DIABETIC NEUROPATHIES

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Disclosures-Pfizer
(Familial Amyloid Polyneuropathy)

Off label use of medications will be discussed

Peripheral Neuropathy

- Common problem
  - non-traumatic peripheral neuropathy
  - prevalence of 2.4% in population
  - prevalence of 8% over the age of 55

Peripheral Neuropathy

- Most common cause (in developed nations) is diabetic mellitus
- Prevalence of diabetic peripheral neuropathy expected to rise in the U.S.

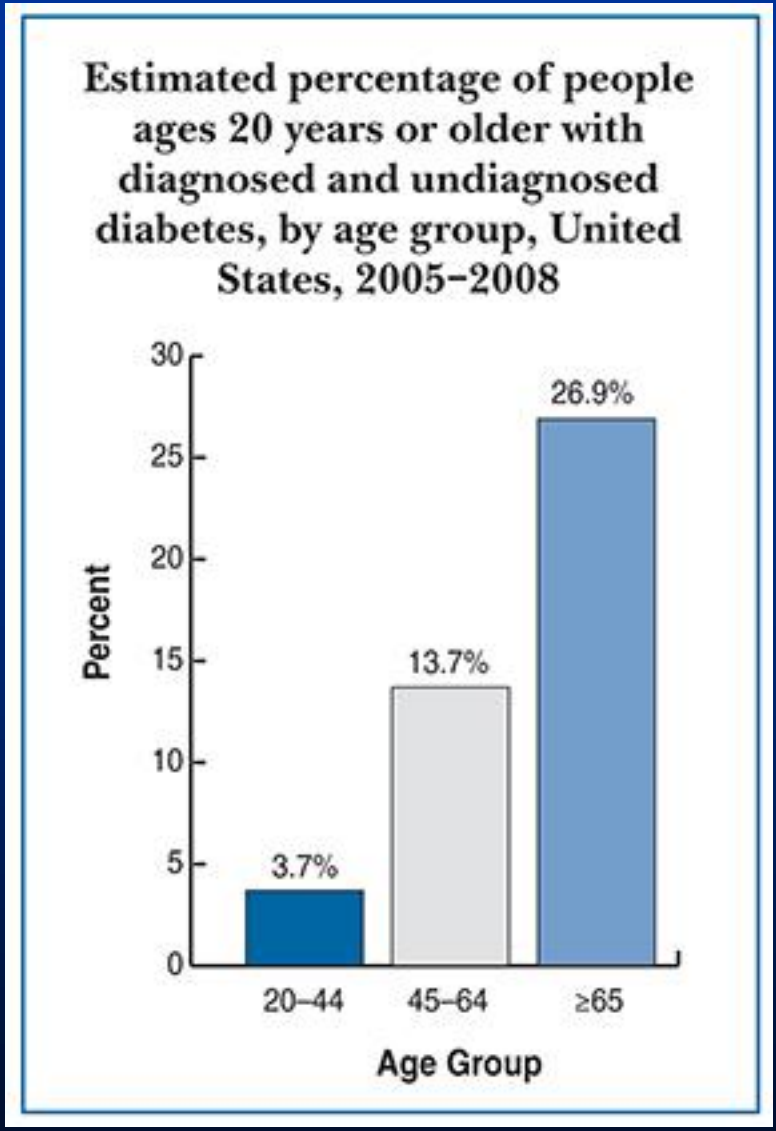
(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/)

Diabetes affects:
25.8 million people of all ages
8.3 percent of the U.S. population

DIAGNOSED
18.8 million people

UNDIAGNOSED
7.0 million people

(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/)



(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/)

Complications of Diabetes

Neuropathy

60-70%

Polyneuropathy, Autonomic Neuropathy, CTS, etc

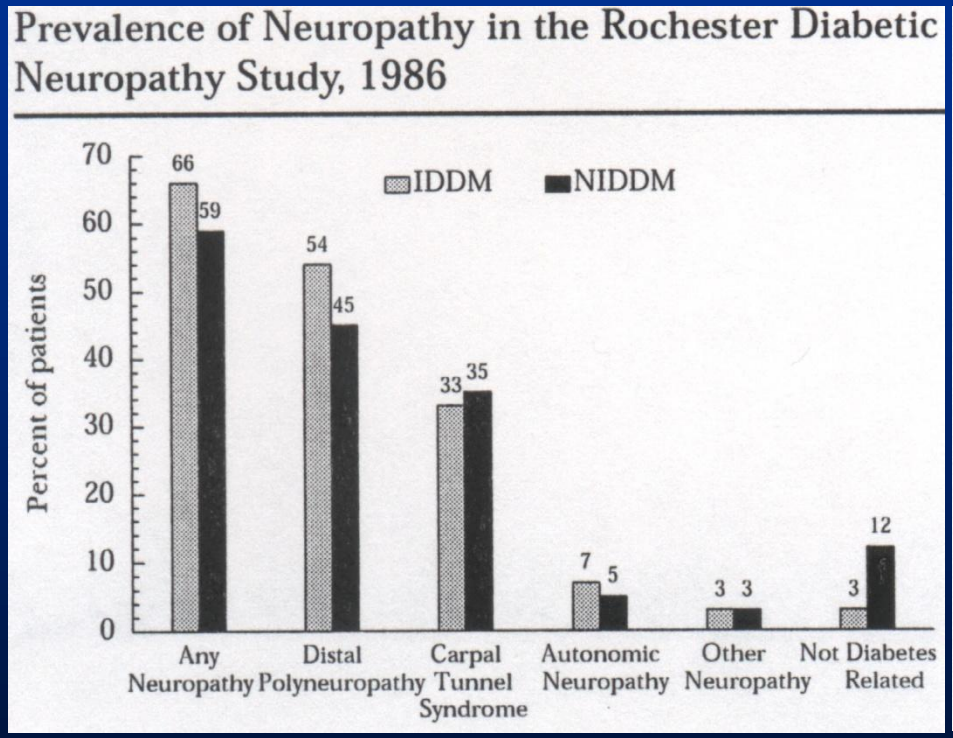
Major contributor of amputations

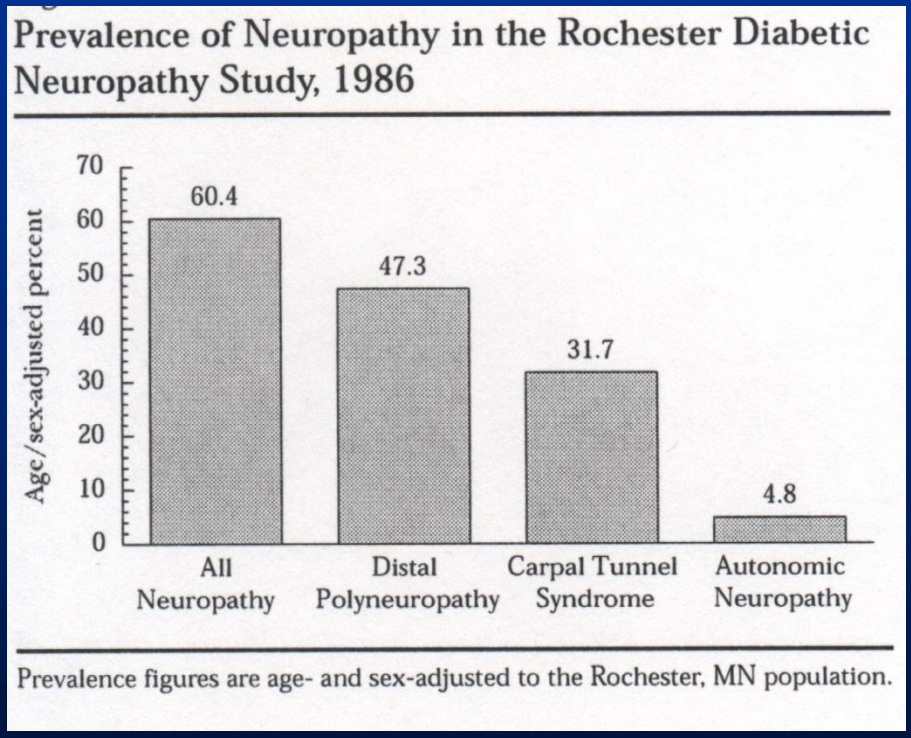
Lower Limb Amputations

>60% of non-traumatic amputations

65,700 amputations from 2006

Prevalence of Diabetic Neuropathies





(Dyck PJ et al. Neurology 1993; 43(4):817-24.)

Diabetic Neuropathies

Table 1—*Classification of diabetic neuropathy*

Generalized symmetric polyneuropathies
- Acute sensory
- Chronic sensorimotor
- Autonomic

Focal and multifocal neuropathies
- Cranial
- Truncal
- Focal limb
- Proximal motor (amyotrophy)
- Coexisting CIDP

Adapted from Thomas (4). Note: Clinicians should be alert for treatable neuropathies (CIDP, monoclonal gammopathy, vitamin B_{12} deficiency, etc.) occurring in patients with diabetes.

(Boulton et al, 2005)

Overview-Diabetic Neuropathies

- Diabetic Polyneuropathy and Autonomic Neuropathy
  - Symptoms
  - Signs
  - Complications
  - Evaluations
  - Management
  - Treatment

Diabetic Neuropathy

Risk Factors

- High blood sugars
- Coronary artery disease
- Increased triglyceride levels
- Body mass index > 24
- Smoking
- High blood pressure

Pathophysiology

- HYPERGLYCEMIA
- Cardiovascular risk factors
- Lipid alterations
- Increased polyol flux
- Accumulation of advanced glycation end products
- Oxidative stress

Diabetic Polyneuropathy (DPN)

Definition of DPN for clinical practice:

"the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes".

Diabetic Polyneuropathy

Diagnosis cannot be made without a careful clinical examination of the lower limbs, as absence of symptoms should never be assumed to indicate an absence of signs

Symptoms of DPN

- Tingling
- Burning pain
- Electrical or stabbing sensations
- Hypersensitivity
- Deep aching pain

- Weakness
- Imbalance
- Fatigue
- Falls

- Worse in feet
- Worse at night

Signs of DPN

- Distal sensory loss:
  - vibration
  - pinprick
  - temperature
  - absent or reduced ankle reflexes
- Distal weakness
  - Toes
  - Fingers

Complications of DPN

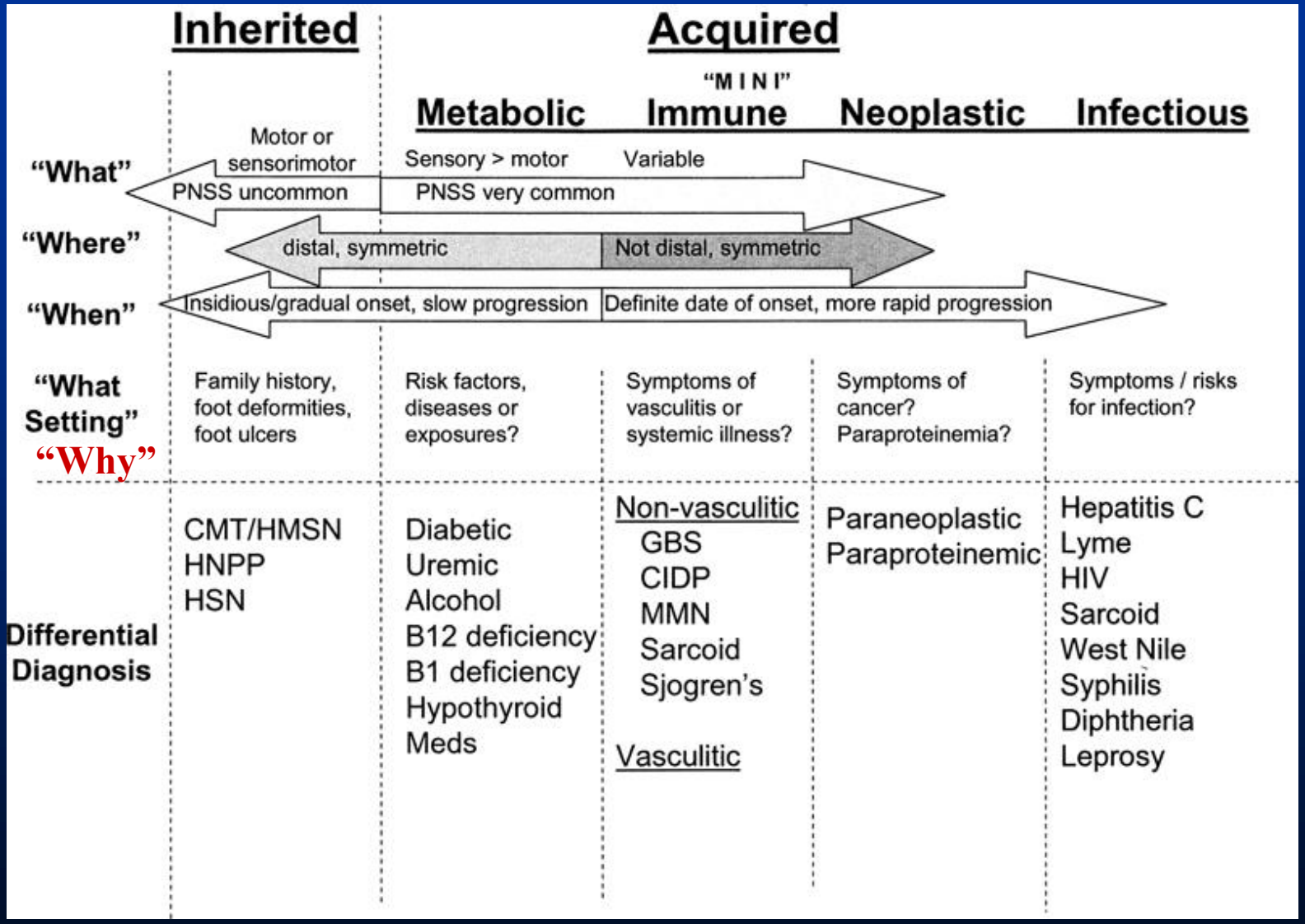
- Risk of injury due to lack of sensation
- Charcot joints
- Foot ulcers
- Amputations

DPN

- Absence of retinopathy and nephropathy
- Exclusion of other causes
- Other causes of polyneuropathy

  -Hypothyroid, Vitamin B12 deficiency, hepatitis C, HIV, medications

(Mauermann and Burns 2008)



Differential Diagnosis in Diabetic Polyneuropathy

- Small fiber neuropathy
- Cervical myelopathy
- Lumbosacral radiculopathy
- Plantar fasciitis
- Osteoarthritis

Diagnosis

- EMG
- Quantitative Sensory Testing
- Skin biopsy

- Autonomic Testing

Electromyography (EMG)

- Two part test:
  - Nerve conduction studies
  - Needle electromyography

- Establish diagnosis of polyneuropathy
- Distinguish demyelinating from axonal
- Differentiate radiculopathy, plexopathy

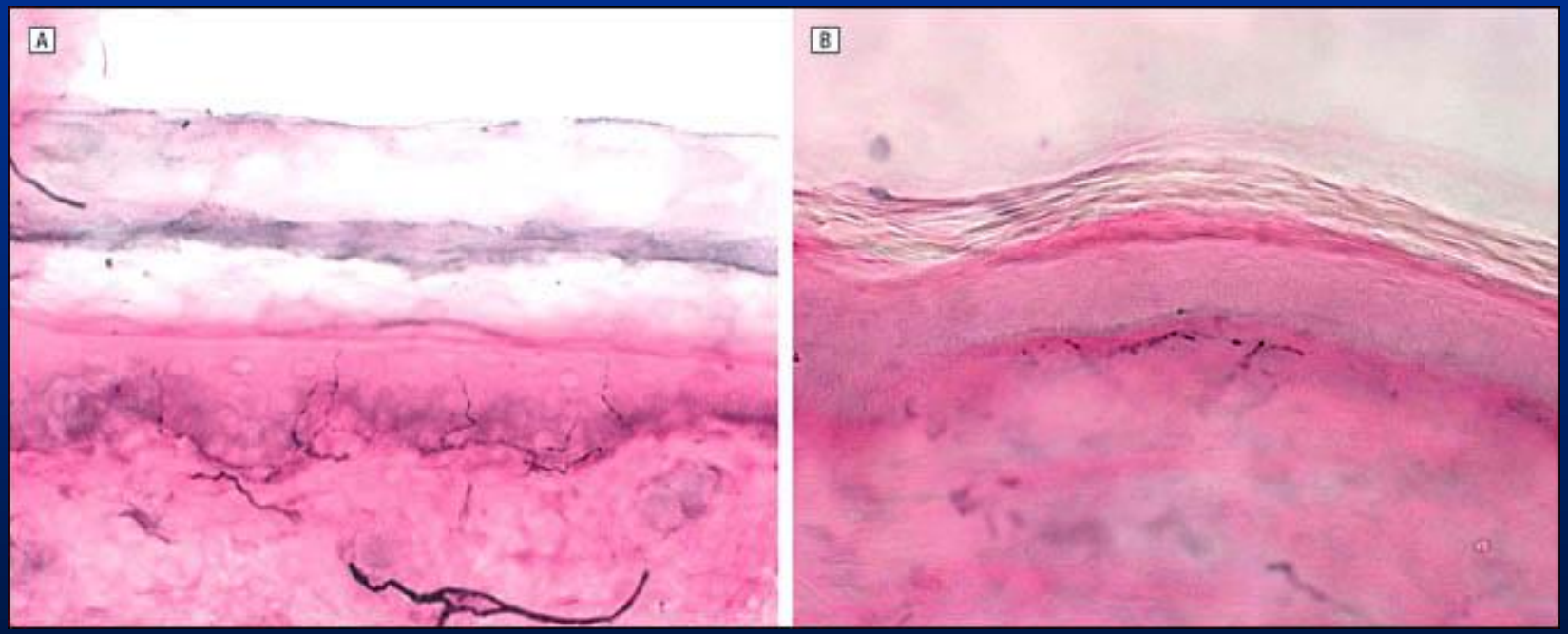
- Normal in small fiber and autonomic neuropathy

Quantitative Sensory Studies

- Quantitative outcomes in research
- Small fiber neuropathy

- Computer assisted sensory testing
  - Vibration
  - Cold
  - Heat-pain

Fixed cryosections of skin biopsy specimens from the distal part of the leg of a healthy subject (A) and patient 4 (B), who has an abnormally low epidermal nerve fiber density (immunoperoxidase stain of protein gene product 9.5 [a panaxonal marker], original magnification x400)



(Brannagan, T. H. et al. Arch Neurol 2005;62:1574-1578.)

Management

- Control of blood sugar levels
  - More frequent monitoring
  - Change in medication
  - HbA1c < 7%
- Avoidance of extreme glucose fluctuations
  - Hyperglycemia
  - Hypoglycemia
  - Nutritional education

(http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/#Nervous)

Diabetic Polyneuropathy: Management

- In general, every percentage point drop in A1C (e.g. from 8.0 to 7.0%) can reduce the risk of microvascular complications—eye, kidney, and nerve diseases—by 40 %.

Management

- Care of feet
  - Inspect feet daily (mirror)
  - Keep feet clean and moisturized
  - Foot care with podiatrist
  - Molded shoes
  - Avoid walking barefoot
  - Checking temperatures of water/sand

Management

- Rehabilitation for weakness and balance
  - Physical therapy
    - maintain strength and flexibility
    - Balance,
    - Fall avoidance
    - cane, braces, walker, motorized vehicle
  - Occupational Therapy
    - Activities of daily living

Treatment

- Analgesics (ASA, acetaminophen, NSAIDS)
- Antidepressants medications
- Anesthetic medications
- Narcotics
- Antioxidant medications (ALA 600 mg)

Table 1. Summary of recommendations

(Evidence based Guidelines: MN 2011)

	Recommended drug and dose	Not recommended
Level A	Pregabalin, 300–600 mg/day	
Level B	Gabapentin, 900–3600 mg/day	Oxcarbazepine
	Sodium valproate, 500–1200 mg/d	Lamotrigine
	Venlafaxine, 75–225 mg/day	Lacosamide
	Duloxetine, 60–120 mg/day	Clonidine
	Amitriptyline, 25–100 mg/day	Pentoxifylline
	Dextromethorphan, 400 mg/day	Mexiletine
	Morphine sulfate, titrated to 120 mg/day	Magnetic field treatment
	Tramadol, 210 mg/day	Low-intensity laser therapy
	Oxycodone, mean 37 mg/day, max. 120 mg/day	Reiki therapy
	Capsaicin, 0.075% four times per day	
	Isosorbide dinitrate spray	
	Electrical stimulation, percutaneous nerve stimulation for 3–4 weeks	

Treatment

- Prevention of secondary issues
  - Osteoporosis
  - Depression
  - Social isolation

Diabetic Autonomic Neuropathy

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Autonomic Symptoms

- Orthostatic (lightheadedness)
- Visual (blurred vision, glare, reduced night vision)
- Secretomotor (dry eyes and dry mouth)
- Gastrointestinal (satiety, diarrhea, constipation)
- Urogenital (bladder dysfunction, ED)
- Sudomotor (decreased/increased)
- Vasomotor (cold extremities)

Postural hypotension

- Fall in SBP>20 mm Hg
- Lightheadedness, dizziness, weakness, fatigue, cognitive changes, syncope
- May be exacerbated by insulin
- Worse postprandial
- Exacerbated by anemia

Diabetic Autonomic Neuropathy (DAN)

- Cardiovascular symptoms
- Unexplained tachycardia
- Orthostatic hypotension
- Poor exercise intolerance

- 2.5-50% prevalence

DAN

- Predictors:
  - Duration of diabetes
  - Glycemic control
  - Polyneuropathy/retinopathy/nephropathy

DAN

- Associated with :
  - Intraoperative cardiovascular instability
  - Silent myocardial infarction and ischemia
  - Increased mortality

(Boulton et al. Diabetes Care 2005;28(4):956-62.)

Testing for DAN

- Screening at diagnosis of type 2 DM
- 5 years after diagnosis of type 1 DM
- Severe DAN-worse prognosis

Autonomic Testing

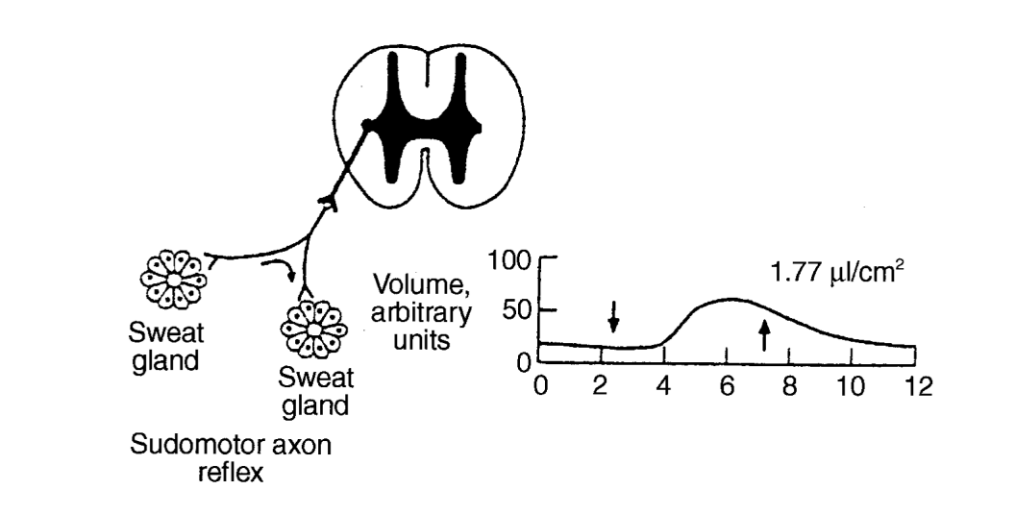
- Battery of non-invasive tests

- Sympathetic cholinergic (sudomotor)
- Parasympathetic cardiovagal
- Sympathetic adrenergic

Autonomic Testing

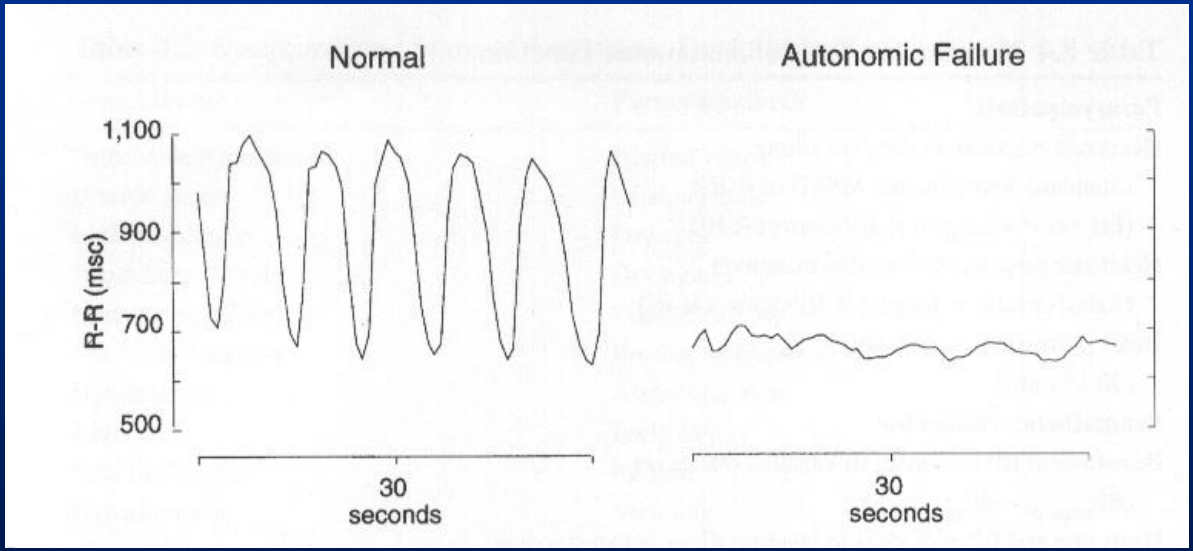
- Quantitative Sudomotor Axon Reflex Test
- Heart rate response to deep breathing
- Valsalva Maneuver (not retinopathy)
- Tilt Table

Quantitative Sudomotor Axon Reflex Test



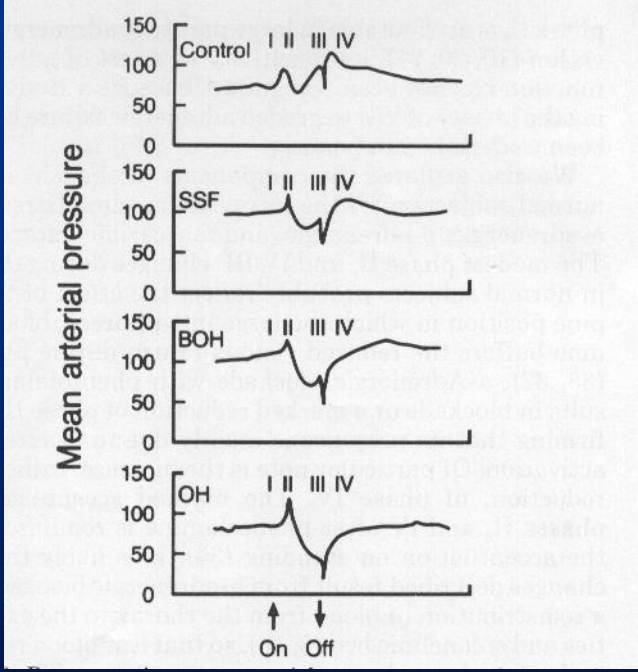
(Low et al. Ann Neurol 1983;14:573)

Heart rate response to deep breathing



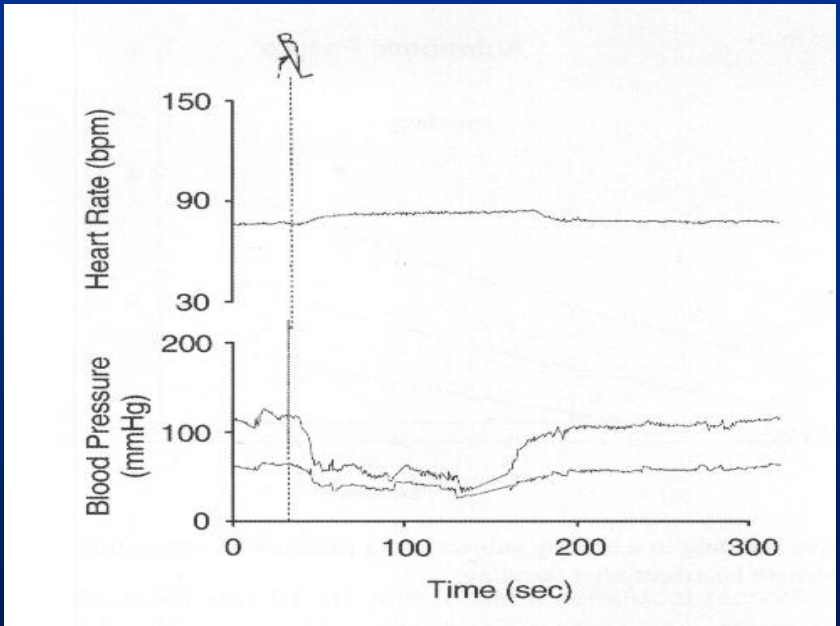
(Wang and Kaufmann. Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders. TE Bertorini ed.)

Valsalva Maneuver



(Sandroni et al. J Appl Physiol 1991;71:1563)

Tilt Table



(Wang and Kaufmann. Clinical Evaluation and Diagnostic Tests for Neuromuscular Disorders. TE Bertorini ed.)

Management

- Cardiac Evaluation
- Review medications (adverse effects)
- Avoid dehydration
- Avoid extreme temperatures

Management

- Orthostatic hypotension
  - Sit on edge of bed/dorsiflex feet
  - Fluids (8 cups/day)
  - Salt
  - 6 small meals
  - Cross legs
  - Compression stockings/Abdominal binder
  - Walker/wheelchair

Treatment

- Fludrocortisone
  - Mineralocorticoid
  - 0.1-0.4 mg/day
  - Monitor potassium
  - Supine hypertension
  - Edema

Treatment

- Midodrine
  - Alpha adrenoreceptor agonist
  - 10 mg three times daily
  - Up to every 4 hours
  - Avoid after 6 pm
  - Goosebumps (piloerection)

Questions