Polyneuropathies — Duchenne Muscular Dystrophy, Limb Girdle Muscular Dystrophies, Channelopathy

This article deals with a number of polyneuropathies. It includes the myopathy junction and dystrophinopathies (Duchenne muscular dystrophy and Becker muscular dystrophy) as well as Limb-Girdle muscular dystrophies and channelopathies, mitochondrial, inflammatory, endocrine and drug induced myopathies. It runs through each disease associated with these pathologies, their etiology/pathophysiology, diagnosis including history, examination and investigation, and the treatment of the diseases where appropriate.

Definition of Polyneuropathies

Polyneuropathies are defined as disorders of peripheral and cranial nerves that are widespread and often symmetrical. They often present with both weakness and sensory loss in a “glove and stocking” fashion.

- Myopathy is a nonspecific term used to refer to disease of the skeletal muscle.
- Dystrophies are hereditary conditions which show dystrophic changes (increased connective tissue, fiber splitting) on biopsy. They are not necessarily due to defects of the dystrophin gene.
- Myositis implies an inflammatory process.
Causes of Polyneuropathies

- Immune mediated
- Metabolic
- Hereditary
- Toxic
- Infectious

Epidemiology/Etiology/Pathophysiology of Polyneuropathies

Dystrinopathies

Duchenne muscular dystrophy

This is an X linked recessive condition that is caused by a deficiency of the protein dystrophin. Dystrophin is involved in the maintenance of the cellular cytoskeleton. DMD results from a mutation in this gene resulting in a nonfunctional protein. Patients usually present between the ages of 3 and 5. The image below shows the dystrophin complex.

Becker muscular dystrophy

This has an incidence of 0.3/1,000 live male births. Also an X linked recessive condition and also caused by a mutation in the dystrophin gene. In this case the dystrophin protein has some limited function. It presents at a later age than Duchenne and is associated with a better prognosis.

Limb-girdle muscular dystrophies

These are a heterogenous group of inherited dystrophies typically inherited in an autosomal dominant/recessive pattern. Mutations can occur in a number of muscle related proteins.

Myotonic dystrophy
Myotonic dystrophy belongs to a class of disease known as the **Trinucleotide repeat expansion diseases**, which include Huntington’s disease, Friedreich ataxia, and Fragile X syndrome. Myotonic dystrophy results from a **trinucleotide expansion of CTG**. It is found on chromosome 19 and is inherited in an **autosomal dominant** pattern. It affects the Cl-channel and is thus a channelopathy.

**Other channelopathies**

These are caused by **mutations in ion channels** that control muscle contraction. All are **autosomal dominant** in their inheritance pattern. Examples include **hyperkalemic periodic paralysis** and **hypokalemic periodic paralysis**. Hyperkalemic periodic paralysis is caused by a defect in the Na+ channel whilst hypokalemic periodic paralysis is caused by a mutation in either the Na+ channel or Ca2+ channel.

**Mitochondrial myopathies**

These are a clinically and genetically heterogenous group of disorders that include mitochondrial encephalopathy with lactic acidosis and stroke like symptoms (**MELAS**), mitochondrial encephalopathy ragged red fibers (**MERRF**), progressive external ophthalmoplegia (**PEO**) and **Kearns-Sayre syndrome**.

These are caused by **mutations on the mitochondrial DNA** and as such are either maternally inherited or caused by sporadic mutation of the mitochondrial DNA.

**Inflammatory myopathies**

- **Inclusion body myositis (IBM)** is caused by the accumulation of tau aggregates not in the central nervous system. It is often termed a peripheral tauopathy.
- **Polymyositis** is an **autoimmune mediated striated muscle inflammation**.
- **Dermatomyositis** has a similar presentation to polymyositis except with involvement of the skin. It affects patients between 50 and 70, with a higher incidence in both females (2:1 female:male) and African Americans.

**Endocrine myopathies**

- **Thyrotoxic myopathy** develops due to the overproduction of thyroid hormone.
- **Hypothyroid myopathy** develops due to the underproduction of thyroid hormone.
- **Steroid myopathy** can either be endogenous or exogenous.

**Drug/toxin induced myopathies**

There are many toxins and drugs that cause myopathies – so many that it is impossible and impractical to list all of them. **HMG-CoA reductive inhibits or statins** are one group that are commonly questioned. Others to know are:

- Fluorinated glucocorticoids (dexamethasone)
- Zidovudine (AZT) - this **HIV drug** can cause a mitochondrial myopathy
- Cimetidine causes inflammatory myopathy.
Diagnosis of Polyneuropathies

Duchenne muscular dystrophy (DMD)

As a pediatric condition, parents will often come complaining that their child is clumsy or grows excessively tired easily.

These patients will have difficulty walking (and will find it even harder to work on their toes). They are usually unable to stand without using their own body to steady themselves and as such present with Gower’s sign (where patients use their own hands to push off the thighs when rising from the floor. They may also waddle.

On examination you may find pseudohypertrophy of gastrocnemius (calf) muscles.

Examine the mental state of the child as retardation is common.

A definitive diagnosis is usually made by a biopsy and negative dystrophin immunostain. Creatinine kinase will be raised (from muscle degeneration). EMG will show “polyphasic” potentials. The biopsy can also show necrotic muscle fibers.

Becker muscular dystrophy

These patients will present later than those with Duchenne muscular dystrophy. They are usually between 5 and 15. On Western blot, their dystrophin levels will appear normal (although the protein itself is abnormal) - this is in comparison to DMD, which has a significantly decreased dystrophin on Western blot.

The symptoms are similar to DMD but often milder and patients are less likely to have mental retardation and have a better prognosis (30-40 years instead of teens).

Limb-girdle muscular dystrophies

When patients present with muscular weakness in their shoulders and pelvic girdle between the ages of 10 and 20, suspect a Limb-girdle muscular dystrophy.

These autosomal dominant conditions are less severe than Beckers or DMD but are severely disabling within 25 years of onset. Patients usually will not have hypertrophy of the muscles involved and the symptoms spare ocular and bulbar muscles.

Cardiomyopathy is rarely seen.

On investigation, expect to find an elevated creatinine kinase. Biopsy and genetic
screening can provide a definitive diagnosis.

Myotonic dystrophy

This is the most common form of adult onset muscular dystrophy. It presents in two different types. Type 1 is known as Steinert’s disease whilst type 2 is known as proximal myotonic myopathy (PROMM).

In myotonic dystrophy there is marked distal weakness. Patients will have myotonic (a state of increased muscle contraction and impaired relaxation). Some develop frontal balding, cataracts and cardiac conduction defects as this is a multisystem disease.

Investigations will find a normal or mildly elevated creatinine kinase (a marker of muscle degeneration). DNA testing can be done to make a definitive diagnosis. EMG can also be performed, where myotonic discharges will be seen.

Other channelopathies

Other channelopathies will typically present with episodic weakness due to muscle ion channel defects.

Mitochondrial myopathies

These disorders are commonly associated with neurological manifestations like seizures, strokes and migraine. A muscle biopsy will show ragged-red fibers which contain accumulations of glycogen and neutral lipids.

Inflammatory myopathies

Inclusion body myositis

Patients are typically older than 50. On examination, patients often have weakness in their quads, fingers or pharyngeal muscles to begin with. Ventral muscles of the extremities are more affected than dorsal muscle groups. Around 3 % of patients become wheelchair dependent.

Image: "Polymyositis: Inflammatory infiltrates in a muscle biopsy. Holes in the muscle cell vacuoles, deposits of abnormal proteins within the cells and in filamentous inclusions (hence the name inclusion body myositis) are clearly visible in the cellular interstitial space." by Jensflorian - Own work. License: CC BY-SA
On histological investigation, ringed vacuoles and intranuclear inclusion are seen. There is no known therapy.

**Polymyositis**

This is more common in older individuals and is associated with a progressive and symmetrical proximal muscle weakness.

On investigation, these patients have an increased creatinine kinase and are positive for anti-Jo-1 antibodies. Muscle biopsy will show muscular inflammation.

**Dermatomyositis**

Can be differentiated clinically from polymyositis as dermatomyositis present with cutaneous involvement. Patients with dermatomyositis may have a heliotrope rash (violaceous periorbital rash) and the “shawl sign” (where there is a rash where a shawl would hang, around the shoulders and back). Patients can also have a dorsal rash on their hands.

Remember they will also have progressive proximal muscle weakness, as in polymyositis.

On investigation, these patients have an increased creatinine kinase and are positive for anti-Jo-1 antibodies. Muscle biopsy will show muscular inflammation.

**Endocrine myopathies**

**Thyrotoxic myopathy**

This can often be subclinical and patients may not know they have the condition. Patients usually have brisk reflexes (as they have thyrotoxicosis). The creatinine kinase is often normal on investigation.

**Hypothyroid myopathy**

Patients can present with a proximal weakness. They may complain of fatigue or muscle pain and cramping. They have relaxation of the reflexes at an advanced stage of the disease. On investigation these patients will have a raised creatinine kinase.

**Steroid myopathy**

On investigation, these patients typically have a normal creatinine kinase.

**Therapy of Polyneuropathies**

**Duchenne muscular dystrophy (DMD)**

Physical therapy can maintain self ambulation although this is an inevitability. Patients can survive around 20 years but the condition is fatal in 100% of cases.
Polymyositis/dermatomyositis

Can be responsive to **steroid treatment**. A high dose of **corticosteroids** can be given. Then decrease the dose until a working maintenance dose is given. Other drugs like **Azathioprine** and **methotrexate** also have some effect.

References


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