# DISEASES OF SKELETAL SYSTEM

## Parts of a Muscle

<table>
<thead>
<tr>
<th><strong>Muscle Fiber Type</strong></th>
<th><strong>Type 1</strong></th>
<th><strong>Type 2</strong></th>
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<td><strong>Action</strong></td>
<td>Sustained force</td>
<td>Sudden movements</td>
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<td><strong>Strength</strong></td>
<td>Weight-bearing</td>
<td>Purposeful motion</td>
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<tr>
<td><strong>Enzyme content</strong></td>
<td>NADH-TR dark staining ATPase at pH 4.2, dark staining ATPase at pH 9.4, light staining</td>
<td>NADH light staining ATPase at pH 4.2, light staining ATPase at pH 9.4, dark staining</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td>Abundant</td>
<td>Scant</td>
</tr>
<tr>
<td><strong>Glycogen</strong></td>
<td>Scant</td>
<td>Abundant</td>
</tr>
<tr>
<td><strong>Ultrastructure</strong></td>
<td>Many mitochondria Wide Z-band</td>
<td>Few mitochondria Narrow-Z-band</td>
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<tr>
<td><strong>Physiology</strong></td>
<td>Slow-twitch</td>
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<tr>
<td><strong>Color</strong></td>
<td>Red</td>
<td>White</td>
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<tr>
<td><strong>Prototype</strong></td>
<td>Soleus (pigeon)</td>
<td>Pectoral (pigeon)</td>
</tr>
</tbody>
</table>
Normal electron microscopy

Dark A-bands

Light I-bands

Z-band is present in the middle of the light band

Thin filaments are attached at the Z-band
General Reactions of the Motor Unit

REATIONS OF THE MUSCLE FIBER

Segmental necrosis, Vacuolation, Regeneration, Fiber hypertrophy

MUSCULAR DYSTROPHIES

“A heterogeneous group of inherited disorders of muscle, often beginning in childhood, that lead to progressive weakness and muscle wasting.”

In advanced cases muscle fibers undergo degeneration and are replaced by fibro fatty tissue and collagen. (Histologically)
This feature distinguishes dystrophies from myopathies which also present with muscle weakness

X-Linked Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD) & Becker Muscular Dystrophy (BMD)
DMD is the most severe and common form of muscular dystrophy
1 per 3500 live male births
DMD becomes clinically manifest by the age of 5 years
It leads to wheelchair dependence by 10 to 12 years of age & thereafter progresses relentlessly.
BMD involves the same genetic locus.
It is less common and much less severe than DMD.

**DYSTROPHIN**

Morphology:
Histopathologic abnormalities common to DMD and BMD include (1) variation in fiber size (diameter) due to the presence of both small and enlarged fibers, sometimes with fiber splitting;
(2) increased numbers of internalized nuclei (beyond the normal range of 3% to 5%);
(3) degeneration, necrosis, and phagocytosis of muscle fibers;
(4) regeneration of muscle fibers; &
(5) proliferation of endomysial connective tissue.
Clinical Course:

- Boys with DMD are normal at birth,
- pseudohypertrophy
- Heart pathologic changes:
  - Develop heart failure or arrhythmias
- cognitive impairment is a component of the disease and is sometimes severe to be considered a form of mental retardation
- Serum creatine kinase is elevated during the first decade of life but returns to normal as muscle mass decreases.
- Death

Boys with BMD:

- develop symptoms at a later age
- The onset occurs in later childhood or in adolescence,
- slower and more variable rate of progression
- considerable variation between pedigrees
- Many patients have a nearly normal life span.
- Cardiac disease is frequently seen in these patients.

Other Muscular Dystrophies:

- less common forms of muscular dystrophy
- share many features of DMD and BMD
- have distinct clinical and pathologic characteristics.

Some of these muscular dystrophies affect specific muscle groups, and the diagnosis is based largely on the pattern of muscle weakness.

Limb girdle muscular dystrophies.
Several autosomal muscular dystrophies, however, affect the proximal musculature of the trunk and limbs, similar to the X-linked muscular dystrophies.

Disease and Inheritance:
Fascioscapulohumeral muscular dystrophy:
autosomal dominant

Gene and Locus:
Type 1A-deletion of variable number of 3.3-kilobase subunits of a tandemly arranged repeat (D4Z4) on 4q35
Type 1B (FSHMD1B)-locus unknown

**Clinical Findings:**
Variable age at onset (most commonly 10-30 years);
weakness of muscles of face, neck, and shoulder girdle

**Pathologic Findings:**
Dystrophic myopathy,
often associated with inflammatory infiltrates in muscle

**Disease and Inheritance:**
Oculopharyngeal muscular dystrophy;
autosomal dominant

**Gene and Locus:**
Poly(A)-binding protein-2 (PABP2) gene; 14q11.2-q13

**Clinical Findings:**
Onset in mid-adult life;
ptosis and weakness of extraocular muscles
difficulty in swallowing

**Pathologic Findings:**
Dystrophic myopathy, but often including rimmed vacuoles in type 1 fibers

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**Disease and Inheritance:**
Emery-Dreifuss muscular dystrophy; X-linked

**Gene and Locus:**
Emerin (EMD1) gene; Xq28

**Clinical Findings:**
Variable onset (most commonly 10-20 years); prominent contractures, especially of elbows and ankles

**Pathologic Findings:**
Mild myopathic changes; absent emerin by immunohistochemistry

**Disease and Inheritance:**
Congenital muscular dystrophies; autosomal recessive (also called muscular dystrophy, congenital, subtypes MDC1A, MDC1B, MDC1C)

**Gene and Locus:**
Type 1A (merosin-deficient type)-laminin α2 (merosin) gene; 6q22-q23
Type 1B-locus at 1q42; gene unknown
Type 1C; fukutin-related protein gene; 19q13.3

**Clinical Findings:**
Neonatal hypotonia, respiratory insufficiency, delayed motor milestones

**Pathologic Findings:**
Variable fiber size and extensive endomysial fibrosis

**Disease and Inheritance:**
Congenital muscular dystrophy with CNS malformations (Fukuyama type);

**Gene and Locus:**
autosomal recessiveFukutin; 9q31

**Clinical Findings:**
Neonatal hypotonia and mental retardation

**Pathologic Findings:**
Variable muscle fiber size and endomysial fibrosis;
CNS malformations such as polymicrogyria

**Disease and Inheritance:**
Congenital muscular dystrophy with CNS and ocular malformations (Walker-Warburg type)

**Gene and Locus:**
Protein O-mannosyl transferases (POMT1, 9q34.1; POMT2, 14q24.3)

**Clinical Findings:**
Neonatal hypotonia and mental retardation with cerebral and ocular malformations

**Pathologic Findings:**
Variable muscle fiber size and endomysial fibrosis;
CNS and ocular malformations
Myotonic Dystrophy

Pathogenesis:
Inherited as: autosomal dominant trait associated with a CTG trinucleotide repeat expansion on chromosome 19q13.2-q13.3.

Morphology:
- variation in fiber size.
- conspicuous chains.
- ring fiber:

Clinical Course
- presents in late childhood
- the abnormalities in gait
- Atrophy of muscles of the face and ptosis ensue
- Cataracts
- Other associated abnormalities
- Dementia has been reported in some cases.

ION CHANNEL MYOPATHIES (CHANNELOPATHIES)
A group of familial diseases featuring myotonia, relapsing episodes of hypotonic paralysis (induced by vigorous exercise, cold, or a high-carbohydrate meal), or both. (SCN4A), which regulates the entry of sodium into muscle during contraction. The gene for hypokalemic periodic paralysis encodes a voltage-gated L-type calcium channel.
CONGENITAL MYOPATHIES

The congenital myopathies are a group of disorders defined largely on the basis of the pathologic findings within muscle. Most of these conditions share common clinical features:
onset in early life
nonprogressive or slowly progressive course
proximal or generalized muscle weakness
hypotonia.
"floppy infants" arthrogryposis

Disease and Inheritance:
Central-core disease;
autosomal dominant
Gene and Locus:
Ryanodine receptor-1 (RYR1) gene; 19q13.1

Clinical Findings:
Early-onset hypotonia and weakness; "floppy infant"; associated skeletal deformities; may develop malignant hyperthermia

Pathologic Findings:
Cytoplasmic cores are lightly eosinophilic and distinct from surrounding sarcoplasm; found only in type 1 fibers, which usually predominate, best seen on NADH-TR stain
CONGENITAL MYOPATHIES

**Disease:**
Myotubular (centronuclear) myopathy

**Inheritance, Gene, Locus and Clinical Findings:**
- XL- myotubularin (MTM1) gene; Xq28
  - Severe congenital hypotonia, "floppy infant"; poor prognosis
- AD- dynamin-2 (and others) DNM2 gene; 19p13.2
  - Childhood or young-adult weakness; slowly progressive weakness
- AR- amphiphysin-2 (BIN1) gene; 2q14
  - Childhood to adolescent presentation; severe weakness and hypotonia with survival into early adulthood

**Pathologic Findings:**
Abundance of centrally located nuclei involving the majority of muscle fibers; central nuclei are usually confined to type 1 fibers, which are small in diameter, but can occur in both fiber types

**Muscle Biopsy from an Infant:**
Centronuclear Myopathy
Oil-red-O stain

Metabolic: Inherited – Mitochondrial
MELAS Syndrome
Mitochondrial myopathy, encephalomyopathy, lactic acidosis, and stroke-like episodes

Mitochondrial Disorders
Electron Microscopy
• point mutations in mtDNA.
• Mutations in genes encoded by nuclear DNA:
  • deletions or duplications of mtDNA.
• Kearns-Sayre syndrome

Noninfectious Inflammatory Myopathies

“a heterogeneous group of disorders that are most likely immune mediated and are characterized by injury and inflammation of skeletal muscle.”
• Three relatively distinct disorders:
  • dermatomyositis,
  • polymyositis, &
  • inclusion body myositis,
These may occur
  • as an isolated myopathy or
  • as one component of an immune-mediated systemic disease, particularly systemic sclerosis
• Dermatomyositis
  • inflammatory disorder of the skin as well as skeletal muscle.
  • skin rash that may accompany or precede the onset of muscle disease.
• Grotton lesions.
• Muscle weakness
• Extramuscular manifestations
• Risk of developing visceral cancers
• Juvenile dermatomyositis:
Polymyositis

symmetric proximal muscle involvement, similar to that seen in dermatomyositis.
lack of cutaneous involvement and its occurrence mainly in adults.
inflammatory involvement of heart, lungs, and blood vessels

Inclusion Body Myositis

• begins with the involvement of distal muscles,
  ▪ extensors of the knee (quadriceps) &
  ▪ flexors of the wrists and fingers.
• the weakness may be asymmetric.
• insidiously developing disorder
• affects individuals over the age of 50 years.
• Most cases are sporadic, but familial cases have been recognized as "inclusion body myopathy"

• Etiology and Pathogenesis; Inclusion Body Myositis

• Hereditary forms (similar morphology)
• autosomal recessive form is caused by mutations in the GNE gene (encoding UDP-\(^N\)-acetylglucosamine 2-epimerase/\(^N\)-acetylmannosamine kinase),
• Autosomal dominant form is caused by mutations in the gene encoding myosin heavy chain lia

• Possible relationship to aging?
• Intracellular deposits of β-amyloid protein, amyloid β-pleated sheet fibrils, and hyperphosphorylated tau protein, features shared with Alzheimer disease.

• Immunologic?
• As in polymyositis, CD8+ cytotoxic T cells are found in the muscle,
• but in contrast to the other two forms of myositis, immunosuppressive therapy is not beneficial

**Dermatomyositis**

**Polymyositis**

*Longitudinal paraffin-embedded section*
Lymphocytic inflammation

**Diagnosis:**
- Clinical symptoms
- Electromyography
- Mixed neurogenic and myopathic changes on EMG
- Elevated serum creatinine kinase &
- Biopsy

Imunosuppressive therapy is beneficial in adult and juvenile dermatomyositis and in polymyositis but not in inclusion-body myositis

**Ethanol Myopathy**

Renal failure.
Clinical acute
On histologic examination
Thyrotoxic Myopathy

- an acute or chronic proximal muscle weakness
- that may precede the onset of other signs of thyroid dysfunction.
- Exophthalmic ophthalmoplegia is characterized by swelling of the eyelids, edema of the conjunctiva, and diplopia.
- In hypothyroidism there may be cramping or aching of muscles, and movements and reflexes are slowed.
- Findings include:
  - fiber atrophy,
  - an increased number of internal nuclei,
  - glycogen aggregates, and, occasionally, deposition of mucopolysaccharides in the connective tissue

In thyrotoxic myopathy, myofiber necrosis, regeneration, and interstitial lymphocytosis.

In chronic thyrotoxic myopathy, there may be only slight variability of muscle fiber size, mitochondrial hypertrophy, and focal myofibril degeneration; fatty infiltration of muscle is seen in severe cases. Exophthalmic ophthalmoplegia is limited to the extraocular muscles, which may be edematous and enlarged.

DISEASES OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Myasthenia gravis is a muscle disease caused by immune-mediated loss of acetylcholine receptor. It has a prevalence of about 30 in 100,000 persons. When arising before age 40 years (women), but it occurs equally in both sexes in older patients. Thymic hyperplasia (65%) & thymoma (15%) patients. Analysis of neuromuscular transmission:

a decrease in the number of muscle acetylcholine receptors (AChRs), & circulating antibodies to the AChR

The disease can be passively transferred to animals with serum from affected individuals.
DISEASES OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis:
Pathogenesis:
Autoantibodies against the AChR lead to loss of functional AChRs at the neuromuscular junction by
(1) fixing complement and causing direct injury to the postsynaptic membrane,
(2) increasing the internalization and degradation of the receptors,
(3) inhibiting binding of acetylcholine.

Lambert-Eaton Myasthenic Syndrome

• Lambert-Eaton myasthenic syndrome is a disease of the neuromuscular junction that is distinct from myasthenia gravis
• It is usually a paraneoplastic process, most commonly with small-cell carcinoma of the lung (60% of cases), but can occur in the absence of underlying malignant disease.
• Proximal muscle weakness and autonomic dysfunction.
• No clinical improvement is produced by anticholinesterase agents,
• Electrophysiologic studies show evidence of enhanced neurotransmission with repetitive stimulation.

Spinal Muscular Atrophy (Infantile Motor Neuron Disease)
Genetics

All forms of SMA are associated with
- mutations affecting survival motor neuron 1 (SMN1),
- a gene on chromosome 5
- that is required for motor neuron survival.
- This region of chromosome 5 also contains variable numbers of copies of a second highly homologous gene, SMN2.
- Homozygous deletions of SMN1 (or less commonly, intragenic mutations) cause SMA.
- The number of copies of the homologous SMN2 modifies the clinical phenotype, with more copies being associated with milder neurologic phenotype.

Spinal Muscular Atrophy (Infantile Motor Neuron Disease)

Genetics

SMN genes expressed in all tissues, so why mutations or deletions of these genes cause only neuronal loss is not clear. It is postulated that the SMN protein is critical for normal axonal transport and integrity of neuromuscular junctions, and thus promotes survival of motor neurons.

Werdiing-Hoffman Disease
(Spinal Muscular Atrophy Type I)

large numbers of atrophic fibers
panfascicular atrophy. scattered large fibers that are two to four times normal size

Clinical Course

The most common form of SMA, Werdnig-Hoffmann disease (SMA type 1), has its onset at birth or within the first 4 months of life with severe hypotonia (lack of muscle tone and "floppiness"). It usually leads to death within the first 3 years of life. The other two forms (SMA 2 and SMA 3) present at later ages, either in early childhood (between 3 and 15 months of age in SMA 2) or in later childhood (after 2 years of age in SMA 3). Those with SMA 2 usually die in childhood after age 4, whereas those with SMA 3 often survive into adulthood.

The end