Pathology of the Peripheral Nervous System

- neuropathies generally result from njury to the axon, neuron, myelin, or their supportive tissues
- several defined clinical patterns of neuropathy can be recognized and the diagnosis of a particular disease is usually arrived at by correlating such patterns with the clinical information

BASIC HISTOLOGICAL PATTERNS

Axonopathic Pattern

- if injury to the neuron or axon is sufficiently sever, there will be rapid disintegration and death of the axon
- Histo:
  - globules of myelin accompanied by simulatneous loss of the axon
  - identical to Wallerian degeneration
- Regeneration occurs (no gliosis in PNS)
  - regenerative clusters – small groups of tiny myelinated axons
- Wallerian Degeneration – the changes occuring distally to the site of transection of a peripheral nerve or damage to a cell body

Axonal

with large fiber involvement (usually sensory-motor)

- DIABETES
- Vit deficiencies
- toxic neuropathies
- some hereditary

with small fiber involvement (heat, pain, and vegetative fibers)

- Amyloidosis
- Leprosy
- Diabetic

without selective fiber involvement

- many advanced or severe neuropathies

Myelinopathic Pattern

- denuded segment of axon
- myelin sheath starts to show irregularities, disintegration and formation of small ovoids
- end result: totally denuded segment of axon
- Remyelination
  - internodes are shorter than normal – intercalated segments
  - much thinner profile or sheath of the newly myelinated segment
- "onion bulbs" – chronic – concentric Schwann cell hyperplasia – recurring bouts of demyelination and remyelination

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DEMYELINATING NEUROPATHIES

Acquired

- Diabetes
- Autoimmune
- Gullian Barre
- Drugs
- Post-infection (hep, HIV, CMV, mycoplasma, vaccination)

Hereditary

- Charcot-Marie-Tooth (hereditary motor sensory neuropathy type I and II)
- porphyrias
- Metabolic disorders

Mixed Pattern

- simulataneous presence of demyelination and axonopathic changes which are independent of each other
- uremic neuropathy
- diabetic neuropathy

Inflammatory and Infiltrative Patterns

- inflammation or inflitrates within the nerve
- vasculitis
- leprosy
- sarcoidosis
- amyloidosis
- tumor infiltration (leukemia, lymphoma, melanoma)

Pathology of Skeletal Muscle

- Two circumstances for muscle biopsies
  1. diagnosis of systemic disease (vasculitis, sarcoidosis)
  2. neuromuscular disease workup
     - workup includes battery of enzyme histochemical reactions

MUSCULAR DYSTROPHIES (MD)

- the dystrophic pattern is characterized by intense fibrosis with thick fibrous bands
- atrophy and hypertrophy
- structural changes
- abundant fiber regeneration and degeneration
- phagocytosis

Duchenne's Dystrophy

- prototype dystrophy
- **X-Linked**
- caused by alterations in the gene that codes for a membrane protein called dystrophin localized on **Xp21**
- 1 in 10,000 males
- 1/3 arise as new mutations
- manifest by 5 years of age
- Clinical Presentation
  - weakness of proximal muscles and pelvic girdle muscles
  - **calf hypertrophy**
  - Gower's sign (because of proximal muscle weakness)
  - Require wheelchair by 10-15 years of age
  - death by 20-30
  - cardiomyopathy – abnormal or reduced dystrophin is also found in cardiac muscle
- intense fiber degeneration
- Pathology
  - fibrosis, fiber splitting, fiber size variablility, phagocytosis, internal nuclei
  - High serum CPK

Becker's Dystrophy

- similar to Duchenne's
- onset later in life
- **less severe**; longer course
- same genetic locus, different mutation – allows for decreased production of dystrophin
- increased serum CPK

Myotonic Dystrophy

- Autosomal Dominant
- distal musculature
- anticipation
- facial involvement, distal atrophy of limbs, myotonia
- frontal parietal baldness, posterior cataracts, hypoplasia of genitals w/ testicular atrophy, endocrine disturbances, cardiac involvement
- **chromosome 19, gene that encodes for myotonin protein kinase (MPK)**
- CTG repeats from generation to generation get longer
- 1000s of repeats in patients

CONGENITAL MYOPATHIES

- typical morphology

Nemaline Myopathy

- presence of intracytoplasmic rods visible by LM and seen best with the trichrome stain
- autosomal recessive
- rods made of actin filaments

Central Core Disease

- Autosomal Dominant
- fibers show a central area devoid of mitochondrial oxidative enzymes
- type I fibers predominantly involved
- **predisposes to malignant hyperpyrexia** – condition which may result in sudden rise in body temperature to extreme levels while receiveing certain anesthetic agents (avoid morphine-like agents)

METABOLIC MYOPATHIES

Mitochondrial myopathies

- abnormalities of size, cristae, or abnormal odd shaped intramitochondrial inclusions
- histologically identified by ragged-red fibers and mitochondrial inclusion w/ trichrome stain

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GLYCOGENOLYSIS

Pompe's Acid maltase deficiency

- can manifest as infant or as 70 year old
- vacuolar myopathy with storage of excessive glycogen in sarcoplasm
- cardiac involvement
- **very high CPK enzyme**

McArdle's

- exercise intolerance with myoglobinuria
- **very high CPK enzyme**
- Myophosphorylase deficiency results in excessive glycogen storage

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INFLAMMATORY MYOPATHIES

Idiopathic Inflammatory Myopathies

- polymyositis and dermatomyositis
- autoimmune
- proximal muscle weakness, dysphagia, skin rash (DM only), **elevated CPK enzyme**, pulmonary fibrosis, myocarditis, myalgias

Polymyositis

- subacute or chronic
- proximal, often painful, muscle weakness
- increased serum CPK
- adult onset

Dermatomyositis

- skin rash – heliotrope rash (upper eyelids by edema and lilac discoloration)
- adults and children
- Muscle biopsy:
  - perifascicular atrophy with chronic inflammation in the perimysium around BV
- can have an elevated CPK

DM and PM Clinical

- any age
- DM – heliotrope skin rash
- may be associated with malignancy or autoimmune
- proximal weakness
- increased CPK
- treat with steroids (to reduce inflammation)