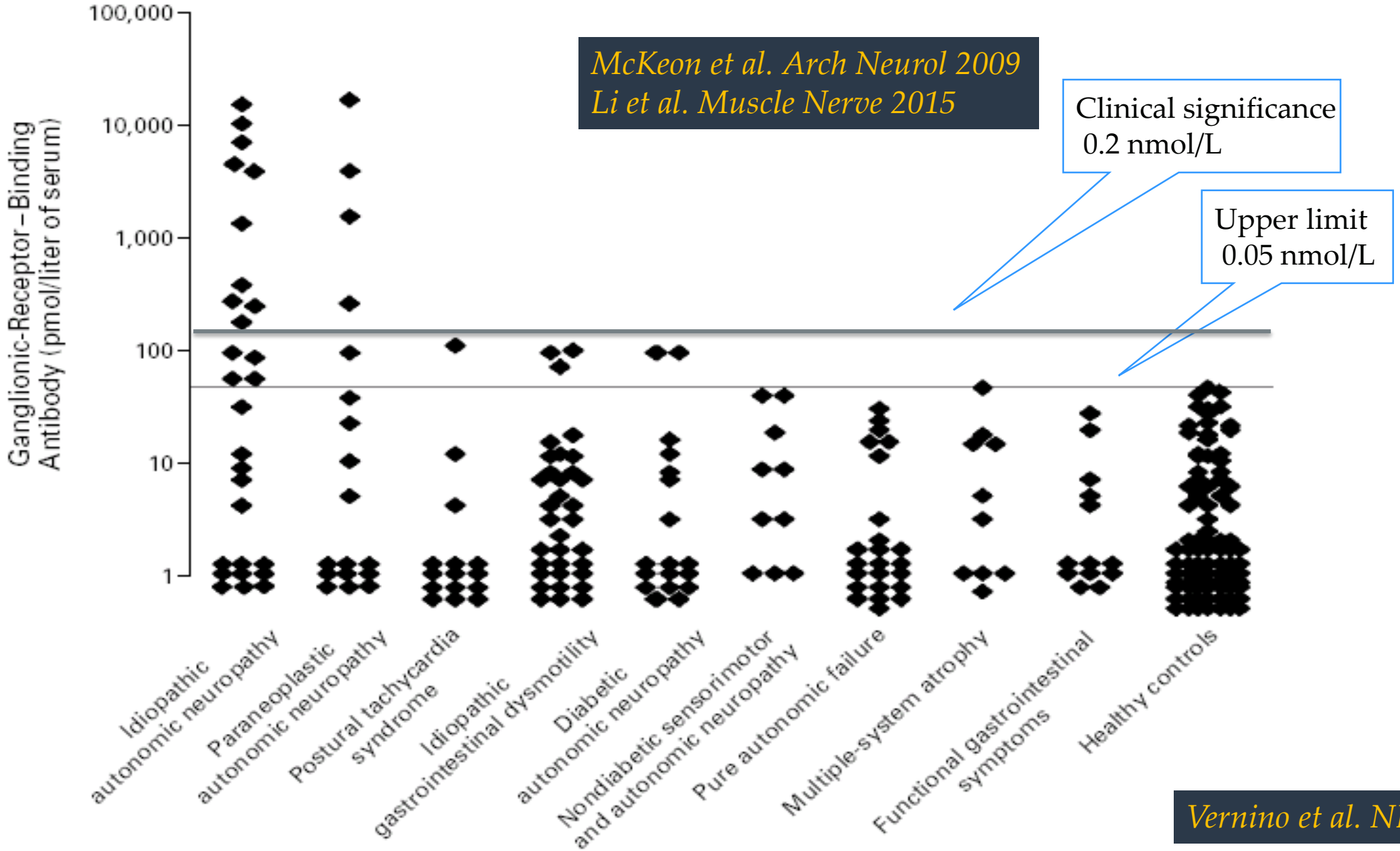
- Autoimmune Autonomic Ganglionopathy (AAG)
- Paraneoplastic autonomic neuronopathy
- Inflammatory sensory and autonomic neuropathy
- Acute cholinergic neuropathy
- Botulism
- Toxic neuropathies
  - Organic solvents
  - Heavy metals
  - Acrylamide
  - Amiodarone
  - Cisplatin, vincristine, taxol

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 sxs (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

Suarez et al. Neurology, 1994
Klein et al. Ann Neurol, 2003
Vernino et al. Autonomic Neurosci., 2001

Ganglionic AChR antibodies



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
  - 20% of SS patients have neuropathy
  - Autonomic symptoms common (with sensory neuropathy)
  - Mixed pattern of autonomic deficits:
    - cholinergic deficits predominate (GI, pupil, anhidrosis, tachycardia)
  - Very rare patients have severe autonomic failure
  - 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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