MUSCULOSKELETAL DISORDERS

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Table 27-1 Muscle fiber types

	Type I	Type II
Action	Sustained force	Fast movement
Activity type	Aerobic exercise	Anaerobic exercise
Power produced	Low	High
Resistance to fatigue	High	Low
Lipid content	High	Low
Glycogen content	Low	High
Energy metabolism	Low glycolytic capacity, high oxidative capacity	High glycolytic capacity, low oxidative capacity
Mitochondrial density	High	Low
Enzyme activity	NADH-TR, dark staining ATPase at pH 4.3, dark staining ATPase at pH 9.4, light staining	NADH-TR, light staining ATPase at pH 4.3, light staining ATPase at pH 9.4, dark staining
Myosin heavy chain gene expressed	*MYH7*	*MYH2*, *MYH4*, *MYH1*
Color	Red (high myoglobin content)	Pale red / tan (low myoglobin content)
Prototype	Soleus (pigeon)	Pectoral (pigeon)

ATPase, Adenosine triphosphatase; NADH-TR, nicotinamide adenine dinucleotide, reduced form, tetrazolium reductase.

Muscle fiber types

	Type I	Type II
Action	**Sustained force**	**Sudden movements**
Strength	**Weight bearing**	**Purposeful motion**
Lipids	**Abundant**	**Scant**
Glycogen	**Scant**	**Abundant**
Ultrastructure	**Many mitochondria Wide Z-band**	**Few mitochondria Narrow Z-band**
Physiology	**Slow twitch Slow oxidative metabolism Red muscle**	**Fast twitch Fast oxidative glycolytic (IIa, red muscle) and fast glycolytic metabolism (IIb, white muscle)**

Skeletal muscle atrophy

- Fiber type grouping and groups of atrophic fibers are seen in neurogenic disease.
- Muscle fiber type is determined by the innervating motor neuron and can switch if the innervating motor neuron changes from one type to the other.
- Following denervation, myofibers undergo atrophy, often assuming a flattened, angulated shape.
- Re-innervation restores fiber size and shape, but may make a denervated myofiber part of a different motor unit and that may lead to a switch in fiber type. (fiber type grouping)

Skeletal muscle atrophy

- Segmental myofiber degeneration and regeneration is seen when only part of a myofiber undergoes necrosis.
- Damaged areas are phagocytized by macrophages
- Fusion of activated satellite cells to damaged myofibers is an important step for regeneration.
- Eventually, new sarcomeres are generated and the continuity of the original myofiber is restored.
- Regenerating myofibers have enlarged nuclei with prominent nucleoli that are often randomly distributed in the cytoplasm, instead of being in their normal subsarcolemmal location.
- Basophilic

Skeletal muscle atrophy

- In chronic disease there is endomysial fibrosis (collagen deposition), dropout of myofibers, and fatty replacement.
- Perifascicular atrophy is seen in dermatomyositis.
- Type II fiber atrophy with sparing of type I fibers is seen with prolonged corticosteroid therapy or disuse.

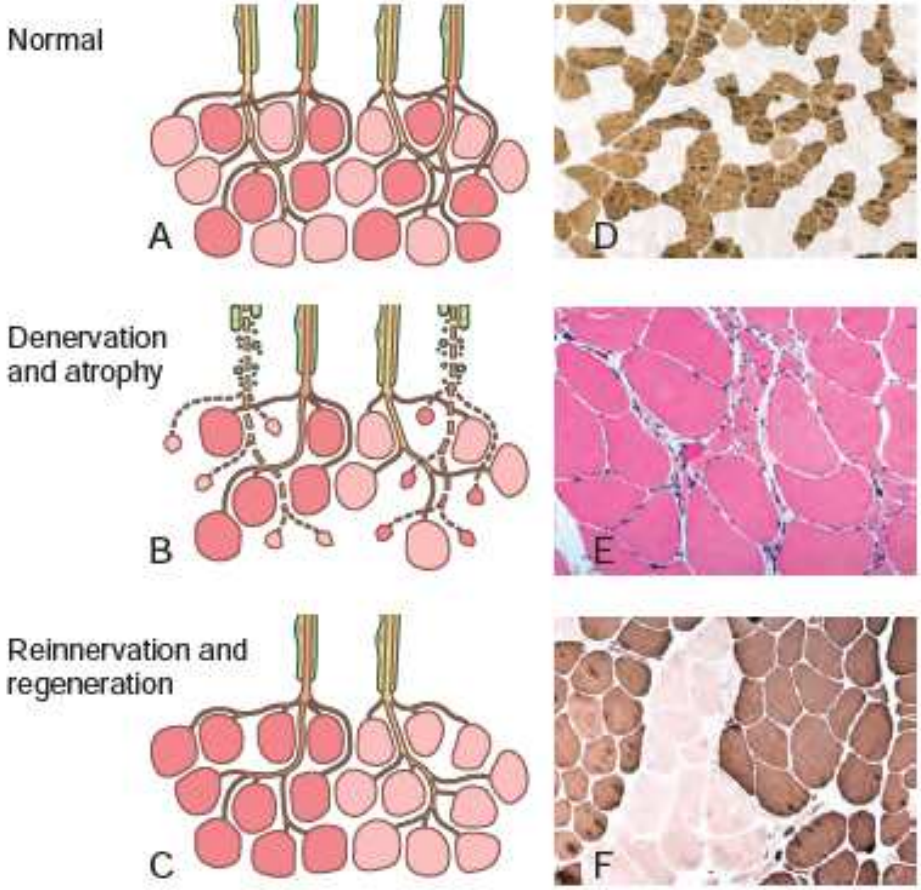


Figure 27-7 **A,** This diagrammatic representation of four normal motor units shows a normal checkerboard type admixture of light and dark stained fibers of opposite type. **B,** Damage to innervating axons leads to loss of trophic input and atrophy of myofibers. **C,** Reinnervation of myofibers can lead to a switch in fiber type and segregation of fibers of like type. As illustrated here, reinnervation is also often associated with an increase in motor unit size, with more myofibers innervated by an individual axon. **D,** Normal muscle has a checkerboard type distribution of type I (light) and type II (dark) fibers on this ATPase reaction (pH9.4) corresponding to findings in **A. E,** Clustered flattened "angulated" atrophic fibers (*group atrophy*) are a typical finding associated with disrupted innervation. **F,** With ongoing denervation and reinnervation, large clusters of fibers appear that all share the same fiber type (*type grouping*).

Kennedy disease

- Distal limb amyotrophy and bulbar signs, such as atrophy and fasciculations of the tongue and dysphagia, associated with degeneration of lower motor neurons in the spinal cord and brainstem.
- An expanded repeat occurs in the first exon of the androgen receptor, and results in androgen insensitivity, gynecomastia, testicular atrophy, and oligospermia.
- AR gene at Xq12

Spinal muscular atrophy

- After cystic fibrosis, is the most common lethal autosomal recessive disease.
- 1 in 6000 live births
- Type 0 evident in the womb.
- Move little in the womb; born with contractures
- Hypotonic
- Type I (Werdnig-Hoffman)
- Presents within few months after birth
- Most severe form as well as most common form
- May present as “floppy infant”
- Cannot sit without assistance
- Cannot control head movements

Spinal muscular atrophy

- Progressive weakness and hypotonia of proximal musculature
- Dysphagia
- Respiratory difficulty
- Short life spans
- Type II (Dulbowitz disease)
- Presents within 6-12 months after birth
- Sit without support
- Involuntary tremors in fingers
- Scoliosis
- Respiratory muscle weakness
- May survive into their early twenties

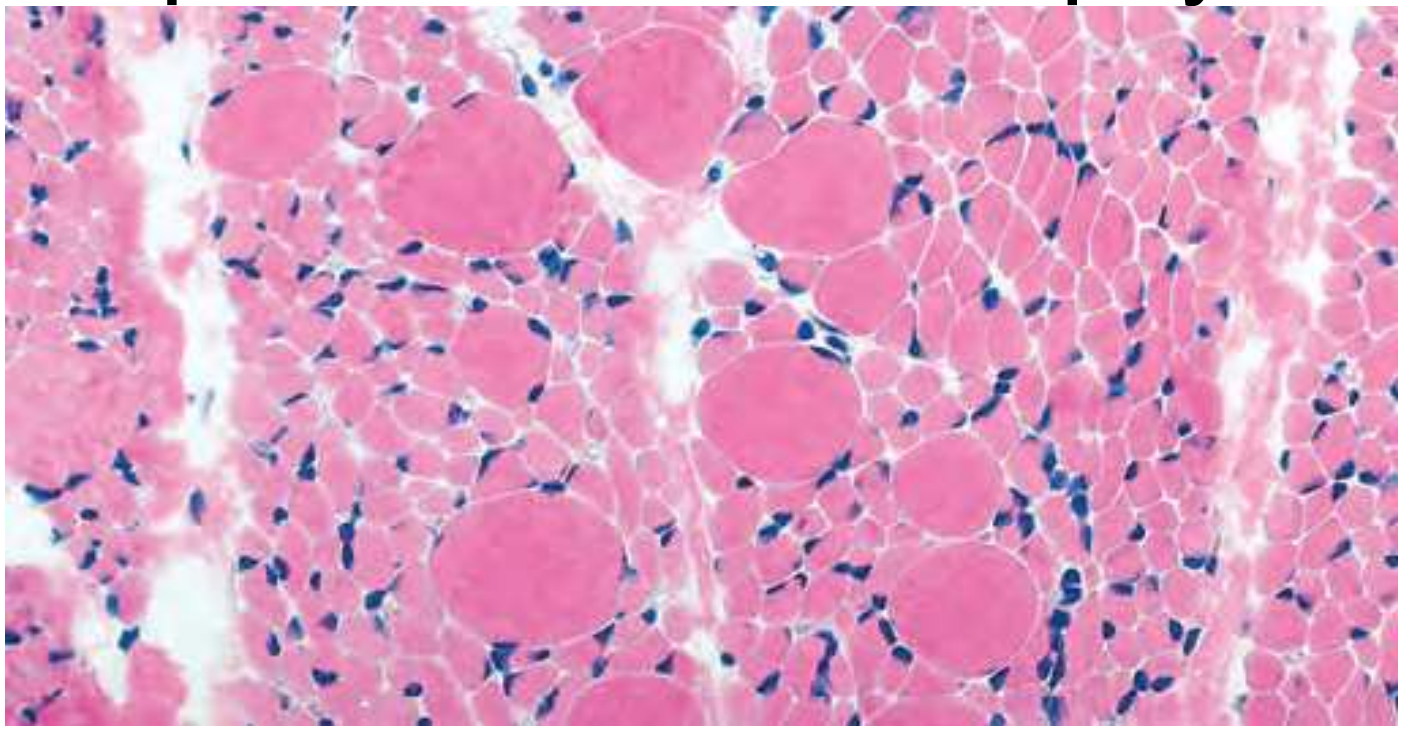
Spinal muscular atrophy

- Type III (Kugelberg-Welander)
- Early childhood
- Progressive weakness and hypotonia of proximal musculature
- Normal life spans
- Type IV
- Early adulthood
- Progressive weakness and hypotonia of proximal musculature
- Normal life spans

Spinal muscular atrophy

- Histopathology:
- Loss of neurons in the anterior horn.
- Hypertrophied type I muscle fibers. (Denervation atrophy).
- No inflammation.
- Molecular changes:
- Homologous loss of function mutation in the survival motor neuron locus (SMN1 at 5q11.2-13.3)
- Amplification of SMN2 at 5q13.2 modifies presentation
- Process pre-RNA (splicing)
- Involved in axon transport

Spinal muscular atrophy



Spinal muscular atrophy with only rare hypertrophied myofibers admixed with numerous atrophic rounded myofibers. The larger fibers are those that are innervated and have undergone compensatory hypertrophy.

Pytel, P, Anthony, DC, “Peripheral nerves and skeletal muscle,” in Kumar, V, Abbas, AK, Aster, JC, (eds), Robbins and Cotran Pathologic Basis of Disease (9th ed.), Elsevier. Philadelphia. (2015) Fig. 27-13 Accessed 10/25/2019

Dystrophy or myopathy

- Both are a heterogeneous group of inherited disorders characterized by progressive muscle weakness and wasting.
- Dystrophies lack dystrophin
- Myotonic dystrophy alone affects intrafusal fibers of muscle spindles.
- May see ring fibers.
- Myopathies contain intracellular inclusions
- Usually Type I fibers affected.

Dystrophy or myopathy

- Dystrophies
- At the interface between the intracellular contractile apparatus and the extracellular connective tissue.
- There is variation in fiber size
- Increased numbers of internalized nuclei
- Degenerative necrosis and regeneration of muscle fibers
- Endomysial connective tissue proliferation
- Replacement by fat.
- .

Dystrophy

- Dystrophies lack dystrophin
- Interface between the intracellular contractile apparatus and the extracellular connective tissue.
- Permit Ca^{2+} influx, leading to myofiber death
- C-terminus interacts with nitric oxide synthetase
- Segmental myofiber degeneration and regeneration associated with an admixture of atrophic myofibers
- Myophagocytosis
- Increased numbers of internalized nuclei
- Endomysial connective tissue proliferation
- Replacement by fat.

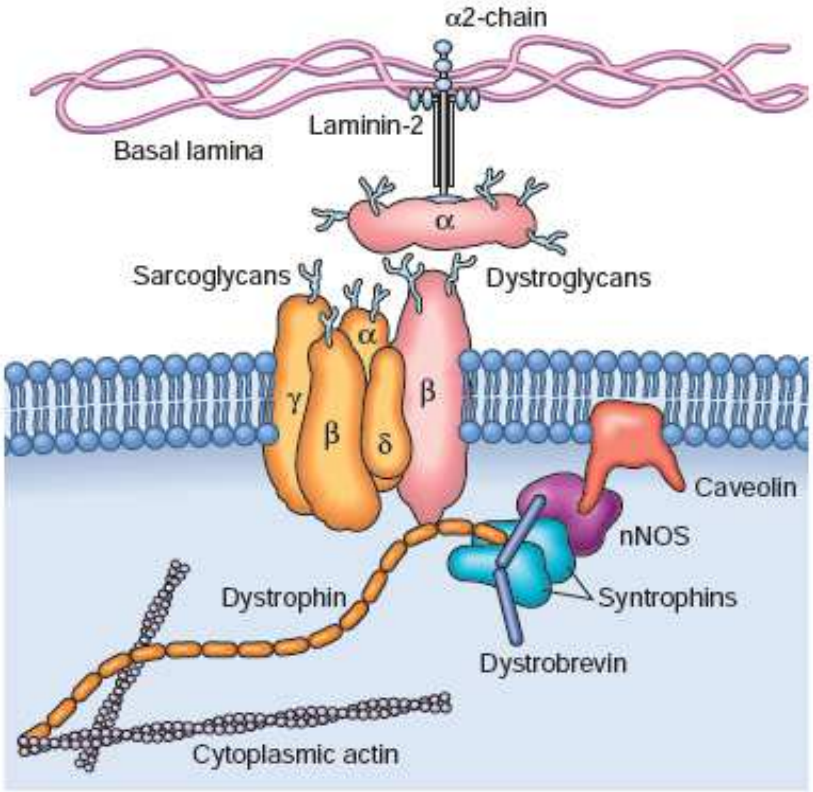
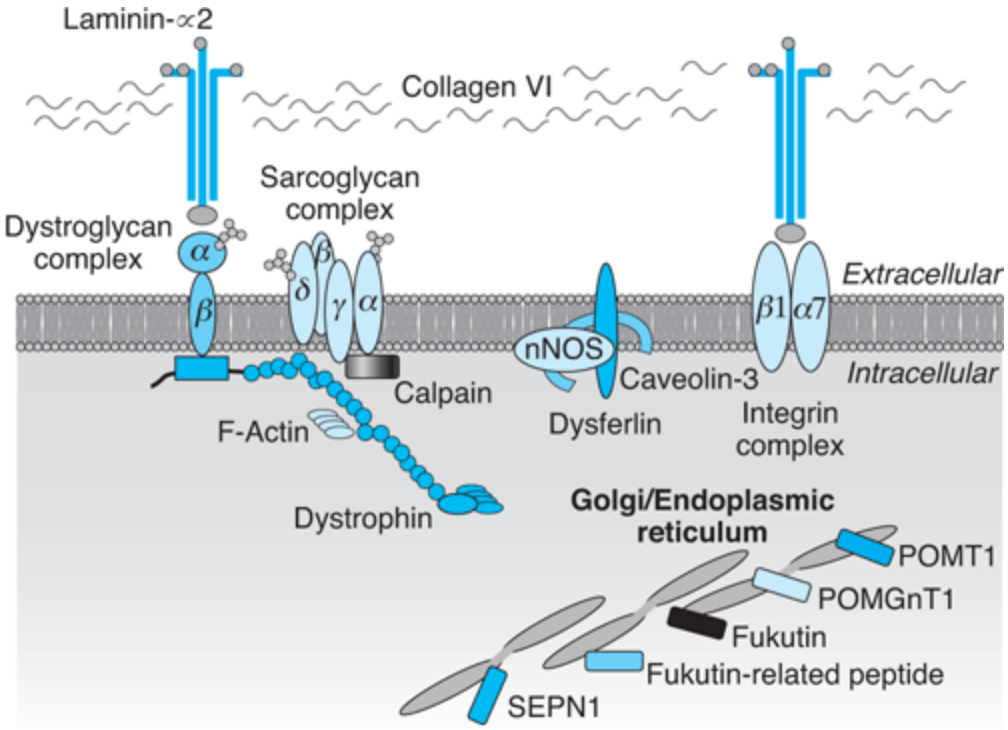


Figure 27-10 Relationship between the cell membrane (sarcolemma) and the sarcolemmal associated proteins. Dystrophin, an intracellular protein, forms an interface between the cytoskeletal proteins and a group of transmembrane proteins, the dystroglycans and the sarcoglycans. These transmembrane proteins have interactions with the extracellular matrix, including the laminin proteins. Dystrophin also interacts with dystrobrevin and the syntrophins, which form a link with neuronal type nitric oxide synthetase (nNOS) and caveolin. Mutations in dystrophin are associated with the X-linked muscular dystrophies; mutations in caveolin and the sarcoglycan proteins with the limb-girdle muscular dystrophies, which can be autosomal dominant or recessive disorders; and mutations in the α_2-laminin (merosin) with autosomal recessive congenital muscular dystrophy.

Dystrophin-glycoprotein complex



Source: Ropper AH, Samuels MA: *Adams & Victor's Principles of Neurology 9th Edition*: http://www.accessmedicine.com

Fig. 50-1 Accessed 07/01/2010

Muscular dystrophy

- Duchene muscular dystrophy
- Begins in pelvic girdle, extends to shoulder girdle.
- Large calf muscle with weakness is characteristic (pseudo-hypertrophy).
- May also see enlargement of deltoid and gluteal muscles.
- Cardiomyopathy
- Onset age 2
- Peak function as measured by 6 minute walk is at 7-8 years of age; stable until 26 years of age

In the early stages, DMD affects the shoulder and upper arm muscles and the muscles of the hips and thighs. These weaknesses lead to difficulty in rising from the floor, climbing stairs, maintaining balance and raising the arms.

Muscular dystrophy

- Becker muscular dystrophy
- Milder form with altered dystrophin.
- Does not show pseudo-hypertrophy of deltoid and gluteal muscles
- Onset age 12.
- Death often at age 45.

Muscular dystrophy

- DMD gene at Xp21
- Largest known human gene
- Encodes dystrophin.
- On cytoplasmic side of membrane, over the Z-band, binds cellular F-actin and dystroglycan (in extracellular matrix).
- Force of contraction transferred to myocyte.
- Usually absent entirely in Duchene muscular dystrophy.

NATURAL HISTORY OF DMD

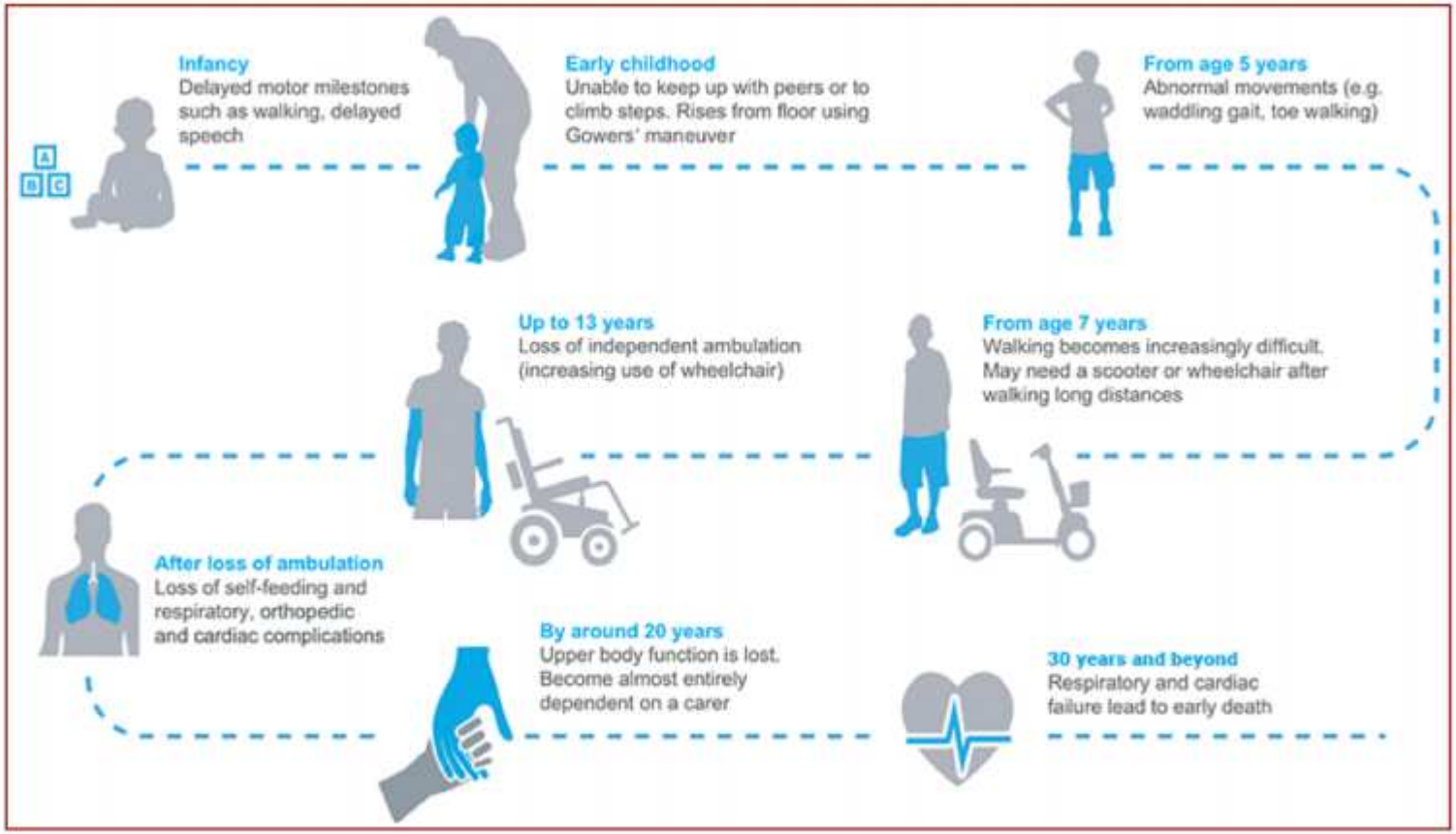


Figure from Duchenne and You, https://duchenneandyou.com/overview/; adapted from Birnkrant DJ, et al. *Lancet Neurol.* 2018;17:445-455; Bushby K, et al. *Lancet Neurol.* 2010;9:177-189; Goemans N, Buyse G. *Curr Treat Options Neurol.* 2014;16:287; Sussman M. *J Am Acad Orthop Surg.* 2002;10:138-51.

FUNCTIONAL ASSESSMENTS USED IN DMD

Study	Description	Reference in DMD
6 Minute Walk Distance (6MWD)	Distance walked in 6 minutes	Mercuri E, et al. *Neuromuscul Disord.* 2016;26(9):576-83.
North Star Ambulatory Assessment (NSAA)	17 items to assess motor function such as: standing, walking, rise from floor, hop, stand on heels, 4-stair step, lie to sit, and lifting head	Muntoni F et al. *PLoS One.* 2019;14:e0221097.
Performance of Upper Limb (PUL) 2.0	Assessment of motor function of upper limbs including: shoulder flexion, hands to mouth, moving weights on table, tearing paper, tracing path, picking up coins	Pane M, et al. 2018. *PLoS One.* Jun 20;13(6):e0199223.
Pulmonary Function Testing (PFT)	Lung function including FVC%, PEF%	Mayer OH, et al. *Pediatr Pulmonol.* 2015 May;50(5):487-94.

Muscular dystrophy

- Beginning at age 10, there is a 6% yearly decline in forced vital capacity (FVC) of lung.
- Mean age of death 25-30 years of age.
- Antisense oligonucleotides to gene hotspots exons 43-55 exist, but only restore dystrophin to 1% levels after one year of continuous use.

Muscular dystrophy

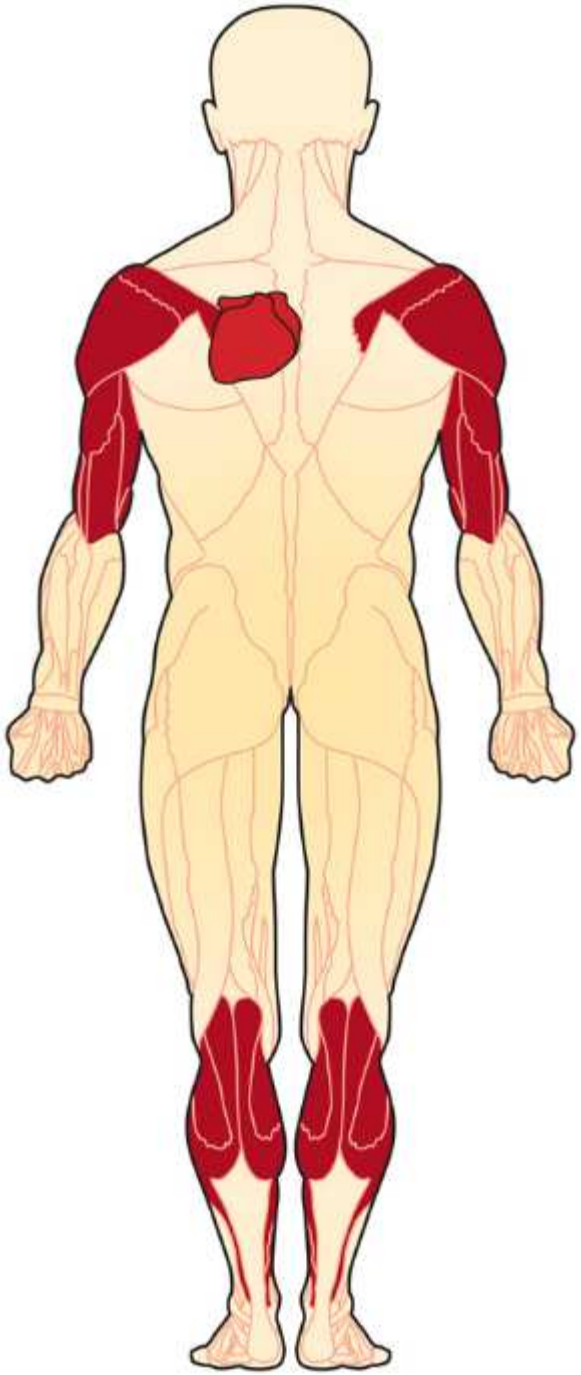
- New therapies involve employing an adenoviral vector (virus shorn of E1 and E2A proteins) to insert one CRISPR-associated endonuclease and a single-guide RNA complementary to the target genomic sequence to enable defective DMD alleles to produce micro-dystrophin.
- Off-target editing and immunogenicity are limiting
- Eteplirsen, goldirsen, vitolarsen approved drugs for exon 53 mutation
- Casimersin approved for exon 45 mutation

Muscular dystrophy

- Limb-girdle muscular dystrophy
- Onset in adolescence; pelvic girdle affected
- Autosomal dominant (type I) or recessive (type 2); dystophin gene normal; sarcoglycan abnormality
- Facio-scapulo-humeral muscular dystrophy
- Onset in adolescence
- Face, shoulder, pelvic girdle affected
- Autosomal recessive
- Dystophin gene normal
- Deletion of tandemly arranged D4Z4 repeat at 4q35

Muscular dystrophy

- Emery-Dreyfuss muscular dystrophy
- Presents by age 10
- Humeroperoneal weakness
- Cardiomyopathy
- Early contractures of Achilles tendon, spine, and elbows
- EMD gene at Xq28 (emerin)
- Affects nuclear envelope
- LMNA gene at 1q22 (laminin)
- Scaffolding proteins



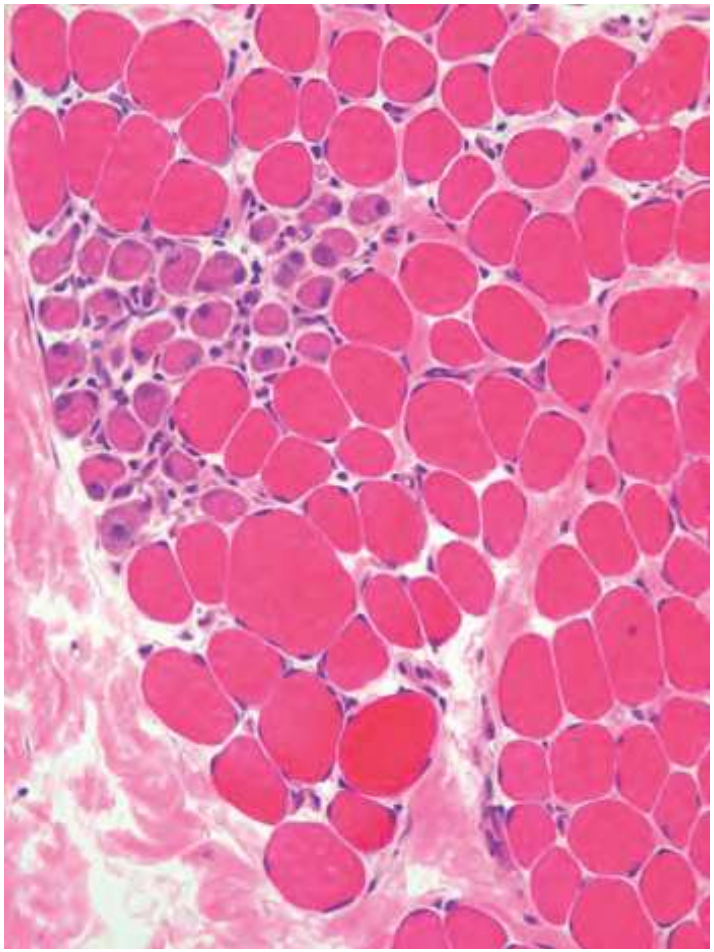
Myotonic dystrophy

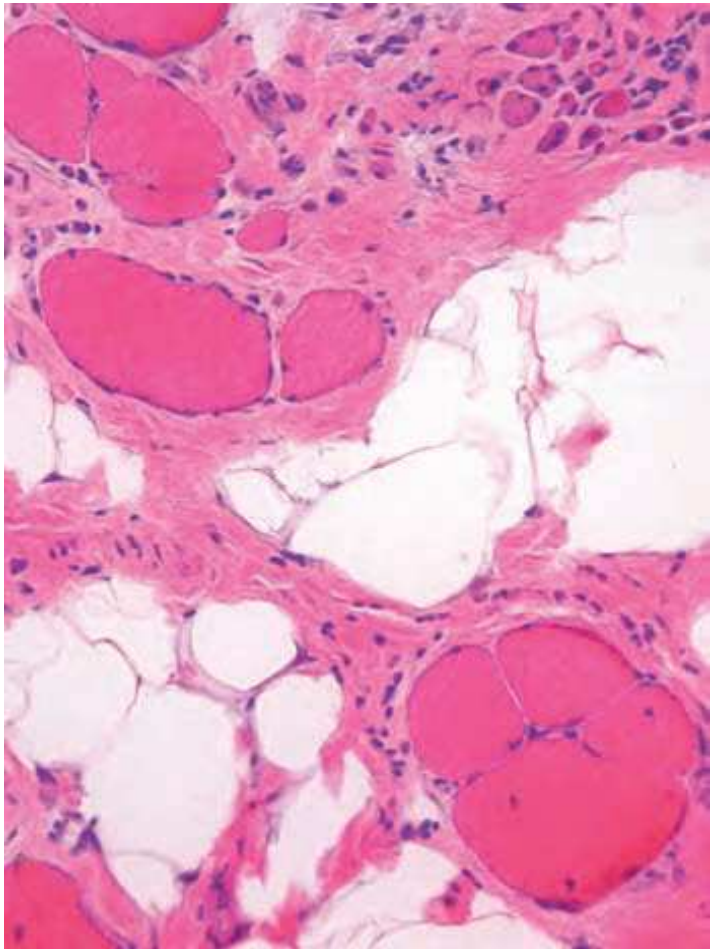
- Most common adult form of muscular dystrophy.
- Head muscles, shoulder girdle, arms, foot dorsiflexors affected.
- Myotonia.
- Stiffness, unable to relax muscle.
- An inverted “V” shape of the upper lip is characteristic of the congenital form of the disorder (and is seen in infants).
- May also see cataracts.
- May require a pacemaker in later life.

Myotonic dystrophy

- Autosomal dominant disorder.
- Excessive CTG repeats on 19q13.2-3 (affects DMPK, a kinase)
- DMPK appears to bind and sequester muscleblindlike-1, leading to misplicing of other RNA transcripts, including the transcript for a chloride channel (CLC1)
- Atrophy of Type I and hypertrophy of Type II fibers.
- Ring fibers common.
- Necrosis and regeneration not prominent

Muscular Dystrophy
Early and Late changes





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Congenital muscular dystrophy

- Classic without distinguishing features
- Rigid spine syndrome
- Spinal muscles atrophy and contractures develop
- SEPN1 mutation at 1p36.11 (selenoprotein)
- Ullrich congenital muscular dystrophy (UCMD)
- Hypotonia, proximal contractures and distal hyperextensibility
- COL6A1-3 mutations at 21q22.3

Congenital muscular dystrophy

- LMN2A mutation at 6q22.3 (merosin)
- A morphologic hallmark of these dystrophies is mismatched expression of normally co-localized matrix proteins perlecan (basement membrane extracellular matrix) and collagen VI.

Congenital muscular dystrophy

- Dystroglycanopathy
- Walker-Warburg syndrome
- Rare to survive beyond age 3
- Hypotonia
- Cobblestone lissencephaly and hydrocephaly
- At least 6 mutations affect posttranslational modification of alpha-dystroglycan by O-linked glycosylation.
- Alpha-dystroglycan expression is important for CNS and eye development. Affect neuronal migration.

Congenital muscular dystrophy

- Fukuyama congenital muscular dystrophy
- Second most common muscular dystrophy in Japan
- Hypotonia
- Ptosis
- Cobblestone lissencephaly and hydrocephalus
- Contractures develop over time
- Rare to survive beyond adolescence
- FKTN gene mutation at 9q31.2
- Posttranslational modification of alpha-dystroglycan in Golgi

Ion channel myopathies

- Associated with myotonia and relapsing hypotonic paralysis.
- Precipitated by cold, large carbohydrate intake, or vigorous exercise.
- Autosomal dominant
- Elevated K^+ associated with mutated Na^+ channel (SCN4A at 17q23) myotonia or periodic paralysis
- Diminished K^+ associated with mutated voltage gated L-type Ca^{2+} channel (RYR1 gene at 19q31)
- Rynodine receptor 1 associated with malignant hyperthermia as well as neonatal hypotonia (Central core disease)
- CCL1 KCNJ2 CACNA1S

Ion channel myopathies

- CCL1 gene at 17q12
- Inflammatory cytokine
- Microglial chemotaxis
- KCNJ2 gene at 17q24.3
- Inward rectifying potassium channel
- Andersen-Tawil syndrome (periodic paralysis)
- CACNA1S gene at 1q32.1
- Calcium channel interacts with RYR1 channel
- 70% of cases of hypokalemic periodic paralysis
- Malignant hyperthermia

Table 27-2 Congenital myopathies

Disease and Inheritance	Gene and Locus	Clinical Findings	Pathologic Findings
Central-core disease; autosomal dominant	Ryanodine receptor-1 (*RYR1*) gene; 19q13.1	Early-onset hypotonia and weakness; "floppy infant"; associated skeletal abnormalities like scoliosis, hip dislocation, or foot deformities; some RYR1 mutations cause central core disease, some malignant hyperthermia, and some both	Cytoplasmic cores represent demarcated central zones in which the normal arrangement of sarcomeres is disrupted and mitochondria are decreased in number
Nemaline myopathy (NEM)	AD NEM1—α-tropomyosin 3 (*TPM3*) gene; 1q22–q23 AR NEM2—nebulin (*NEB*) gene; 2q22 AR NEM3—α-actin-1 (*ACTA*) gene; 1q42 AR NEM4—tropomyosin-2 (*TPM2*) gene; 19p13.2–p13.1 AR NEM5—troponin T1 (*TNNT1*) gene; 19q13.4 AR NEM7—coffilin-2 (*CFL2*) gene; 14q12	Childhood weakness; some with more severe weakness, hypotonia at birth ("floppy infant")	Aggregates of spindle-shaped particles *(nemaline rods)*; occur predominantly in type 1 fibers; derived from Z-band material (α-actinin) and best seen on modified Gomori stain or by electron microscopy
Centronuclear myopathy	XL—myotubularin (*MTM1*) gene; Xq28 AD—dynamin-2 (and others) *DNM2* gene; 19p13.2 AR—amphiphysin-2(*BIN1*) gene; 2q14)	Severe congenital hypotonia, "floppy infant" and poor prognosis in X-linked form ("myotubular myopathy") Childhood onset or young adult onset with other variants with weakness and hypotonia	Many fibers contain nuclei in the geometric center of the myofiber; central nuclei are more common in type 1 fibers, which are small in diameter, but can occur in both fiber types
Congenital fiber type disproportion	Selenoprotein 1 *(SEPN1)* gene; 1p36.11 Alpha-actin-1 *(ACTA1)* gene; 1q42.13 Tropomyosin 3 *(TPM3)* gene; 1q21.3	Hypotonia, weakness, failure to thrive, facial and resp. weakness, contractures Wide phenotypic spectrum Mutations in SEPN1 are also associated with protein aggregate myopathy and rigid spine muscular dystrophy; mutations in ACTA1 are also associated with nemaline myopathy and protein aggregate myopathy; mutations in TPM3 are also associated with nemaline myopathy	Predominance and atrophy of type I fibers (not specific)

AD, Autosomal dominant; AR, autosomal recessive; XL, X-linked.

Nemaline myopathy I

- Neonatal hypotonia
- Autosomal dominant
- TPM3 gene at 1q22-23
- Slow muscle α-tropomyosin 3 deficient
- Slow twitch fiber contraction impaired
- Muscles involved with posture
- Nemaline rods occur in Type I fibers
- Best seen on GMS stain (or EM)
- Contain actin, actin and tropomyosin

Inherited myopathies

- Nemaline myopathy II
- Autosomal recessive
- Present at birth or early childhood
- Delayed motor development
- 50% of cases
- NEB gene at 2q22.3
- Nebulin protein required for sarcomere contraction

Nemaline myopathy III

- Autosomal recessive
- 15-25% of cases
- Mild type
- Onset age 12
- Gluteal and anterolateral thigh involved
- Scapuloperoneal type
- Onset infancy to third decade
- “Scapular winging” prominent
- Also involves distal musculature
- Die of respiratory failure by 40’s
- ACTA gene at 1q42
- α-actin accumulates

Nemaline myopathy

- NEM IV
- TPM2 gene at 19p13.1-2
- β-tropomyosin unable to bind actin and myosin
- NEM V
- Presents in infancy
- Pennsylvania Amish families
- TNNT1 gene at 19q13.42
- Troponin cannot bind tropomyosin
- Die of respiratory failure by age 2
- NEM VII
- CFL2 gene at 14q13.1
- Cofillin bind F-and G-actin in actin rods

Centronuclear (myotubular) myopathy

- Neonatal Hypotonia
- Facial muscle weakness
- Ophthalmoplegia (not nuclear)
- Autosomal recessive
- Childhood
- Slowly progressive
- DNM2 gene at19p32
- Gain of function leads to excess dynamin and inability of contracted muscle to relax
- Survival into childhood if BIN gene at 2q14
- Amphiphysin loss impairs endocytosis
- Abundance of centrally located nuclei in type I fibers

Centronuclear (myotubular) myopathy

- X-linked recessive
- Severe
- Poor prognosis
- MTM1 on Xq28
- Myotubularin loss impairs myotubulin structure

Myasthenia gravis

- Associated with loss of acetylcholine receptors and the presence of antibodies to those receptors.
- 35% of the cases are associated with hyperplasia of the thymus
- 10%, thymoma.
- Myasthenia gravis first affects extra-ocular muscles (ptosis, diplopia) and then progresses to generalized muscle weakness.
- Worsens as the day progresses
- Nerve conduction falls with repetitive stimulation.
- Improves with anticholinesterase.

Myasthenia gravis

- Neuromuscular end-plate dysfunction.
- Antibodies to acetylcholine receptor
- Improvement of ptosis following rest is indicative of myasthenia gravis (positive likelihood ratio, LR+, 53; LR- , 0.01).
- Disuse atrophy of type II fibers

Lambert-Eaton syndrome

- 60% associated with small cell carcinoma of the lung.
- Characterized by proximal muscle weakness with associated autonomic dysfunction.
- Ptosis, diplopia, and weakness improve during day
- Nerve conduction improves with repetitive firing.
- It does not improve with anticholinesterase.
- Neuromuscular end-plate dysfunction.

Acquired myopathies

- Inflammatory myopathies
- Polymyositis, dermatomyositis, Churg-Strauss
- Drug induced
- Alcohol, cocaine, statins, corticosteroids

Toxic myopathy

- Chloroquine and hydrochloroquine
- Interfere with lysosomal function
- The muscle tissue shows myopathic changes including vacuolation that predominantly affects type I fibers.
- Ultrastructural studies identify aggregates of whorled, lamellar membranous structures, including curvilinear bodies.
- Ethyl alcohol (binge drinking) as well as cocaine use may be associated with rhabdomyolosis

Endocrine myopathies

- Thyroid myopathy involves proximal musculature.
- Thyrotoxic disease is associated with extraophthalmic ophthalmoplegia.
- Thyroid myopathy principally affects males (4:1).
- Fiber atrophy with an increased number of abnormally localized nuclei, glycogen aggregates, and (occasionally) deposition of mucopolysaccharides in connective tissue.
- Steroid myopathy
- Type II fiber atrophy with sparing of type I fibers

Fat metabolic disorders

- Carnitine palmitoyltransferase (CPT) deficiency.
- Most common disorder of lipid metabolism to induce muscle damage with exercise or fasting.
- Hypoketotic hypoglycemia
- CPT deficiency types I (at 11q13.3) and II (at 1p32.3).
- Symmetrical, proximal, progressive.
- Autosomal recessive.
- Impairs transport of free fatty acids into mitochondria

Carbohydrate metabolic disorder

- McArdle's disease
- There is a deficiency of muscle glycogen phosphorylase.
- Type V Glycogen Storage Disorder affecting Type IIb fibers.
- Autosomal recessive.
- Painful muscle cramps and unusual fatigue on exercise (rise of inorganic phosphate.)
- There is a fall in pH in the cell that inhibits phospho-fructokinase-1 as well as inhibits the release of Ca^{2+} from the sarcoplasmic reticulum.
- Lactate levels do not rise.
- May see rhabdomyolysis

Carbohydrate metabolic disorder

- Pompe's disease
- Classic infantile onset
- Hypotonia, myopathy, hepatomegaly, cardiomyopathy
- Rare to survive past age 1
- Non-classic infantile onset
- Presents by age 1
- Delayed motor skills
- Weakness of trunk, leg, respiratory muscles
- Cardiomegaly
- Live until early childhood

Carbohydrate metabolic disorder

- Late onset
- Presents in late childhood
- Weakness of trunk, leg, respiratory muscles
- GAA gene at 17q25.3 (acid maltase or α-glucosidase)
- Lysozome unable to break down glycogen efficiently

Carbohydrate metabolic disorder

- Glycogen storage disease type VII
- Infantile form associated with hypotonia, myopathy, and cardiomyopathy.
- Rarely live past 1 year of age
- Classic form presents in childhood
- Exercise induce rhabdomyolysis
- Late onset disease presents with myopathy
- Hemolytic form not associated with myopathy
- PFKM at 12q13.11
- Phosphofructokinase deficiency
- Unable to breakdown glycogen

Mitochondrial disease

- Myoclonic encephalopathy with lactic acidosis and stroke-like syndrome (MELAS)
- Presents in childhood
- Myoclonus
- Myopathy
- Red ragged muscle fibers noted on biopsy
- Epilepsy
- Spasticity, ataxia, and dementia develop
- X-linked
- MT-NK gene (tRNA)
- Exertional myoglobiuria

Mitochondrial disease

- Infantile X-linked cardioskeletal myopathy (Barth syndrome)
- Dilated cardiomyopathy
- Skeletal myopathy (hypotonia)
- Males have neutropenia
- TAZ gene at Xq28 (taffazin deficiency impairs addition of linoleic acid to cardiolipin)
- Mitochondrial structure impaired
- Increased 3-methylgutaconic acid in urine
- Ragged red fibers with increased numbers of mitochondria, some with paracrystalline inclusions.

Leigh syndrome

- Infants
- Hypotonia and dystonia
- Psychomotor regression
- Ophthalmoparesis
- Optic atrophy
- Hypertrophic cardiomyopathy
- CSF lactate increased
- Death within 1-2 years

Leigh syndrome

- Multifocal regions of destruction of brain tissue associated with a spongiform appearance and proliferation of blood vessels.
- Brainstem nuclei, thalamus, and hypothalamus are typically involved, usually in a symmetric manner

Leigh syndrome

- 33% of cases involve NADH-ubiquinone oxidoreductase
- Transfer electrons from NADH to CoQ10
- Transfer H+ across membrane
- Mutations in pyruvate dehydrogenase genes affect CoQ10 production
- 25% of cases involve MT-ATP6 gene at base pairs 8,527 to 9,207 (X-linked)
- ATP generation
- 15% of cases involve SURF1 gene at 9q34.2 (cytochrome c oxidase)
- Mitochondrial respiratory chain and protein synthesis defects.

Kerns-Sayre syndrome

- Onset before age 13.
- Chronic progressive ophthalmoplegia
- High grade heart block
- Retinal pigmentary degeneration (“salt and pepper retina”)
- Ptosis
- Ataxia
- Proximal myopathy
- Ragged red muscle fibers
- 4997 nucleotides lost in mitochondrial DNA
- Oxidative phosphorylation impaired
- Cerebral folic acid levels diminished

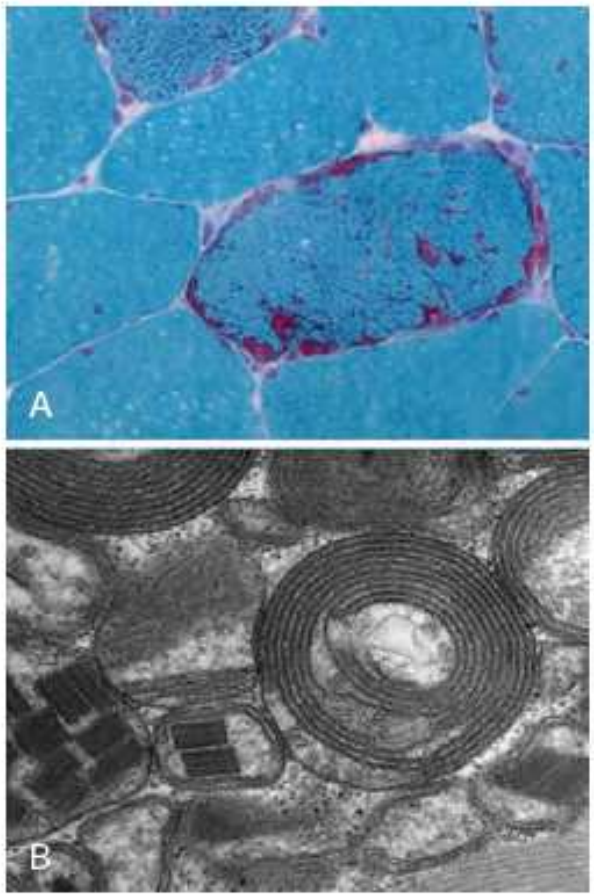
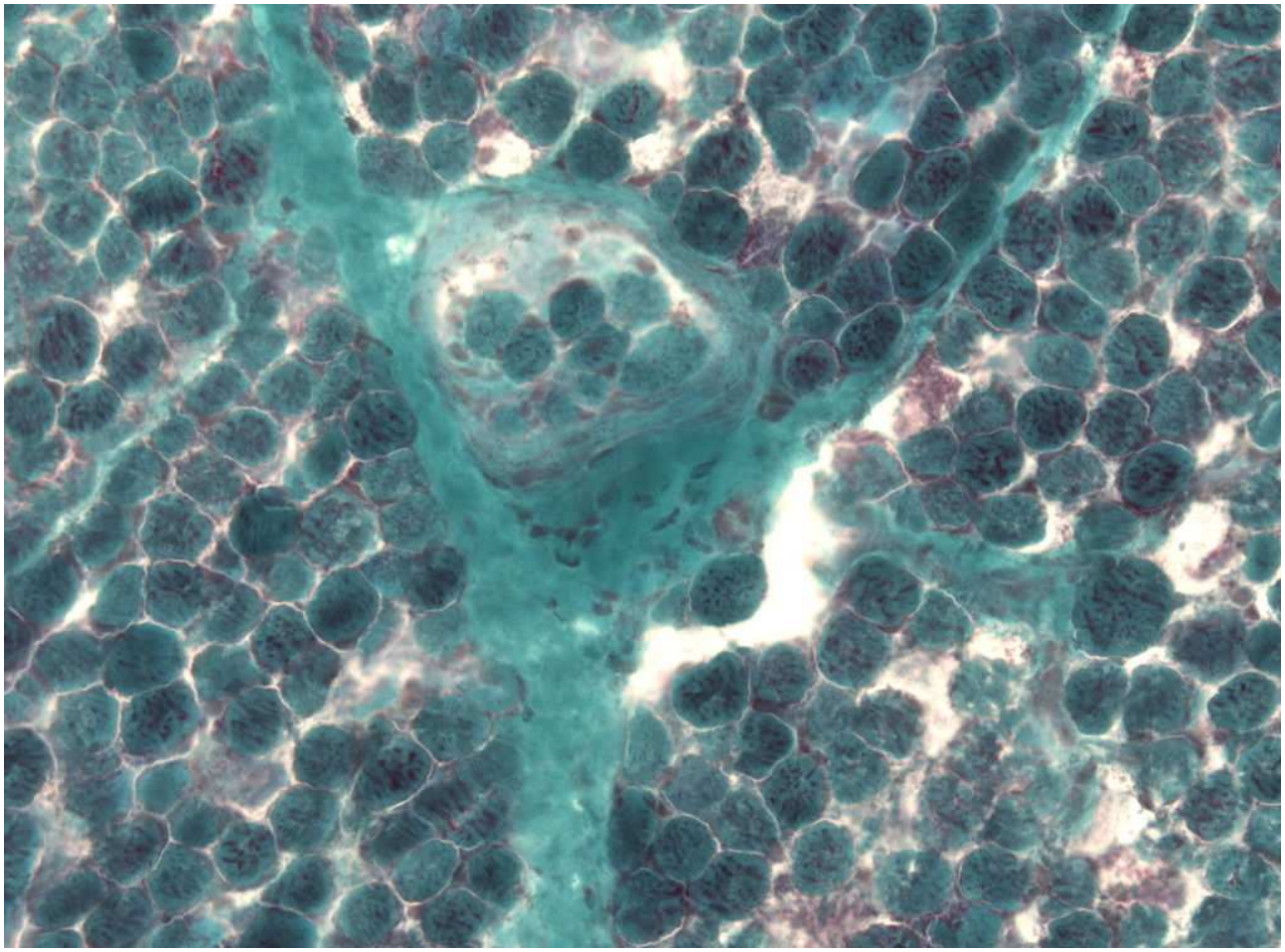


Figure 27-12 **A,** Ragged red fiber with increased reddish granular subsarcolemmal staining reflective of abnormal aggregation of mitochondria. **B,** Electron micrograph showing morphologically abnormal mitochondria with concentric membranous rings (so-called "phonograph records") and rhomboid paracrystalline inclusions (*lower left side*).

Ragged red fibers



https://en.wikipedia.org/wiki/Leigh_syndrome#/media/File:Leigh_Trichrom.jpg Accessed 03/20/2020

Lafora disease

- Progressive myoclonic epilepsy
- Seizures present in late childhood
- Myoclonus
- Rapid decline in cognitive function
- Later, ataxia and dysarthria
- Dead within 10 years
- Lafora bodies contain abnormal glycogen
- Two mutations account for 90% of cases:
- EMPA gene at 6q24.3 (laforin glucan phosphatase)
- NHLRC1 gene (malin)
- E3 protein ubiquitin kinase that degrades laforin

MERRF syndrome

- Appears in childhood or adolescence
- Myoclonus, myopathy, spasticity
- Recurrent seizures
- Ataxia
- Peripheral neuropathy
- Dementia
- Optic atrophy
- 80% MT-TK mutation (base pairs 8295-8364)
- $tRNA^{Lys}$ mutation

Unverricht-Lundborg syndrome

- Onset ages 6-15
- Myoclonic seizures, progressive
- May stabilize over time
- Ataxia, intention tremor, and dysarthria develop
- CSTB gene at 21q22.3
- Over 30 dodecamer repeats, CCCCG-CCCCG-CG
- Cystatin B needed to inhibit cathepsins

Juvenile myoclonic epilepsy

- 7% of all epilepsies
- Appears in early adolescence
- Myoclonic seizures, progressing to tonic-clonic seizures
- Occur frequently in the morning, after awakening
- GABRA1 gene at 5q34 (GABA receptor)
- EFHC1 gene at 6p12.2
- Affects Ca^{2+} channel and calcium homeostasis

Lennox-Gastaut syndrome

- 4% of children with epilepsy
- More common in males than in females
- Usual onset is between the ages of three and five
- Children can have no neurological problems prior to seizure
- 90% occur in non-REM sleep
- CHD1 gene at 15q26.1 (helicase)
- West syndrome (infantile spasms) is diagnosed in 20% of patients before it evolves into LGS at about 2 years old.
- SCN2A gene at 2q24.3 (sodium channel)
- Slow spike waves on EEG
- Poor response to anti-epileptics

Antibodies to tRNA synthetases

- Dermatomyositis
- Lilac discoloration of upper eyelids with periorbital edema.
- May have scaling red eruption over knuckles, elbows, knees (Grotton lesions).
- Proximal muscle weakness, bilaterally.
- Dysphagia.
- Usually an underlying malignancy (ovary).
- Microvasculature attacked by antibodies with complement activation.
- Perivascular distribution of CD4 cells.

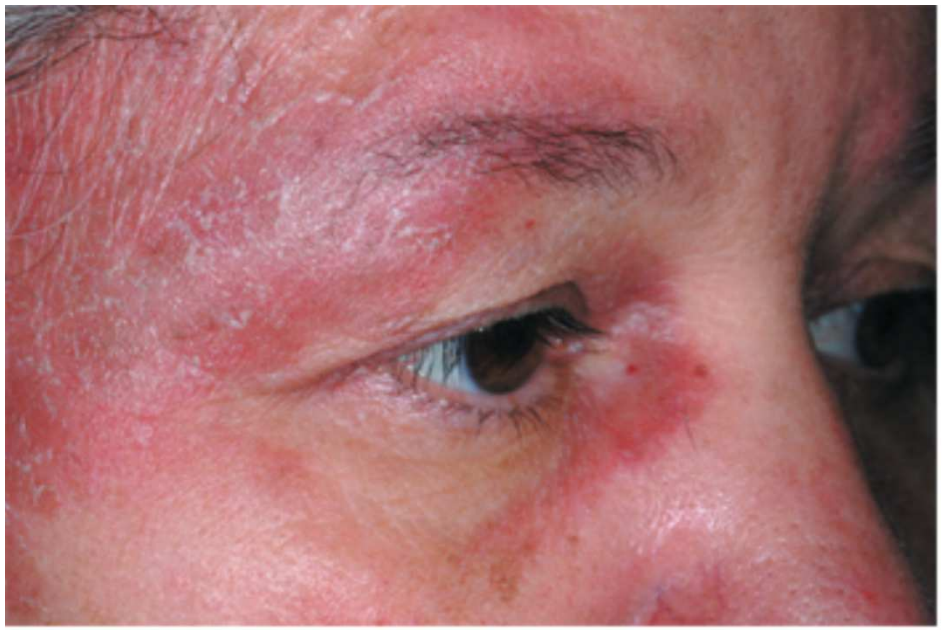
Antibodies to tRNA synthetases

- Infiltrates of mononuclear inflammatory cells (rich in CD4+ T cells) are most pronounced in the perimysial connective tissue and around blood vessels.
- There is a distinctive pattern in which myofiber atrophy is accentuated at the edges of the fascicles (perifascicular atrophy**).**
- Segmental fiber necrosis and regeneration may also be seen.
- Deposition of the complement membrane attack complex (C5b-9) within capillary beds

Antibodies to tRNA synthetases

- Anti-Mi2 antibodies (directed against a helicase implicated in nucleosome remodeling) show a strong association with prominent Gottron papules and heliotrope rash.
- Anti-Jo1 antibodies (directed against the enzyme histidyl t-RNA synthetase) are associated with interstitial lung disease, non-erosive arthritis, and a skin rash described as “mechanic’s hands.” (antisynthetase syndrome)
- Anti-TIF1 (p155/p140) antibodies (directed against several transcriptional regulators) are associated with paraneoplastic as well as juvenile cases of dermatomyositis.

Dermatomyositis



Heliotrope (violaceous) rash around the eyes in a patient with dermatomyositis

(Reproduced with permission from Richard P. Usatine, MD).

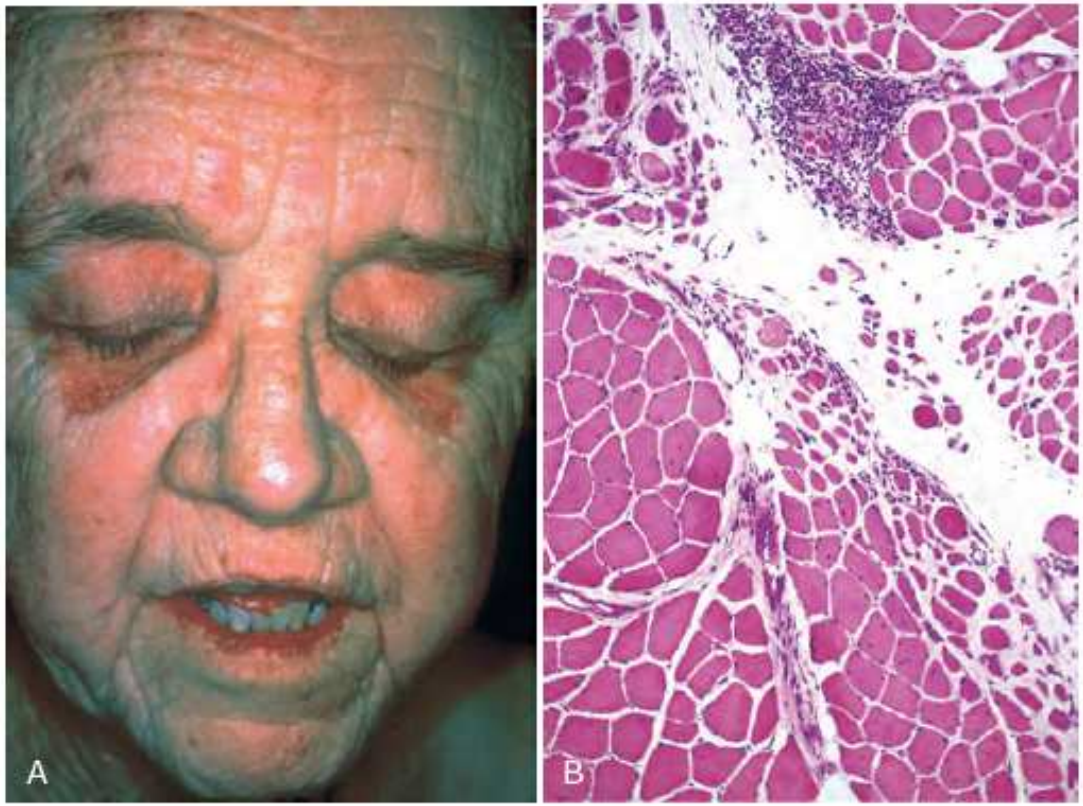


Figure 27-8 **A,** Dermatomyositis. Note the heliotrope rash affecting the eyelids. **B,** Dermatomyositis. The histologic appearance of muscle shows perifascicular atrophy of muscle fibers and inflammation. (Courtesy Dr. Dennis Burns, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Antibodies to tRNA synthetases

- Polymyositis lacks skin changes.
- CD8 cells are seen near damaged myocytes
- HLA class I and II molecules increased in sarcolemma
- Heart, lung, blood vessels affected.

Antibodies to tRNA synthetases

- Inclusion body myositis
- Occurs after the age of 50.
- Quadriceps weakness
- Dysphagia
- Rimmed vacuoles in muscle.
- Ragged red muscle fibers.
- Intracellular deposits of β-amyloid protein, amyloid β-pleated sheet fibrils, and hyperphosphylated tau protein are found.
- HTLV-1 association in 15%

Antibodies to tRNA synthetases

- Polymyositis lacks skin changes seen in dermatomyositis
- Affects truncal and proximal muscles
- Dysphagia
- Vascular injury is minimal
- CD8 cells are found in the endomysium and may invade the muscle
- Patchy atrophic change (not perifascicular)
- HLA class I and II molecules increased in sarcolemma
- Heart, lung, blood vessels affected.

Inflammatory myopathy

- Immune mediated necrotizing myopathy
- Usually 40-60 years of age
- Affects truncal and proximal muscles
- Prominent myofiber necrosis with little associated inflammation
- Complement activation leads to muscle injury
- Anti-HMGCR (associated with statin use)
- Younger patients with more severe myopathy if no statin history
- Anti-SRP
- In children, may mimic muscular dystrophy
- Dysphagia is common

Inflammatory myopathy

- Sporadic inclusion body myositis begins with distal muscles.
- Occurs after the age of 50.
- More common in men
- Most common inflammatory myopathy in those >65 years of age
- Most severe in quadriceps
- HTLV-1 association in 15%

Inflammatory myopathy

- Patchy often endomysial mononuclear inflammatory cell infiltrates rich in CD8+ T-cells
- Increased sarcolemmal expression of MHC class I antigens
- Focal invasion of normal appearing myofibers by inflammatory cells
- Admixed degenerating and regenerating myofibers
- Rimmed vacuoles in muscle.
- Intracellular deposits of β-amyloid protein, amyloid β-pleated sheet fibrils, and hyperphosphylated tau protein are found.

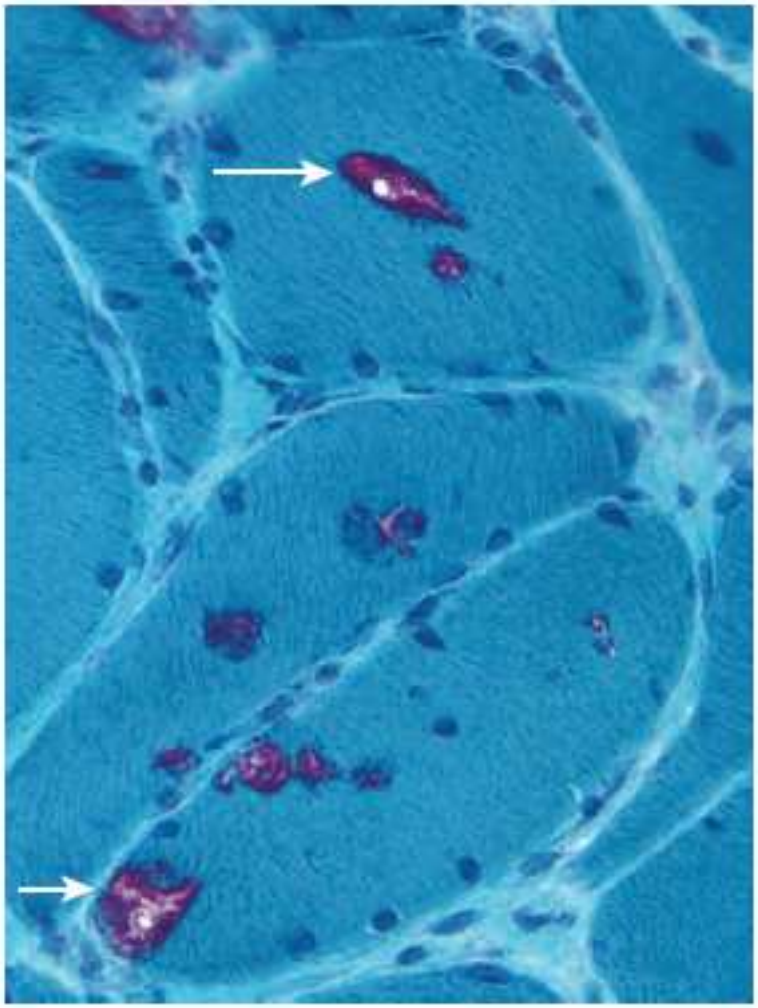


Figure 27-9 Inclusion body myositis, showing myofibers containing rimmed vacuoles—inclusions with reddish granular rimming (*arrows*). Modified Gomori trichrome stain.

Hereditary inclusion body myopathy 2

- Presents in adolescence or early twenties
- Initially presents with damage to tibialis anterior muscle (difficulty walking)
- Weak index finger
- Rimmed vacuoles in muscle.
- Ragged red muscle fibers.
- Intracellular deposits of β-amyloid protein, amyloid β-pleated sheet fibrils, and hyperphosphylated tau protein are found.
- Autosomal recessive
- GNE gene at 9p13.3 (sialic acid biosynthesis)

Neuronal ceroid lipofucsinosis

- Lipid pigment stored in lysosomes.
- Normal development in infancy
- Autosomal recessive.
- Type 1 Infantile
- By 18 months, present with developmental regression, hypotonia, and seizures
- PPT1 gene at 1p34.2 (palmitoyl-protein thioesterase 1 enzyme)
- Type 2 Late infantile
- At 24 months, present with ataxia and seizures
- TPP gene at 11p15.24 (tripeptidyl peptidase)

Neuronal ceroid lipofucsinosis

- Type 3 Juvenile (Spielmeyer-Vogt-Sjögren-Batten disease)
- Presents between 5-8 years of age with seizures and ataxia
- Most common
- CLN 3 gene at 16p12.1 (spans membrane surrounding lysosome, facilitating communication)
- Type 4 Adult
- Present at age 40 with milder symptoms
- CLN 6 gene at 15q23 (regulates transport from endoplasmic reticulum to lysosome)

Sphingolipidoses

- GM_1 is the prototype ganglioside:
- Monosialotetrahexosylganglioside.
- Terminates in formation of ceramide.
- GM_1 gangliosidosis.
- Autosomal recessive.
- β-galactosidase deficiency
- accumulates GM_1
- Acute infantile disease
- Psychomotor retardation
- Hepatosplenomegaly
- Coarse features

GM_1 gangliosidosis

- Juvenile form
- Onset age 1
- Only cerebral accumulation of ganglioside
- No cherry-red spot
- No visceral or bone accumulation
- No visual disturbances

Sphingolipidoses

- Tay-Sachs disease is the prototype of a disease affecting gray matter primarily.
- Gray matter symptoms and signs are:
- Irritative
- Myoclonic seizures
- Inhibitory
- Apathy, lethargy and dementia.
- Cortical blindness if optic neurons involved

Tay-Sachs disease

- Autosomal recessive.
- GM2A gene at 5q33.1 (ganglioside activator necessary for β-hexosaminidase A to function)
- Hexosaminidase A deficiency
- Accumulate ganglioside GM_2
- Type 1 (chronic non-neuronopathic)
- Most common presentation.
- Prevalent in Ashkenazi.
- Type 2 (acute neuronopathic) is characterized by central nervous system involvement.
- Rarely survive beyond age 2.

Tay-Sachs disease

- Type 3 (subacute neuronopathic) has a variable course.
- Cluster described in Norbotten, Sweden.
- “Ballooned” neurons filled with lipid staining material
- On electron microscopy, cells contain lamellated bodies

Tay-Sachs disease

- Early infantile form presents with:
- Cranio-facial abnormalities
- Seizures.
- 50% have cherry-red spot in macula.
- Between age 1-3 years, presents with:
- Flaccid paralysis
- Nystagmus
- Hepatosplenomegaly
- If presents after 3 years of age:
- Dystonia
- Angiokeratomas

Gaucher's disease

- Perinatal form associated with hydrops fetalis and is lethal
- Bulbar weakness
- Retroflexion of the head
- Hepatomegaly
- Present in childhood or adulthood

Gaucher's disease

- Type 1 (non-neuronopathic)
- Most common
- Hepatosplenomegaly with pancytopenia
- Lung disease
- Skeletal abnormalities
- Psychomotor retardation

Gaucher's disease

- Types 2 and 3 (neuronopathic)
- Type 2 presents in infancy; Type 3 has later onset
- Hepatosplenomegaly with pancytopenia
- Lung disease
- Skeletal abnormalities
- Psychomotor retardation
- Supranuclear ophthalmoplegia
- Seizures
- There is also a cardiac form which is further associated with calcified valves

Gaucher's disease

- All types are autosomal recessive
- GBA gene at 1q22 (β-glucocerebrosidase deficiency)
- Accumulate glucocerebroside rather than metabolize it further to ceramide
- Enzyme replacement therapy

Nieman-Pick disease

- Type A (Crocker's)
- Hepatomegaly by 3 months of age
- Failure to thrive
- Psychomotor retardation
- Interstitial lung disease
- Cherry-red spot in macula
- Rarely survive childhood
- Type A accounts for 85% of cases
- Only type with lipid abnormalities in the brain
- SMPD1 gene at 11p15.4 (sphingomyelinase deficiency)
- Accumulate sphingomyelin

Nieman-Pick disease

- Type B
- Presents in mid-childhood
- Hepatosplenomegaly with thrombocytopenia
- Short stature
- Recurrent lung infections
- 30% have Cherry-red spot in macula
- Survive into adulthood
- Type B does not produce neurologic symptoms.
- SMPD1 gene at 11p15.4 (sphingomyelinase deficiency)
- Accumulate sphingomyelin

Nieman-Pick disease

- Types C1 and C2
- Present in childhood
- Ataxia
- Supranuclear gaze palsy
- Dystonia
- Interstitial lung disease
- Severe liver disease
- Dysarthria
- Progressive intellectual decline
- 30% have seizures
- Survive into adulthood

Nieman-Pick disease

- Survive into adulthood
- NPC1 genes at 18q11.2 (defect in the cholesterol trafficking enzyme)
- NPC2 genes at 14q21.3 (defect in the cholesterol trafficking enzyme)
- Accumulate cholesterol

- All Nieman-Pick disorders are autosomal recessive

Malignant hyperthermia

- Mutation in RYR1 gene at 19q13.2
- Ca2+ release channel opens more easily and remains open longer, flooding cell with Ca2+.
- Elevated intracellular Ca2+ stimulates sustained muscle contraction (rigidity) while also accelerating glycogen breakdown and glycolysis (excess heat produced).
- Dantrolene as treatment.

Vitamin deficiency

- Wernicke-Korsakoff
- Thiamine deficiency
- Alcohol abuse.
- Hemorrhagic changes seen in mammilla bodies.
- Abrupt onset of psychotic symptoms or
- Ophthalmoplegia.
- Memory disturbances and confabulation are late developments.
- Thiamine replacement may reverse early symptoms.

Vitamin deficiency

- Subacute combined degeneration
- Vitamin B_{12} deficiency.
- Numbness, tingling, and ataxia in lower extremities may progress to spastic weakness.
- Involves both ascending and descending tracts
- Begins segmentally in mid-thoracic cord.
- May not resolve although megaloblastic anemia treated.