

AUTONOMIC DISORDERS AND AUTONOMIC TESTING

Kamal R. Chémali, MD

Associate Professor of Clinical Neurology

Eastern Virginia Medical School

Director, Sentara Neuromuscular and Autonomic Center

Director, Sentara Music and Medicine Center

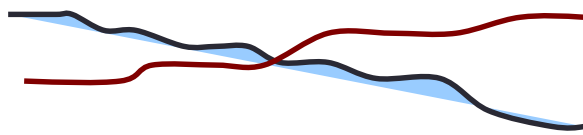
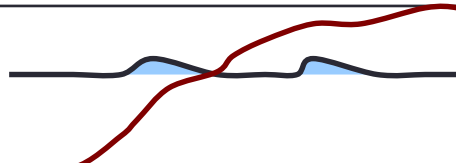

Kevin McNeeley

Sentara Autonomic Laboratory Coordinator

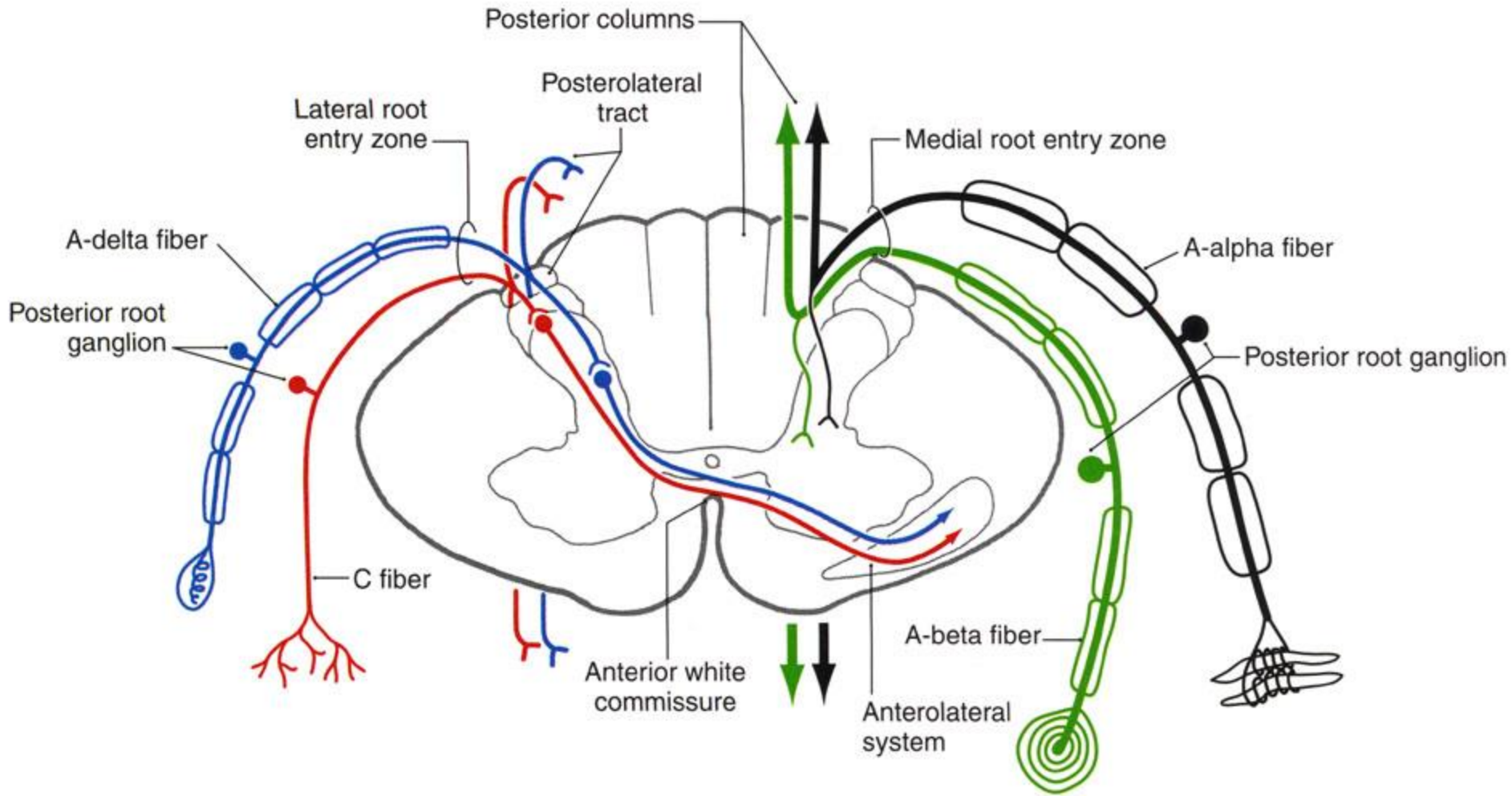
The Upright Posture

- Significant stress on the body to maintain adequate cerebral flow
- Pooling of 500ml to 1000ml of blood
- Decreased venous return to the heart
- Reduced cardiac output and blood pressure
- Compensatory baroreflex activation (CNS, afferent and efferent PNS pathways)
- When this system fails, OH, cerebral hypoperfusion, syncope occur

The 3 Orthostatic Syndromes

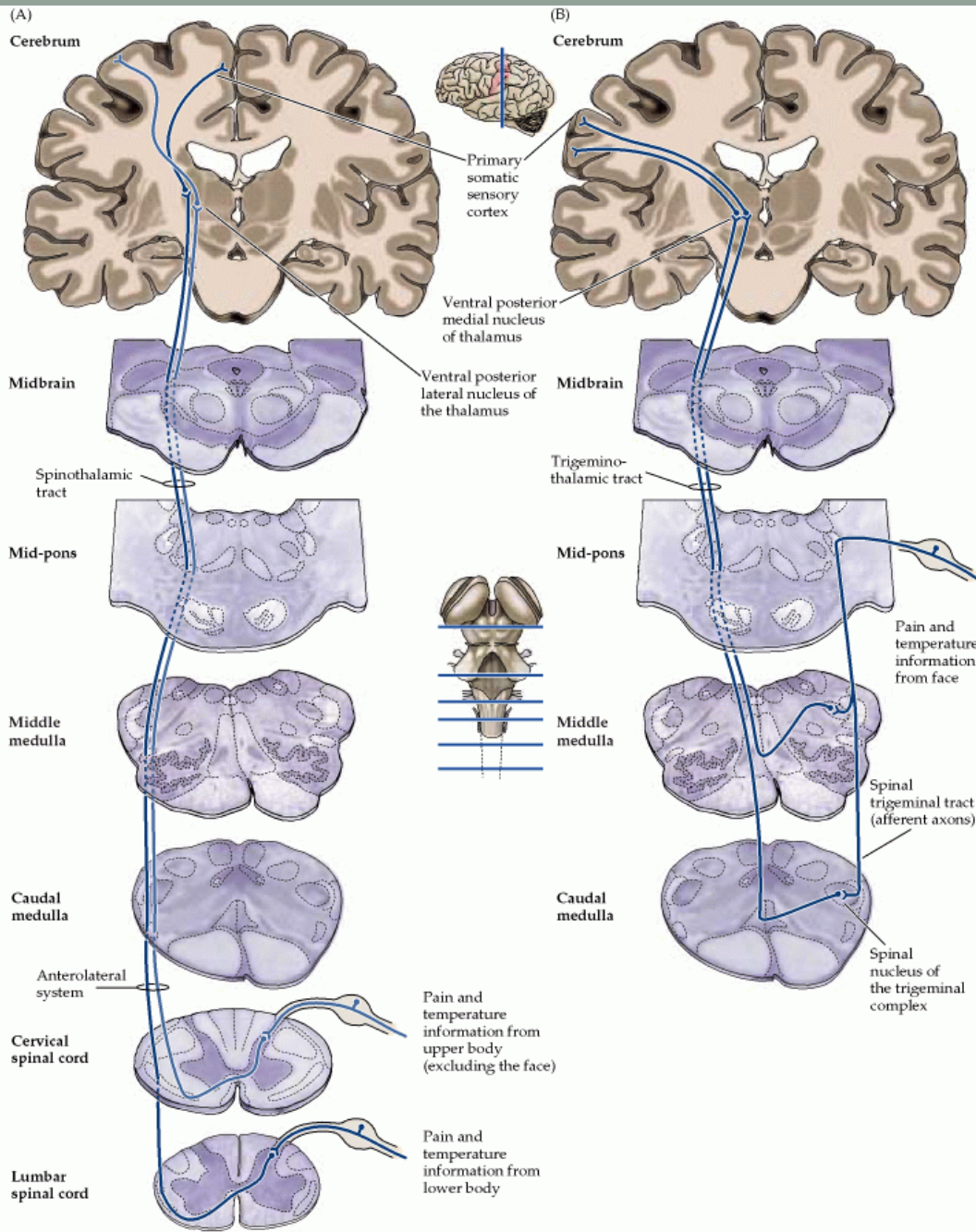
	Orthostatic Hypotension	Postural Tachycardia	Reflex Syncope
Definition	Gradual, Sustained ↓sBP>20 or ↓dBP>10	↑HR>30 1 st 10' up; no ↓ BP	Sudden ↓BP & HR
BP Pattern			
Physiology	Arterial denervation – main impact <i>diastole</i>	Venous return impact <i>systole</i>	Brainstem <i>threshold</i>
CV reflexes	Usually abnormal	Usually normal	Usually nl
Associated Dysauton.	Disease-based Poor prognosis	Syndromic Good Prognosis	Syndromic
SFN Type	Severe, Diffuse	Mild, Focal	None

Somatic Small Fiber System



Small fiber anterolateral system

**Large fiber dorsal column –
medial lemniscal system**



Case 1 (Somatic Small Fiber Neuropathy)

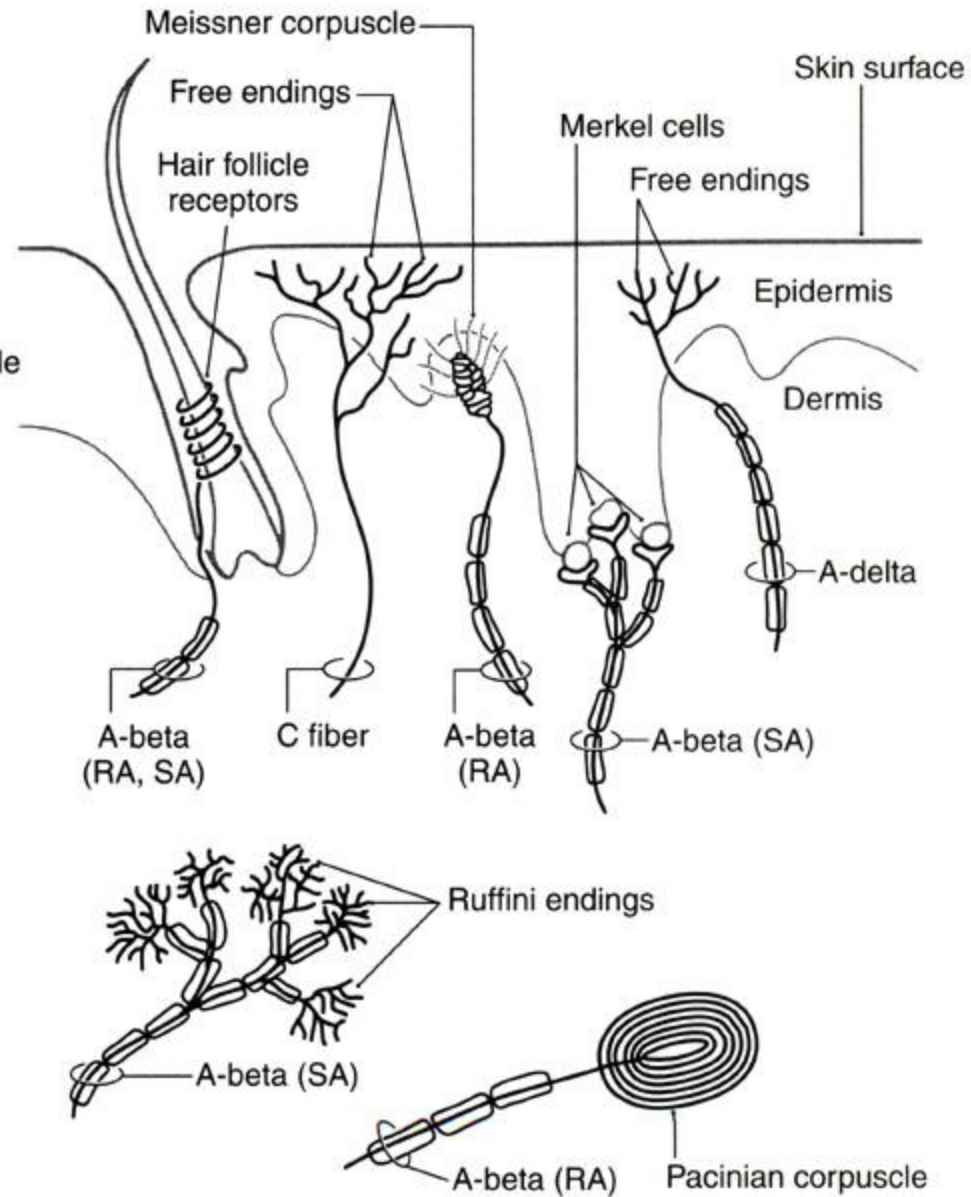
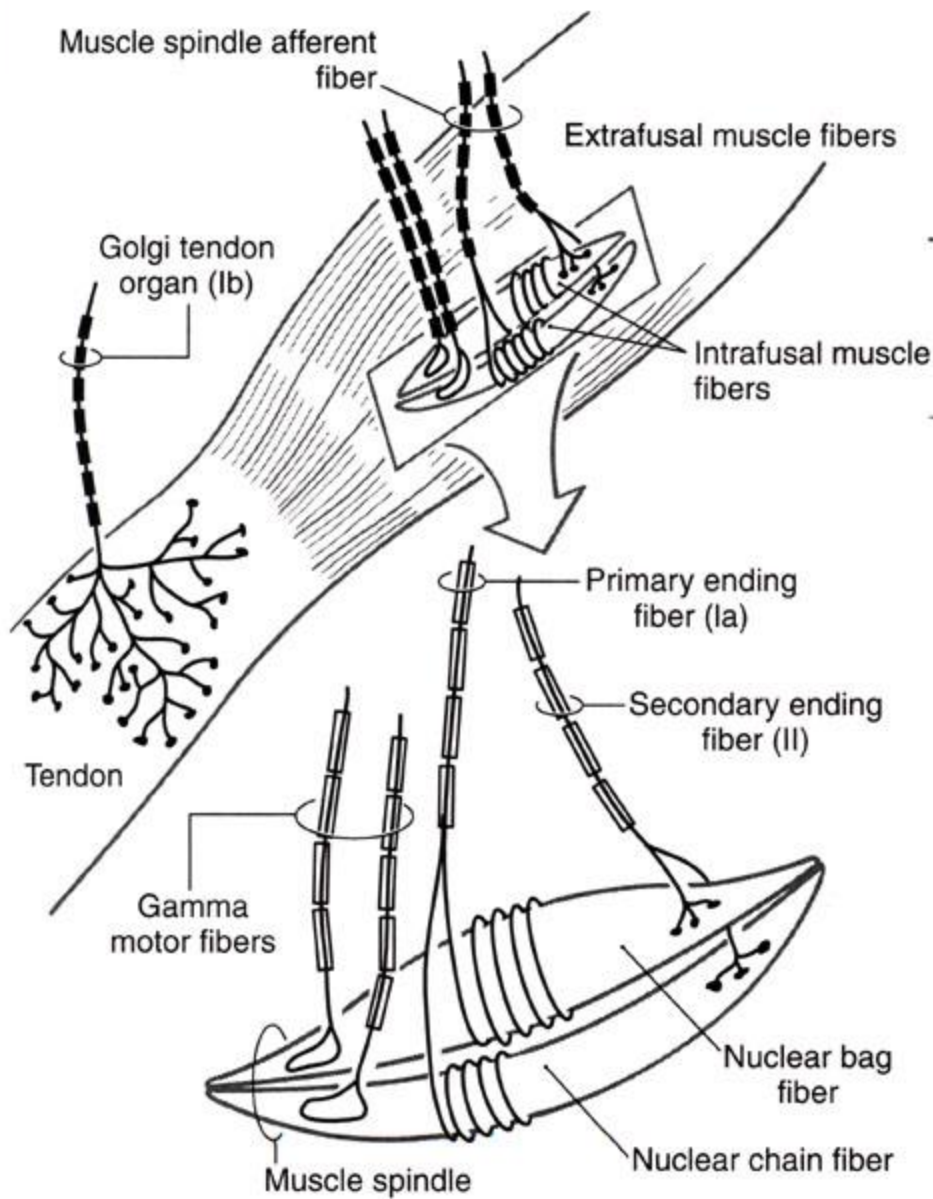
- A 48 year-old man presents to your clinic because of a **burning sensation** in his toes that started 3 months ago and has progressed to involve the entire foot up to the ankle bilaterally. He denies any past medical history but has gained 25 lbs in the past year, due to overeating and inactivity.
- On examination, he has a mild sensory gradient to **pinprick and temperature** in stockings distribution up to the ankles. Vibration is mildly reduced at the toes and joint position sense is intact. His gait is normal and the Romberg test is negative.

Case 1

- A 48 year-old man presents to your clinic because of a **burning sensation** in his toes that started 3 months ago and has progressed to involve the entire foot up to the ankle bilaterally. He denies any past medical history but has gained 25 lbs in the past year, due to overeating and inactivity.
- On examination, **motor strength is normal, including intrinsic foot muscles**, there is a mild sensory gradient to **pinprick and temperature** in stockings distribution up to the ankles. Vibration and joint position sense are intact. **Reflexes are graded at 2+ NINDS at the knees and 1+ NINDS at the ankles**. His gait is normal and the Romberg test is negative.

Sensory fiber diameters and conduction velocities

Fiber type	Diameters	Velocities
Ia, Ib	13-20 microns	80 to 120 m/s
A beta	6 to 12 microns	35 to 75 m/s
A delta	1 to 5 microns	5 to 30 m/s
C	0.2 to 1.5 microns	0.5 to 2 m/s



Definition & Diagnosis of Small Fiber Neuropathy

- In general, a conceptual framework where small myelinated or unmyelinated fibers involved more than the thickly myelinated nerves.
- SFN includes autonomic neuropathy as a subset
- No consensus on definition at this point
 - Research criteria: involvement restricted to efferent (autonomic) nerves and afferent (temperature/pain/visceral) nerves only
 - Clinical criteria: may have loss of distal reflex (ankle jerk), toe strength and distal large fiber sensation, but small fiber involvement clearly disproportionate
- Distal vs Proximal: We also include the entity of small fiber radiculo-ganglionopathy in this group of disorders (which could be more common in diabetes, for example)

Prevalence (Inferred from data below)

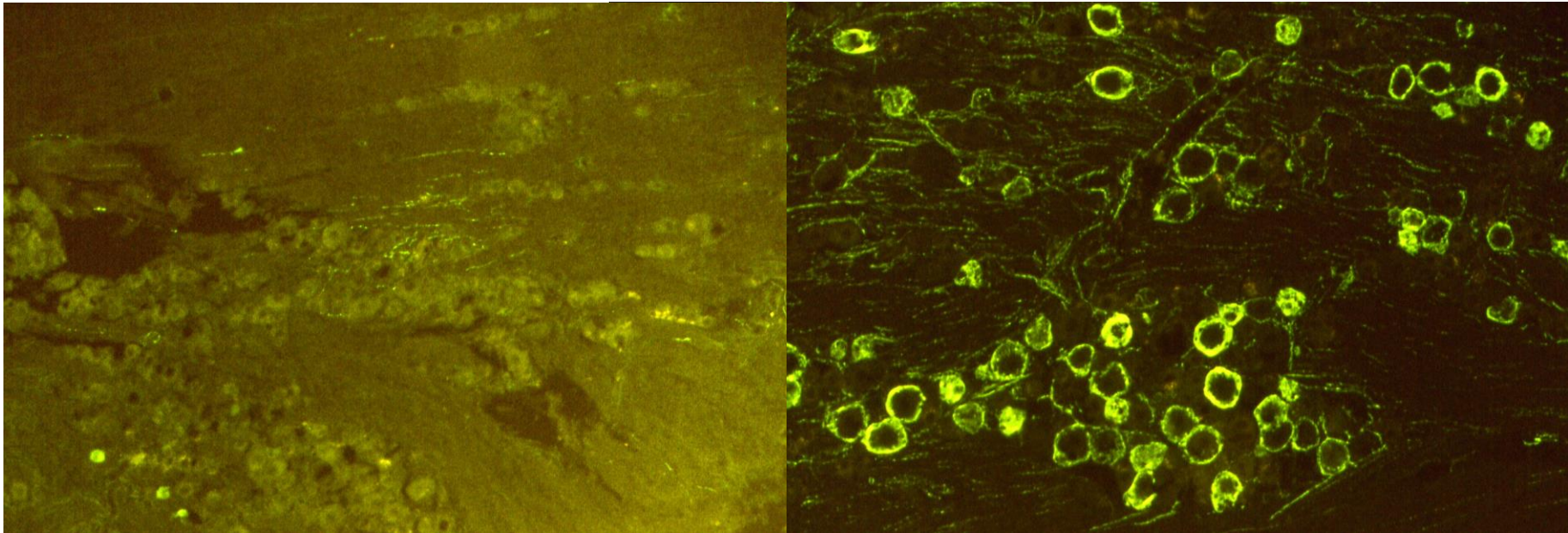
- Sjögren's: 45% to 60% with burning pain (Lopate, 2006)
- Diabetes: SFN in 50-70%, not all with burning pain (Low, 2004)
- Inferred prevalence:
 - Diabetes is at approx. 6% of population (CDC).
 - Distal burning pain occurs in 50% of diabetics, or 3% of entire population
 - Primary physicians may often ignore this symptom, so perhaps one-third are referred to neurology clinic for management (1% of entire population)
 - Of patients referred for the evaluation of SFN, about 1/3 have diabetes
 - **If this represents sample of overall population, prevalence of SFN would be 3 times the prevalence in diabetes, so prevalence could be as high as 9% of the general population. Conservative estimate: 3-5% of population.**
 - Italian study found prevalence of 3% (Beghi, 1995)
 - Compare Parkinson's Disease 1%.
 - Question for audience: do you agree that burning pain is 3 to 5 times as common as PD?

Prognosis is poor

- If an autonomic neuropathy is part of the small fiber neuropathy, the prognosis is quite poor
- 5 Studies conducted between 1980 and 1993 showed 23% to 56% mortality from all-causes at 5 years!
- Mortality from cardiovascular causes in patients with DM and abnormal autonomic parameters is two-fold (the HOORN Study, 2001)

Sympathetic Stimulation Post Nerve Injury

- Alpha-receptors normally not present on nerve
- After injury, they develop on various neural moities, for example, dorsal root ganglion cells



Control

Courtesy David Katz

Axotomized

Approach to SFN

- Define which fibers are involved and where by examination and testing:
 - Large somatic fibers – EMG, Quantitative Sensory Testing (QST) to Vibration
 - Small somatic fibers – QST to Heat and Pain
 - Small autonomic fibers – Autonomic testing including sudomotor axon reflex test (QSART), thermoregulatory sweat test, pupillometry
 - Small autonomic and somatic fibers: skin biopsy
- Autonomic Testing
- Etiological blood tests

Case 2 - SFN testing

- 60 year old right handed Caucasian male.
- Past 15-18 months: Ball of feet felt swollen, occasional pain of knees, elbows and shoulder. Dry eyes, dry mouth. Recent total impotence.
- He denies, urine problems, sweating or swallowing problems. Slight orthostatic dizziness.
- It is only on further questioning that he admits to mild burning of the feet that is worse at night than during the day.

Case 2 - Examination

- Neurological examination normal except for borderline orthostatic hypotension (drop of 20mm Hg systolic and no tachycardia).
- Further testing confirmed the diagnosis of a non-length dependent small fiber neuropathy.

What tests would benefit the evaluation?

- Autonomic Testing
- NCS/EMG
- Blood work
- Skin biopsy
- Lip biopsy
- Fat biopsy

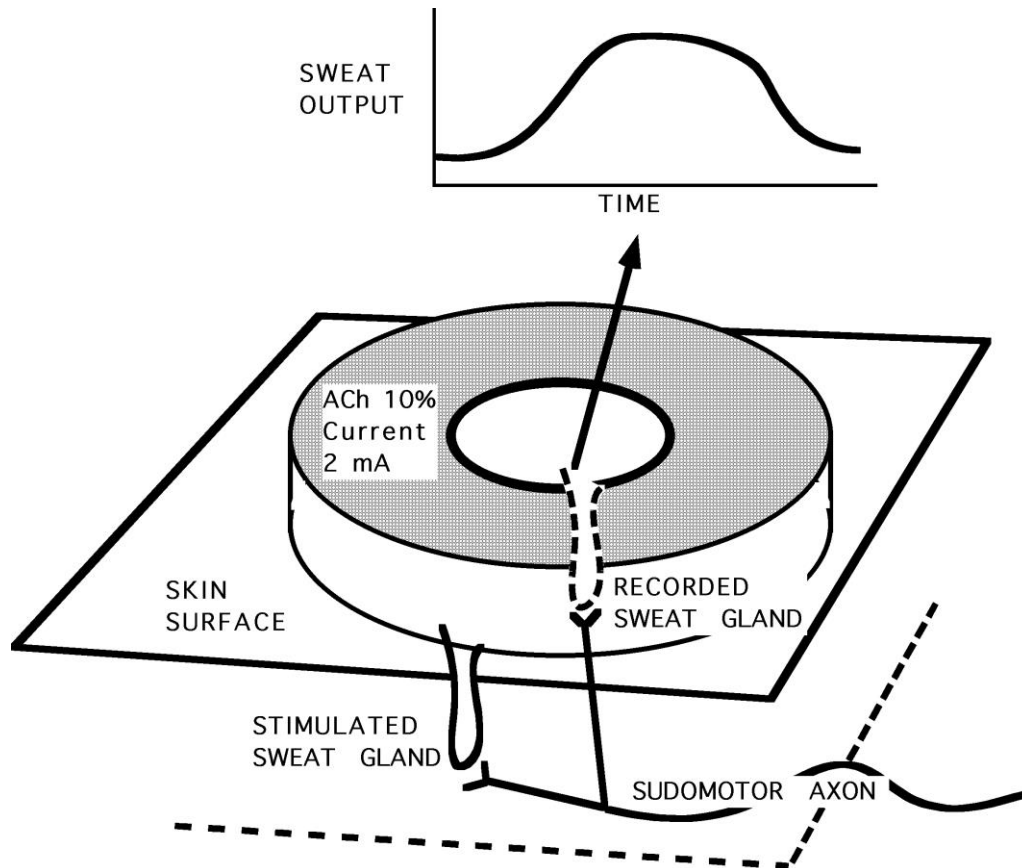
What does Autonomic Testing Add?

- Establish presence or absence of autonomic fiber involvement
- Differentiates between CNS and PNS etiology when abnormal
- Defines Prognosis
 - Disease-based dysautonomias (MSA, DM) more serious than syndromic (POTS)
 - Autonomic neuropathy in diabetes very serious.

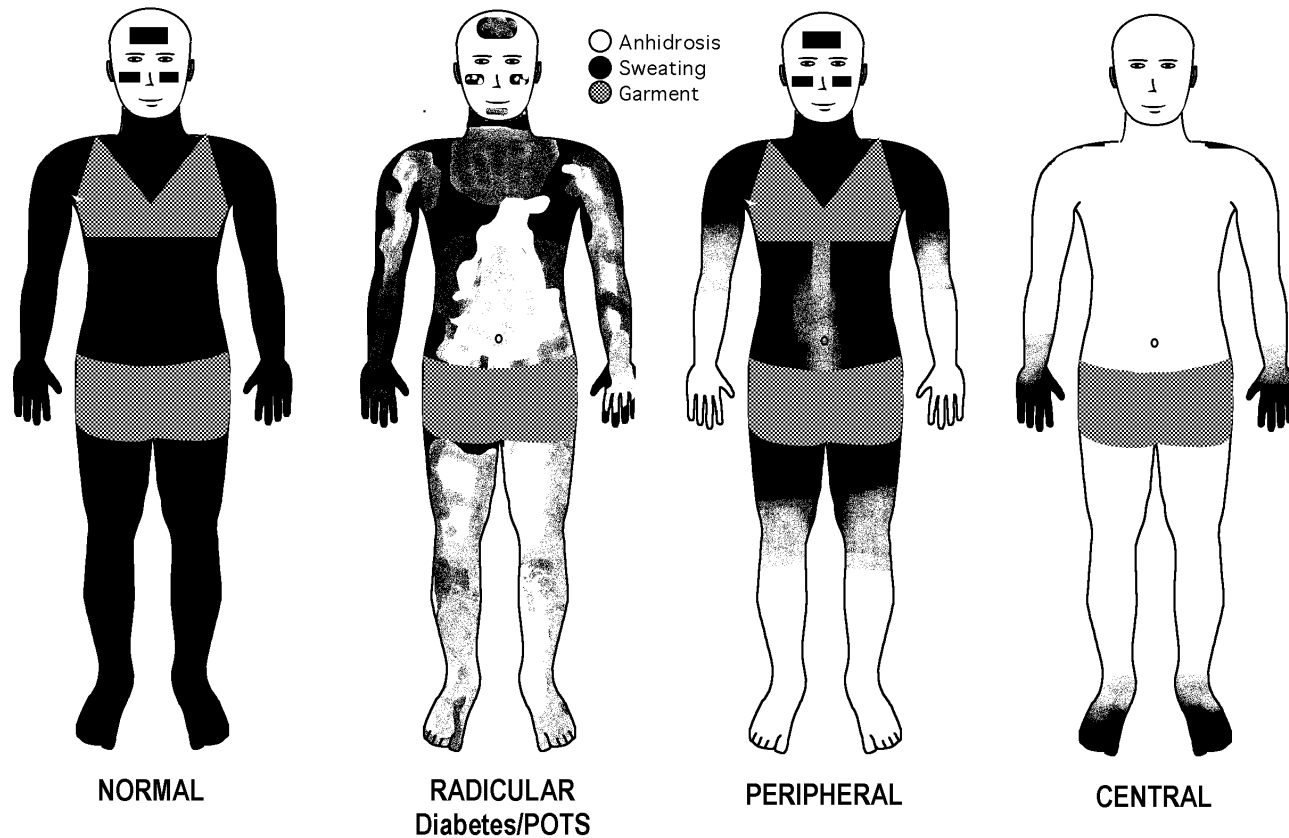
Autonomic Testing

- Answers 4 questions:
 - Localizes the lesion in the neuraxis
 - 2 tests of sweating
 - Identifies which branches are affected
 - 3 cardiovascular tests
 - Addresses differential diagnosis and work-up
 - All tests combined
 - Directs management of syncope and orthostasis
 - Tilt induced changes, related to timing of symptoms

Axon Reflex Sweat Test



Thermoregulatory Sweat Test

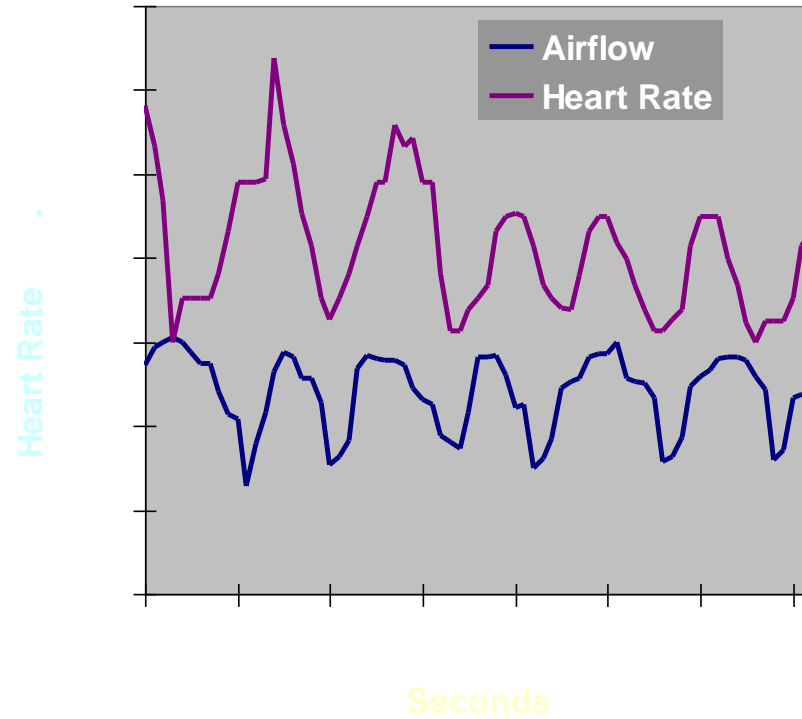


Heart Rate Variability to Deep Breathing

- One of the most commonly performed
- Simple to perform
- Involves the vagal efferents and baroreceptor sensitivity changes
- Sensitive, specific and reproducible indirect measure of cardiovagal nerve function

- The patient is laying down on the tilt table, five second inhalation period and five second exhalation period times 6 times
- Maximal HR-minimal HR or ratio of shortest RR during inspiration to longest RR during exhalation

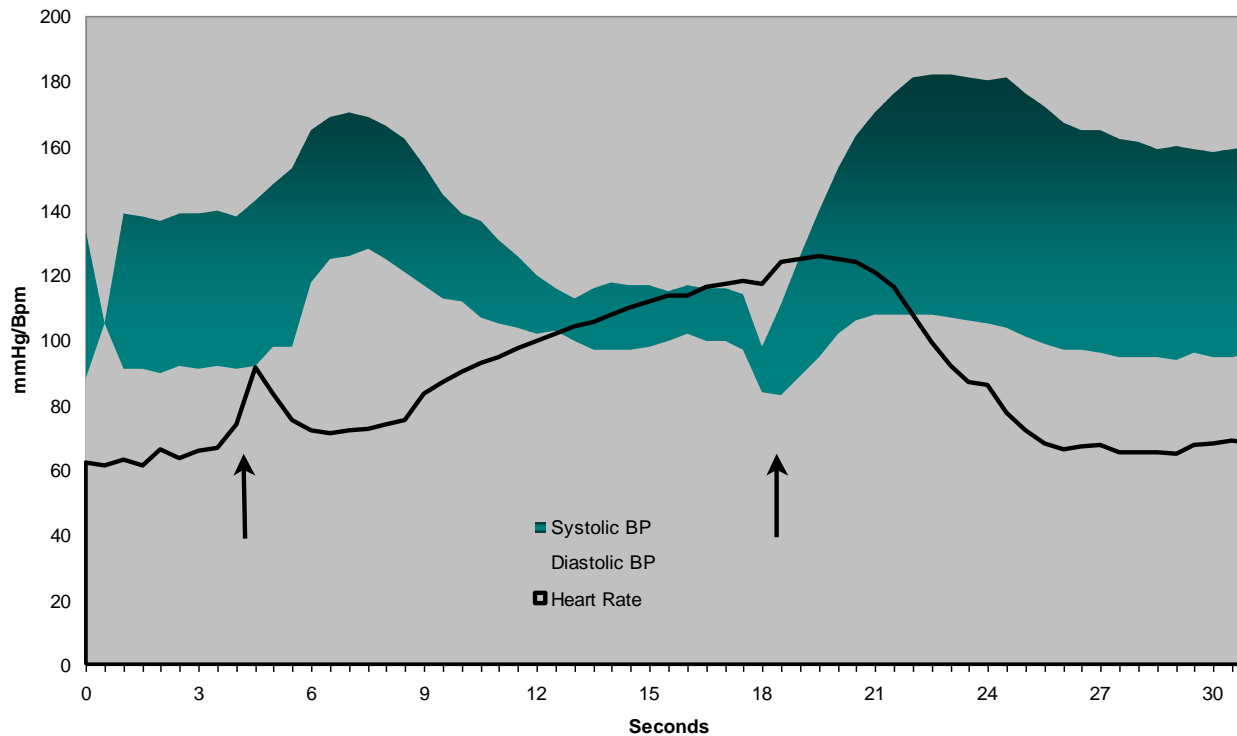
Cardiac Response to Deep Breathing



Valsalva Maneuver

- Tests the cardiovascular sympathetic and parasympathetic autonomic nerves
- The Valsalva Ratio (maximal HR to minimal HR)
- The patient exhales into a one way valve mouthpiece connected to a sphygmomanometer

Cardiac Response to the Valsalva Maneuver



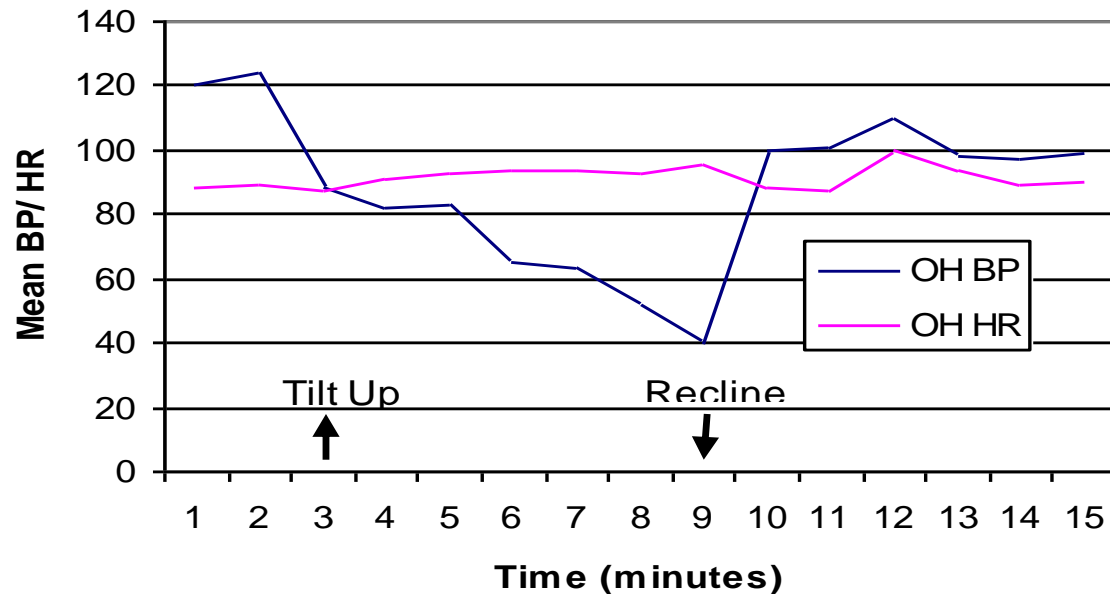
Tilt Table Test

Tests cardiovascular sympathetic nerves

- How to perform the Tilt Table Test
 - 3 minute baseline supine
 - 70 degree tilt for 10 minutes or 40 minutes syncope episode
 - Then returns to supine and monitor VS until back to baseline

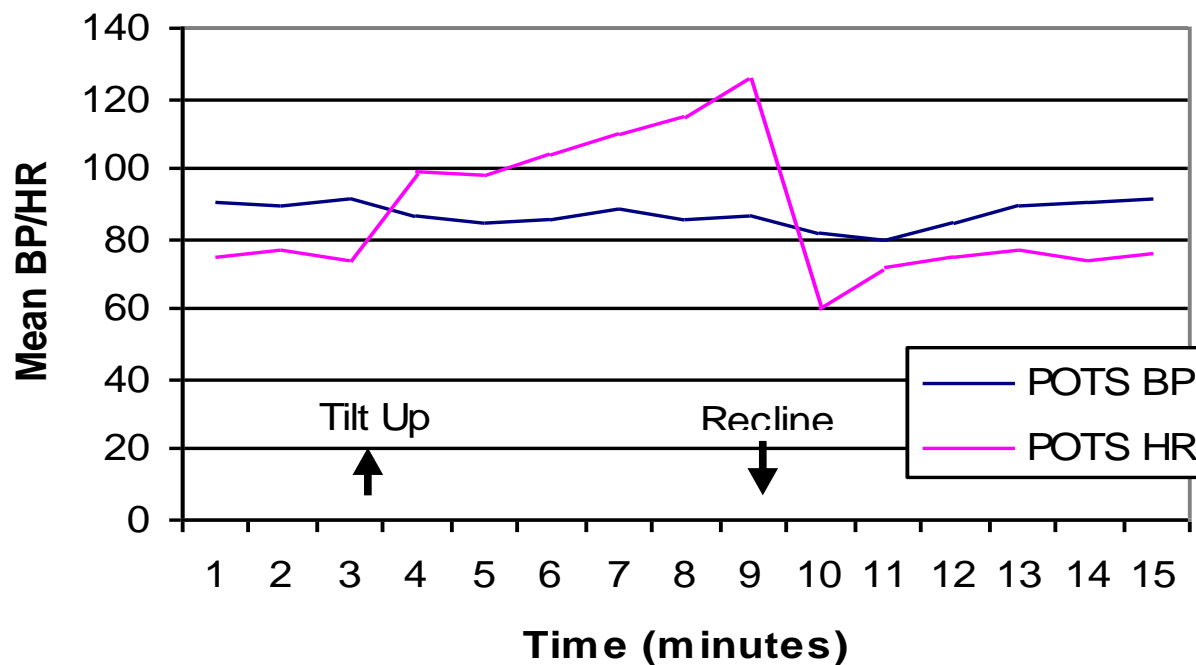
Tilt Table: Orthostatic Hypotension

Figure 1: 70 degree tilt table in OH



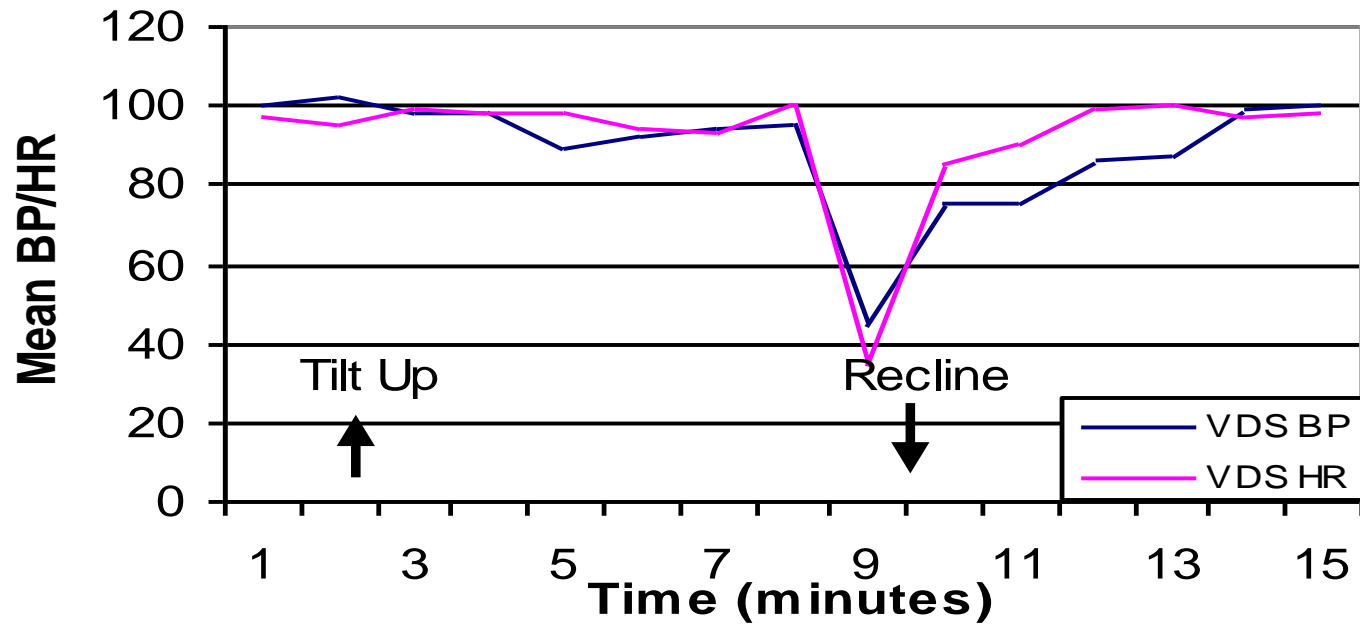
Tilt Table: Postural Tachycardia

Figure 2: 70 degree tilt table in POTS



Tilt Table: Vasodepressor Syncope

Figure 3: 70 degree tilt table in VDS



Test Results

- EMG: Normal.
- QSART: Mildly reduced in forearm, proximal leg and calf but not the foot.
- Deep Breathing Response: 5 bpm (NI > 8)
- Valsalva Ratio: 1.12 (NI > 1.25)
- Tilt Table: moderately severe OH

Case 2- Skin Biopsy

Three 3-mm skin punch biopsy specimens

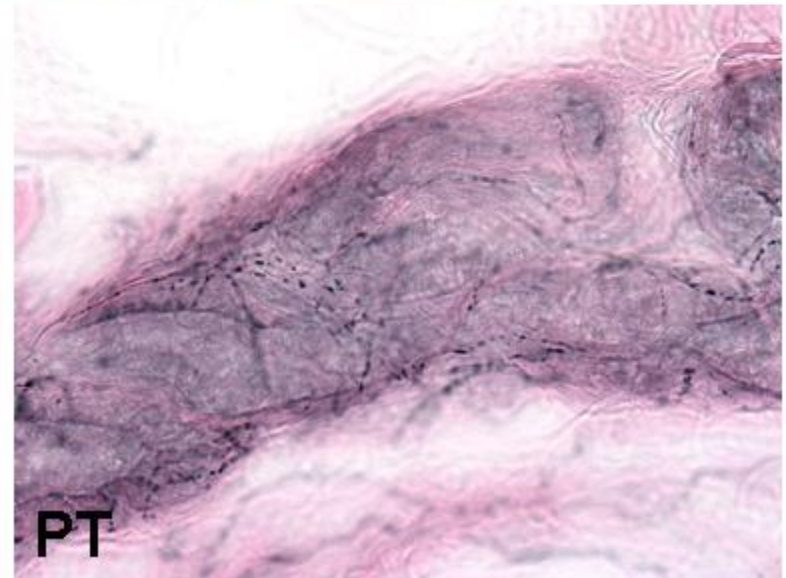
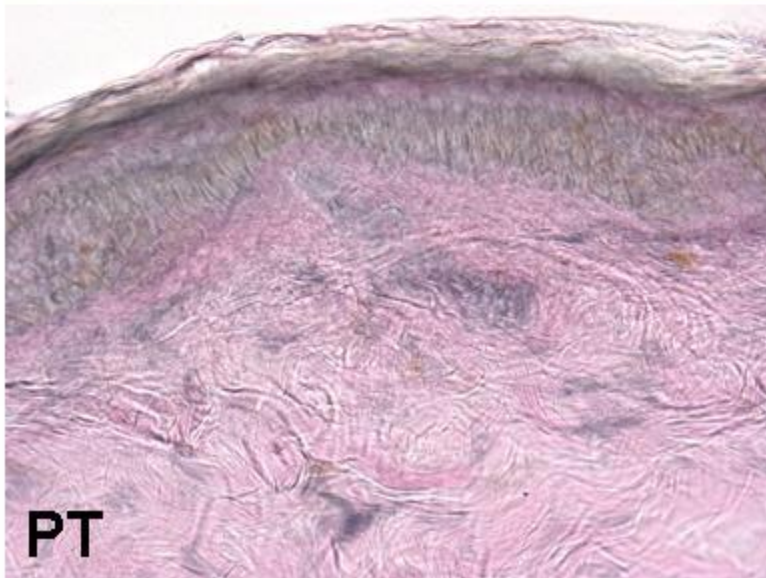
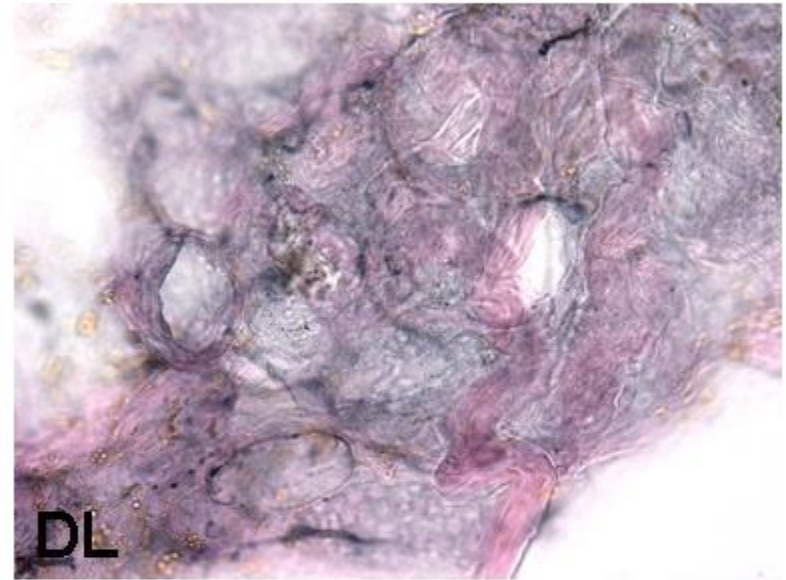
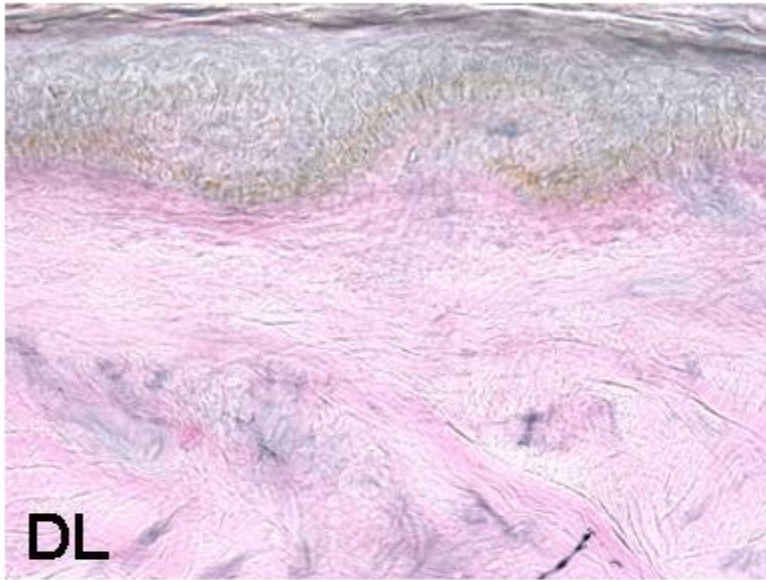
Specimens fixed in 2% PLP, cryo-protected in 20% glycerol, sectioned at 50 um, and immunostained using the polyclonal rabbit anti-human PGP9.5 antibody and the SG chromogen kit to develop the immunostaining signals.

Skin biopsy:

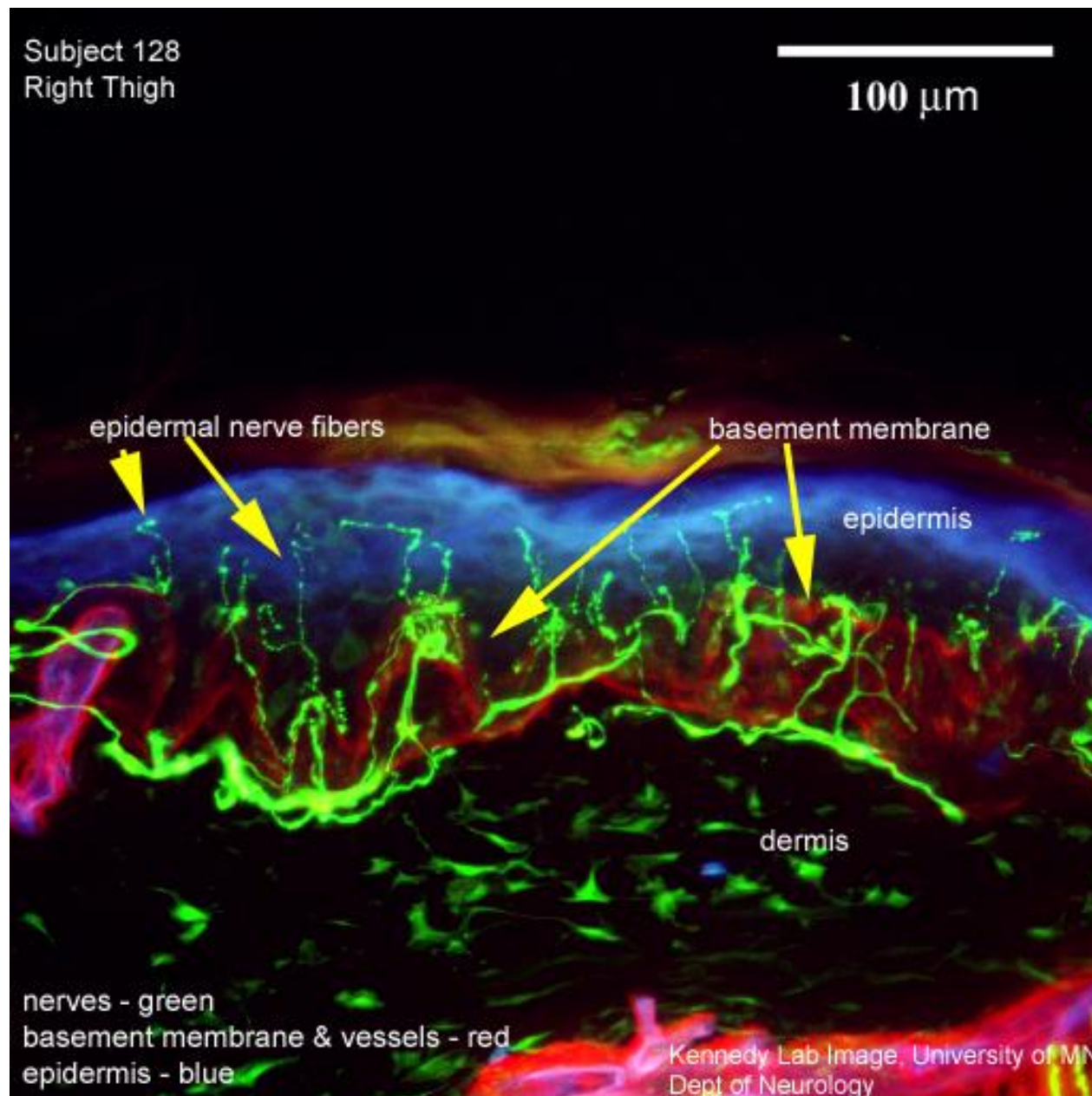
Shows a moderate length-dependent neuropathic process affecting small caliber sensory nerve fibers.

Skin Biopsy

07014



Skin Biopsy



Additional History Case 2

- Tongue has become thickened
- 25# Weight loss in last year

Case 2- Diagnosis

Fat biopsy showed congo-red positive fibrils.

Genetic testing

“This individual possesses a DNA sequence alteration in the coding region of the Transthyretin (TTR) gene that is a known disease-associated mutation and therefore is expected to be affected with or predisposed to developing the disease phenotypes of Transthyretin-associated amyloidosis syndromes”.

Dysautonomia

Disease-Based

Syndromic

Peripheral

Central

Pure Autonomic Failure

MSA

Small Fiber Neuropathy

LBD

Diabetes

Immune

Genetic

Metabolic

Inflammatory

Mitochondrial

Postural Tachycardia

Migraine

Functional GI Disorders

Interstitial Cystitis

Complex Regional Pain

Fibromyalgia

ETIOLOGICAL TESTING

Impaired Glucose Tolerance, Diabetes and Autonomic SFN

Most or 2nd most common cause in the Western world

- Undiagnosed dysmetabolism of sugar
 - 38% normal
 - 38% impaired fasting glucose
 - 100 to 126 mg/dL FBS
 - 100 to 200 mg/dL:120 minute value on GTT
 - 24% frank diabetes
 - FBS > 126 mg/dL
 - 120 minute glucose > 200 mg/dL

Hoffman-Snyder et al, 2006

Diabetes

- Impaired glucose tolerance: OGTT (2nd hour >140 mg/dl and <200 mg/dl)
- Fasting glucose >126mg/dl
- SFN: initial presentation vs progression into LFN: 50% of patients with DM
- Autonomic manifestations in IGT: early death risk

IGT and Metabolic Syndrome

- Hypertriglyceridemia: possible association at low levels (>150)
- Hypertension
- Obesity
- IGT: 30 to 50% of idiopathic SFN

Amyloidosis

Any M-protein with beta-pleated sheets

- 10 to 20 nm in diameter non-branching filaments
- Affinity for Congo red stain with “apple-green birefringence” under polarized light
- Deposition in tissues

Acquired and hereditary (transthyretin, apolipoprotein A-1, gelsolin)

Amyloidosis

- Can deposit on distal peripheral nerves
- Can deposit on nerve roots and in dorsal root ganglia
- 20%: manifestations of SFN at time of diagnosis
- Gradual autonomic features, most severe is syncope
- Liver, cardiac and renal disease

Other Monoclonal

Monoclonal Gammopathy

- Multiple Myeloma
 - Waldenström Macroglobulinemia
 - MGUS
 - Cryoglobulinemia
 - Amyloidosis
- Immunofixation in serum and urine: best technique

Vitamin B12 deficiency

- Clear association with LFN and with autonomic dysfunction
- Association with SFN less certain
- A borderline vitamin B12 level (<300) should raise suspicion. Obtain MMA and Homocysteine.
- CBC: increased MCV

Alcohol and toxins

- Association with PN well-established (32%-76%)
- Probably mixed SFN and LFN with predominance of SFN early on
- Chemotherapy (vincristine, cisplatin, bortezomib)
- Anti-arrhythmic: amiodarone
- Ciguatera poisoning
- Organic solvents, hexane, acrylamide, heavy metals (arsenic, mercury, thallium), rat poison

Autoimmune diseases

- Definite association: Sjögren's syndrome.
- Loose associations: anti-sulfatide antibodies, sarcoidosis, celiac disease, autoimmune thyroiditis, anti N-type Calcium Channel, anti VGKC Ab, Anti Ganglionic Ab, etc.

Sjögren's syndrome

- Common: 1 to 2 million people worldwide
- 4th-5th decades
- Female:Male (9:1)
- Sicca symptoms
- SFN, Pure sensory PN, sensorimotor PN, sensory ganglionopathy (45-60%, Lopate, 2006)

Sjögren's Syndrome

- **Ocular signs:** Positive Schirmer's test (<5 mm in 5 min)
- **Histopathology:** Minor salivary gland (lip) biopsy: Focus score ≥ 1
- **Salivary gland involvement:** Salivary scintigraphy, parotid sialography, or salivary flow (≤ 1.5 mL in 15 min)
- **Autoantibodies** Antibodies: [Ro \(SS-A\)](#) or [La \(SS-B\)](#)

Infections

HIV, Botulism, Diphtheria, Chagas, Leprosy

- HIV + Diphtheria: GBS-like + cells in the CSF
- HIV: Painful distal sensory neuropathy: most common neurological complication (Mc Arthur)
- HIV: SFN about 35% in lifetime

Hereditary causes

- Strong family history in SFN
- HSAN types I to V
- HSAN III is Familial Dysautonomia
 - Absent fungiform papillae
 - Pain insensitivity
 - Absent tearing
 - No flare on histamine flare test
 - Autosomal recessive in Ashkenazi Jews mutation of IKBKAP on chromosome 9.
- Fabry's disease
- Porphyrias

Paraneoplastic

- ANNA (Anti-Hu): SCLC
- Anti-VGCC Ab: Lambert-Eaton Myasthenic Syndrome: SCLC
- Ganglionic Acetylcholine Receptor Antibodies: autoimmune, rarely associated with cancer (acute to subacute dysautonomia)
- Anti-VGKC Ab: neuromyotonia, Morvan's disease, enteric neuropathy