Diabetic Neuropathy

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Types of Neuropathies Associated with Diabetes Mellitus

- **Chronic distal sensorimotor polyneuropathy**
- Focal compression neuropathies
- Autonomic neuropathy
- Acute reversible sensorimotor polyneuropathy associated with hyperglycemia
- Insulin neuritis
- Acute cranial neuropathy (III, IV, VI, VII)
- Acute or subacute lumbosacral radiculoplexus-neuropathy (diabetic amyotrophy)
- Acute thoracic radiculopathy
- Mononeuritis multiplex
- CIDP
Epidemiology

- Diabetes is the most common cause of polyneuropathy in Western countries, though the exact prevalence is unknown
  - EURODIAB study found a prevalence of polyneuropathy of 28% in 3250 randomly selected patients with IDDM
  - Olmstead County, MN study found 55% of pts with IDDM and 45% of pts with NIDDM had polyneuropathy. However, only 15% of pts with IDDM and 13% of pts with NIDDM were symptomatic
- Estimated that patients with type 2 diabetes develop neuropathy at a rate of 6.1 per 100 person-years
Who develops neuropathy?

- Rochester Diabetic Neuropathy Study
  - 264 patients with diabetes followed in a longitudinal cohort study
  - Multivariate analysis demonstrated that duration of diabetes and glycosylated hemoglobin concentration were the most important risk factors for development of neuropathy

Pathophysiology

Axonal loss due to:
- Microvascular injury from formation of reactive oxygen species
- Sorbitol formation via action of aldolase reductase
- Protein kinase C activation
- Immune complex deposition
- Development of advanced glycation end products and impairment of normal cellular processing including axonal transport

Early Clinical Manifestations

- Distally-predominant, spontaneous positive or negative sensory symptoms
- Neuropathic pain is a typically an early clinical feature
- Small fiber involvement typically develops before large fiber, but not always
Clinical Manifestations

- On sensory examination, gradient to pin and cold, reduction in vibratory threshold and joint position sense
- On motor examination, can see early involvement of foot and toe extensors and flexors (slight wasting of extensor digitorum brevis is often the first sign)
- Absent ankle jerks
- Antalgic gait
Differential Diagnosis:

Other Causes of Polyneuropathy

- Associated with underlying medical illnesses?
  - Renal, hepatic, thyroid dysfunction, monoclonal gammopathies, amyloidosis, nutritional deficiencies, HIV, etc.

- Alcohol use?

- History of toxin exposure?
  - Arsenic, thallium, lead

- History of medication use known to lead to neuropathy?
  - Amiodarone, isoniazid, pyridoxine, chemotherapeutic agents

- Family history of neuropathy?
  - Charcot-Marie-Tooth disease
Useful Mnemonic

- I (inflammatory/immune)
- N (nutritional)
- D (diabetes)
- I (infectious)
- C (cancer)
- A (alcohol)
- T (toxic-metabolic)
- E (endocrine)
Diagnostic Workup

- **Exclusion of other causes of polyneuropathy**
  - RFTs, LFTs, TFTs, vitamin B12 level with methylmalonic acid level, SPEP and IFE, UPEP, RPR; other tests based on history and risk factors

- **Electrodiagnostic testing**
  - Not mandatory if diagnosis is clear
  - Indications include atypical features (e.g. rapid course, marked asymmetry, weakness > sensory loss, upper extremity > lower extremity involvement)

- **Autonomic testing**

- **Quantitative Sensory Testing (QST)**

- **Skin biopsy and evaluation of intra-epidermal nerve fiber (IENF) density**
  - Sensitivity for polyneuropathy 40-95%, specificity 85-97%
  - Most useful for confirming the presence of a small fiber neuropathy
Electrodiagnostic Testing

- Normal
- Demyelinating
- Axonal
Skin Biopsy

- Normal
- Reduced IENF density
Treatment

- Tight glycemic control
- Symptomatic treatment of neuropathic pain
  - Tricyclic antidepressants
  - Anticonvulsants
  - SNRIs
  - Others
- Experimental treatments
  - VEGF
  - Others
Glycemic Control

Complications

- Foot ulceration
- Restless legs syndrome
- Cramps
- High morbidity and mortality with concomitant autonomic neuropathy (due to cardiac involvement)