

Introduction to Peripheral Neuropathies and Iatrogenic Myopathies

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Peripheral Neuropathy

- The prevalence of peripheral neuropathy is approximately 10%.
- Most people complain of numbness, tingling, and pain in the distal extremities.
- In the Western world diabetes is the most common cause.

ANATOMY

- The peripheral nervous system consists of motor, sensory, and autonomic neurons that extend outside of the central nervous system.
- The large myelinated axons include motor neurons and large fiber sensory nerves that are responsible for vibration and position sense.

- The small, thinly myelinated and unmyelinated axons are responsible for nociception and autonomic function.

AN APPROACH

- The use of a systematic approach is essential to evaluate a patient with peripheral nerve disease.
- There are a multitude of lab abnormalities, hereditary and acquired disorders that can cause peripheral neuropathy.
- A shotgun approach is not appropriate.

- History
- Physical Examination
- Neurophysiological testing to characterize the nature of the underlying process.

LABORATORY

- Chemistry Panel(renal function)
- Hemogram(hgb and rbc morphology)
- Vitamin B12 and TSH
- Serum Immunofixation electrophoresis(monoclonal gammopathy)

Diabetic Neuropathies

- Diabetes is thought to be the most common cause of peripheral neuropathy in the Western world.
- Diabetes is associated with a wide spectrum of neuropathy syndromes.

DPN

- Symmetric, distal, lower limb, sensory polyneuropathy with variable degree of motor and autonomic involvement.
- It is predominantly sensory, but in severe cases distal weakness and footdrop may be present.

PATHOGENESIS

- There are three main theories to explain diabetic neuropathy:
 - Polyol Pathway Theory
 - Microvascular Theory
 - Glycosylation end-product Theory

Polyol Pathway

- Glucose is converted into sorbital via the polyol pathway.
- Ultimately there is a decrease in nitric oxide which buffers oxidative injury.
- Decreased nitric oxide, inhibits vascular relaxation, leading to chronic ischemia.

Microvascular Ischemic Changes

- Pathologic changes in diabetic nerves include:
 - capillary basement membrane thickening
 - endothelial cell hyperplasia
 - neuronal ischemia and infarction

Glycosylation End Products

- Chronic hyperglycemia produces glycating agents known as advanced glycosylation end products.
- Glycosylation products deposit within and around peripheral nerves.
- These products interfere with axonal transport causing nerve conduction slowing.

Impaired Glucose Tolerance

- Prediabetes is defined by the American Diabetes Association:
 - Fasting glucose of 100 to 125mg/dL.
 - 2-hour serum glucose between 140 and 199 mg/dL on OGTT.

- Glucose uptake in the peripheral nerves is not dependent on insulin.
- High blood glucose levels lead to high nerve glucose concentration.

- The neuropathy associated with prediabetes:
 - Symmetric
 - Distal
 - Predominantly sensory
 - Neuropathic pain is almost a universal feature

- Oral glucose tolerance testing has been shown to be:
 - More likely to detect problems with glucose handling than either fasting glucose or hemoglobin A1c.
- Singleton et al. Muscle Nerve 2001; 24:1225
- Singleton et al. Diabetic Care 2001; 24:1448

- Glycemic Control is effective treatment for neuropathy associated with diabetes and prediabetes.
- Diet and exercise counseling reduces hyperglycemia and lowers risk of progression to diabetes.

Diabetes Prevention Program Research Group. NEJM 2002; 346:393

Tuomilehto et al. NEJM 2001; 344:1343

- These studies looked at 7% reduction in weight and 150 minutes of moderate exercise performed weekly.

Neuropathic Pain

- Neuropathic pain is a multifaceted process.
- Involves degeneration and biochemical changes involving:
 - Peripheral nerve axon
 - Spinal root entry zone
 - Spinal cord
 - Brain

Neuropathic Pain

- Pain is transmitted to the spinal cord by A-fibers and C-fibers.
- A-fibers are thinly myelinated and are responsible for the initial pain.
- C-fibers are not myelinated, carry afferent signals slowly, and are thought responsible for the lingering pain.

Neuropathic Pain

- Damage to A and C fibers is what causes the sensory complaints in patients.
- Injury to these fibers are prominent in:
 - Neuropathies associated with hyperglycemia.
 - Painful neuropathies.
 - Amyloidosis.

Neuropathic Pain

- C-fiber injury leads to:
 - Hyperexcitability of the damaged nerve fibers.
 - Down regulation of potassium channels.
 - Proliferation of sodium channels.

Neuropathic Pain

- These changes cause the afferent fibers to depolarize spontaneously and respond more robustly to painful stimuli.
- This activity likely generates spontaneous sensations such as paresthesias and hyperalgesias.

Neuropathic Pain

- Several antiepileptic drugs and tricyclic antidepressants act partially by reducing sodium channel excitability to reduce neuropathic pain.

Neuropathic Pain

- Central Sensitization occurs when dorsal horn afferent fibers increase their responsiveness to synaptic inputs.
- This results from:
 - Spontaneous C-fiber activity and dorsal horn excitement.
 - C-fiber release of glutamate and substance P.
- Woolf et al. Science 2000; 288:1765

Neuropathic Pain

- Spontaneous C-fiber firing results in central sensitization, which potentiates pain perception.
- Opiates and possibly gabapentin act by reducing dorsal horn sensitivity to glutamate and inhibit central transmission of pain.

Iatrogenic Myopathy

- There are many commonly used drugs that are known to cause myopathies:
- Necrotizing:
 - Cholesterol Lowering Agents.

Inflammatory:

Corticosteroids

Drugs of Abuse:

Alcohol

HMG-Coa Reductase Inhibitors

- Statins inhibit HMG-Coa reductase, which is the controlling enzyme for cholesterol synthesis.
- Lovastatin, Simvastatin, Pravastatin, Atorvastatin, Fluvastatin, and Cerivastatin have been implicated.

HMG-Coa Reductase Inhibitors

- Signs and symptoms include:
 - Asymptomatic hyper-CK-emia
 - Myalgias
 - Proximal weakness
 - Myoglobinuria

HMG-Coa Reductase Inhibitors

- Pathogenesis of myopathy related to HMG-Coa Reductase Inhibitors is unclear.
- It is possible that statins may decrease cholesterol in muscle membranes and predispose muscle fibers to rhabdomyolysis.
- Decrease Coenzyme Q, impairing energy production.

HMG-Coa Reductase Inhibitors

- Treatment:
 - Discontinue statin medication.
 - In some cases use of immunosuppressant medication is required.

Corticosteroid Myopathy

- Any synthetic glucocorticoid can cause a myopathy.
- Prednisone at doses of 30mg/day or more is associated with increased risk.
- Women appear to have higher risk than men to develop a steroid myopathy.

Corticosteroid Myopathy

- Signs and symptoms include:
 - Proximal muscle weakness and atrophy.
 - Legs more involved than arms.
 - Sensation and reflexes are typically normal.

Corticosteroid Myopathy

- Different features:
 - CK level is normal.
 - EMG is normal, type 2 muscle fibers involved.
 - Muscle biopsy will reveal atrophy in type 2 fibers.

Corticosteroid Myopathy

- Treatment:
 - Alternate day dosing may reduce risk of weakness.
 - Reduction in the dose.
 - Exercise to prevent disuse atrophy.

Alcohol Associated Myopathy

- Several forms of toxic myopathy related to ETOH has been described:
 - Acute necrotizing myopathy.
 - Acute hypokalemic myopathy.
 - Chronic alcoholic myopathy.
 - Alcoholic cardiomyopathy.

Argov et al. Disorders of Voluntary Muscle, 5th edn. Edinburgh, Churchill-Livingstone, 1988 p981-1014

Mastaglia et al. Handbook of Clinical Neurology, Vol 18, No 62 1992 p595-622.

Victor et al. Myology 2nd edn. New York: McGraw-Hill 1994, p1697-1725.

Alcohol Associated Myopathy

- Acute necrotizing myopathy:
 - Acute muscle pain and tenderness to palpation.
 - Muscle cramping.
 - Swelling
 - Weakness
- Occur during or following an intense drinking binge.

Alcohol Associated Myopathy

- May be associated with myoglobinuria and renal failure.
- Markedly elevated CK levels during attacks.

Treatment involves supportive medical care and proper nutritional supplementation.

Alcohol Associated Myopathy

- Acute Hypokalemic Myopathy:
 - Alcohol abuse can cause hypokalemia leading to generalized muscle weakness.
 - Hypokalemia can be significant.
 - CK elevated.
 - Myopathy improves with correction of potassium.
 - Patients may exhibit proximal limb-girdle weakness, particularly in the legs.

- Chronic ETOH abuse is more often associated with causing a neuropathy.
- Your history and neurologic examination will guide your implication to muscle or nerve.