Disorders of Skeletal Muscle

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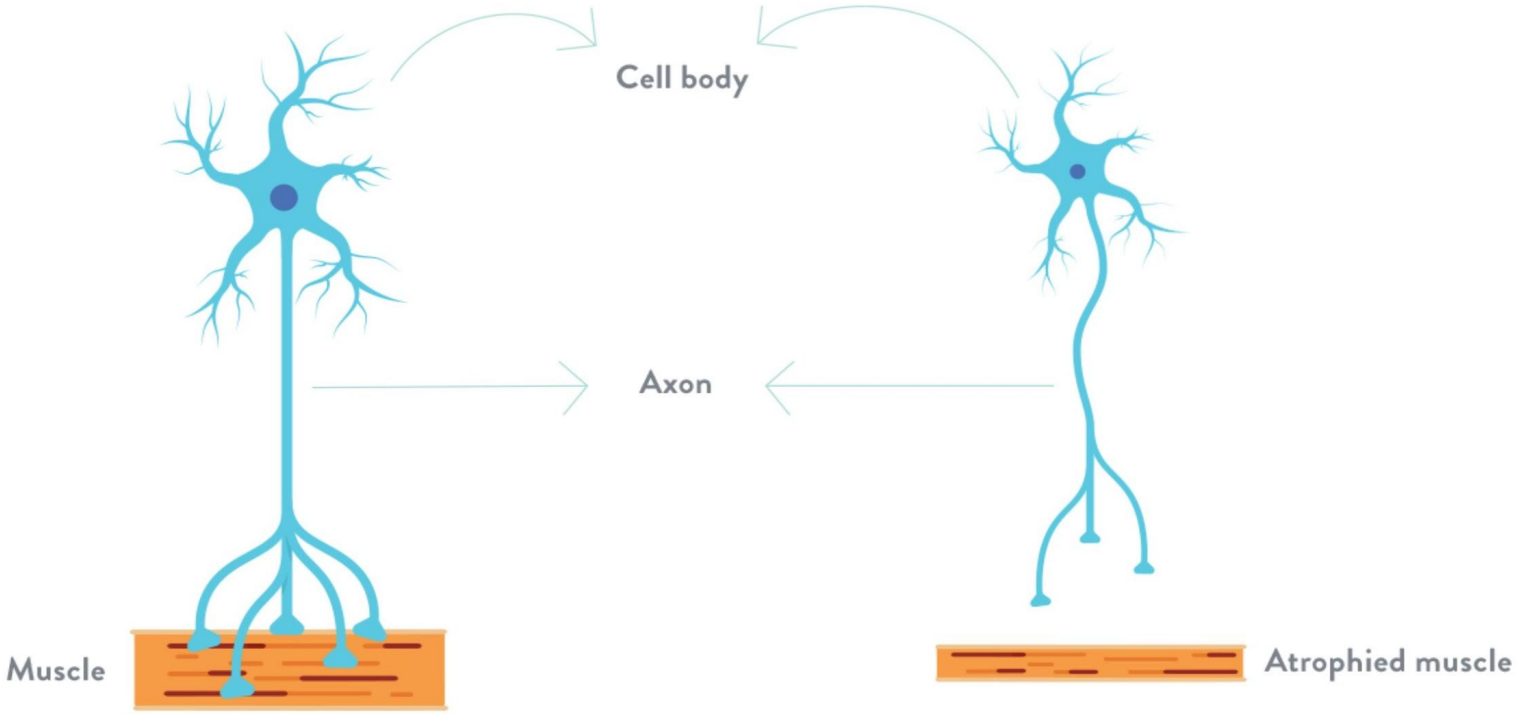
Spinal Muscular Atrophy



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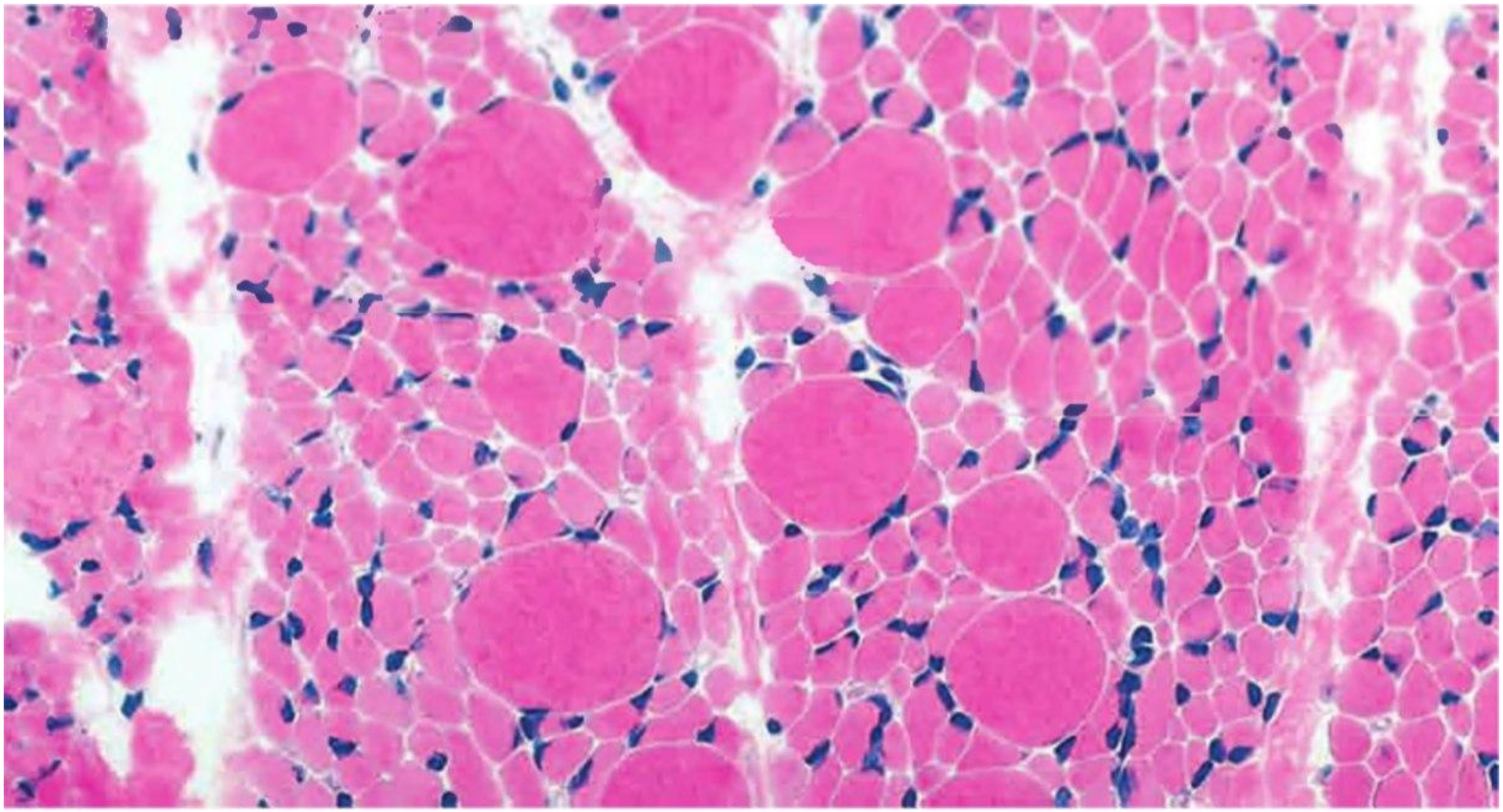


Disorders of Neuromuscular Junction

- *Myasthenia gravis* is an autoimmune disease with fluctuating muscle weakness that is caused by autoantibodies that target the neuromuscular junction. The most common antigenic target is the postsynaptic acetylcholine receptor (AChR). Clinically, myasthenia gravis frequently manifests with *ptosis (drooping eyelids) or diplopia (double vision)* because of weakness in the extraocular muscles. This pattern of weakness is distinctly different from that of most primary myopathic diseases, in which there is relative sparing of facial and extraocular muscles.

Disorders of Neuromuscular Junction

- *Lambert-Eaton syndrome* is caused by autoantibodies that inhibit the function of presynaptic calcium channels, thereby reducing the release of acetylcholine into the synaptic cleft. Patients with Lambert-Eaton syndrome experience improvement in weakness with repetitive stimulation, in contrast to those suffering from myasthenia gravis. Repetitive stimulation serves to build up sufficient intracellular calcium to facilitate acetylcholine release. *Lambert-Eaton syndrome often arises as a paraneoplastic disorder,* particularly in patients with small cell lung carcinoma.

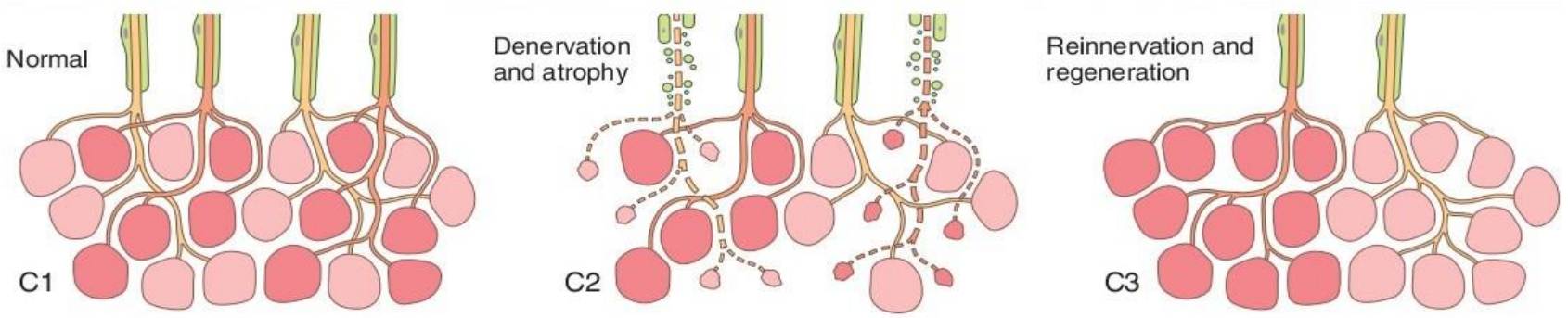
Miscellaneous Neuromuscular Junction Disorders

- *Congenital myasthenic syndromes* comprise a heterogeneous group of diseases that result from mutations that disrupt the function of various neuromuscular junction proteins.
- *Infections with exotoxin-producing bacteria* may be associated with defects in neural transmission and muscle contraction. *Clostridium tetani* and *Clostridium botulinum* both release extremely potent neurotoxins that interfere with neuromuscular transmission.

Muscle Fiber Atrophy

- *Neuropathic changes*. Loss of innervation causes atrophy of myofibers. The two main morphologic hallmarks of neurogenic changes, grouped atrophy and fiber type grouping are the result of multiple rounds of denervation and reinnervation. Loss of an axon or lower motor neuron results in atrophy of the myofibers that are part of this motor unit. Atrophic myofibers can be reinnervated by axonal branches from adjacent motor units, increasing the size of these motor units and returning trophic input to the atrophic myofibers. In this setting loss of innervation will therefore produce large clusters of atrophic myofibers, grouped atrophy.
- *Prolonged disuse of muscles* from any cause (e.g., prolonged bed rest in the sick, casting of a broken bone) may cause focal or generalized muscle atrophy, which tends to affect type II fibers more than type I fibers.
- *Glucocorticoid exposure*, whether exogenous or endogenous (e.g., in Cushing syndrome), also may cause muscle atrophy. Proximal muscles and type II myofibers are affected preferentially in this setting.

Patters of skeletal muscle injury



Inherited Disorders of Skeletal Muscle

- *Muscular dystrophies* are associated with progressive muscle injury in patients who have normal muscle function at birth.
- *Congenital muscular dystrophies*, by contrast, are progressive, early-onset diseases. Some are also associated with malformations of the central nervous system.
- *Congenital myopathies* typically present in infancy with muscle defects that tend to be static or to even improve with time. They are often associated with distinct structural abnormalities of the muscle.

Dystrophinopathies: Duchenne and Becker Muscular Dystrophy

- The most common muscular dystrophies are X-linked and are caused by mutations that disrupt the function of a large structural protein called dystrophin. As a result, these diseases are referred to as dystrophinopathies - *Duchenne muscular dystrophy (DMD)* and *Becker muscular dystrophy (BMD)* are the two most important diseases in this group.
- Both DMD and BMD are caused by mutations disrupting the function of the dystrophin gene located on the short arm of the X chromosome (Xp21). Dystrophin is a very large protein (427kD in molecular weight) found in skeletal and cardiac muscle, brain, and peripheral nerves; it is part of the dystrophin-glycoprotein complex.

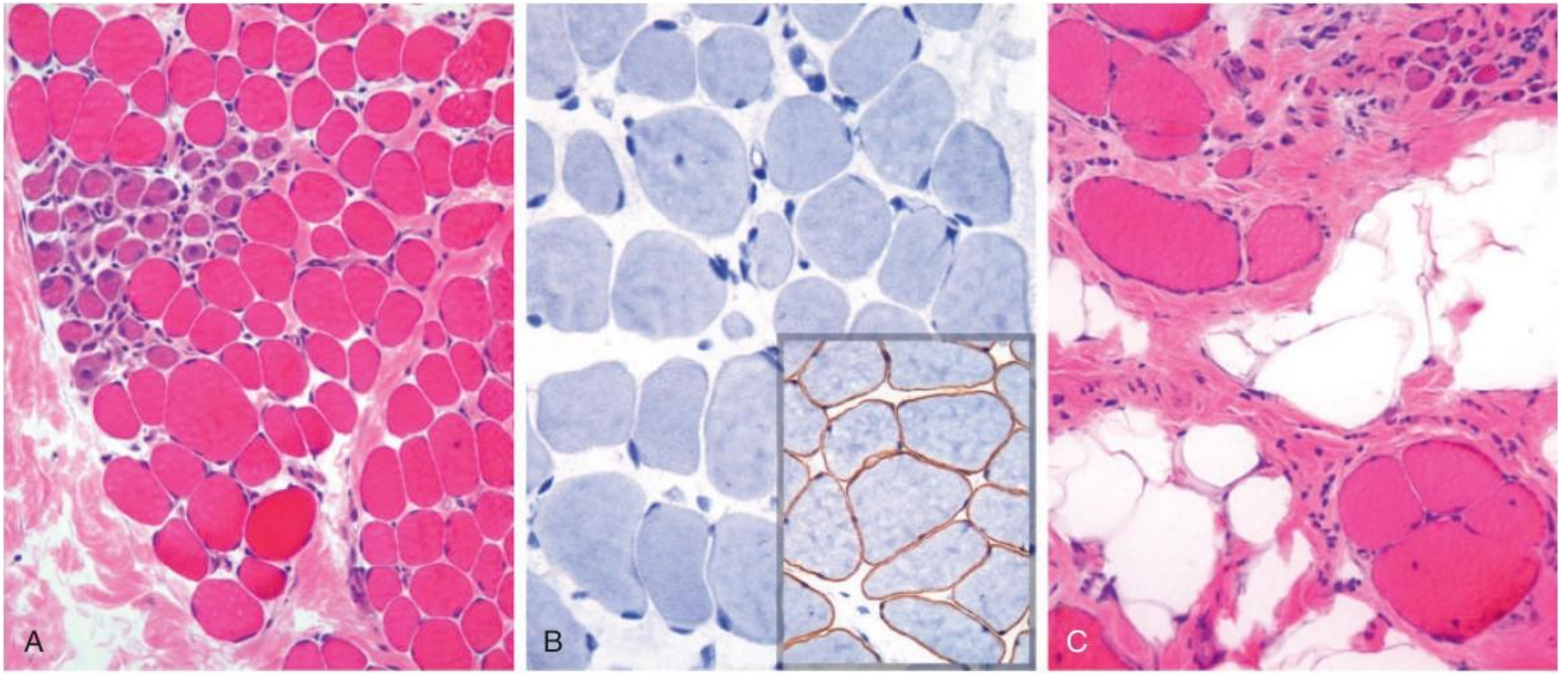
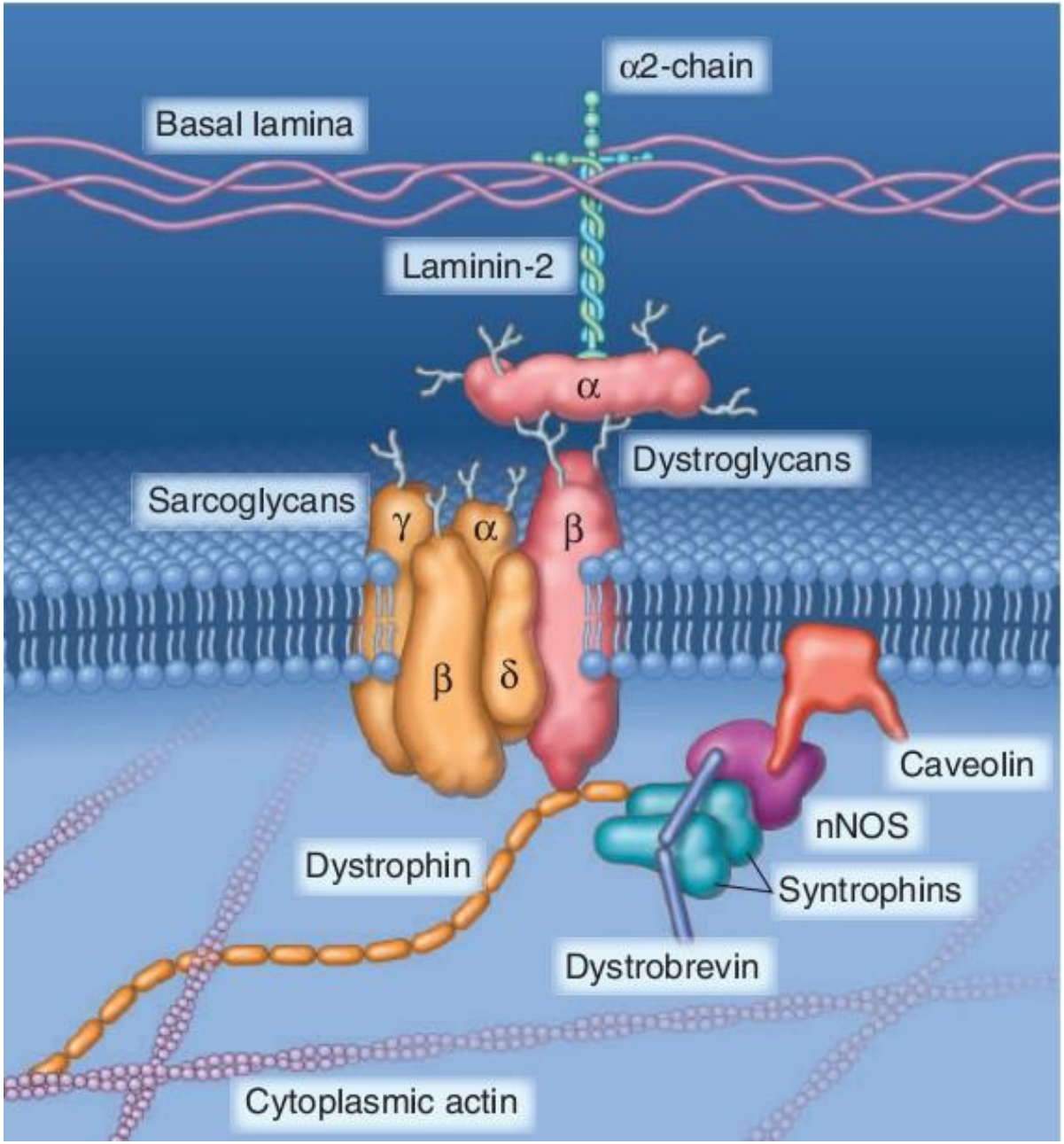


Fig. 22.5 Duchenne muscular dystrophy. Histologic images of muscle biopsy specimens from two brothers. (A–B) Specimens from a 3-year-old boy. (C) Specimen from his brother, 9 years of age. As seen in (A), at a younger age fascicular muscle architecture is maintained, but myofibers show variation in size.


α2-chain
Basal lamina
Laminin-2
α
Dystroglycans
Sarcoglycans
γ
α
β
β
δ
Caveolin
nNOS
Dystrophin
Syntrophins
Dystrobrevin
Cytoplasmic actin

Other X-Linked and Autosomal Muscular Dystrophies

- *Myotonic dystrophy.* Myotonia, the sustained involuntary contraction of a group of muscles, is the cardinal neuromuscular symptom in myotonic dystrophy. Patients often complain of stiffness and difficulty in relaxing their grip, for example, after a handshake. Myotonic dystrophy is a nucleotide repeat expansion disease that is inherited as an autosomal dominant trait. More than 95% of patients with myotonic dystrophy have mutations in the gene that encodes the dystrophia myotonica protein kinase (DMPK).
- *Limb-girdle muscular dystrophies.* These muscular dystrophies preferentially affect the proximal musculature of the trunk and limbs. Their genetic basis is heterogeneous. The growing list includes at least 7 dominant subtypes and 15 autosomal recessive subtypes. Some of the responsible mutations affect components of the dystrophin-glycoprotein complex other than dystrophin. Others affect proteins involved in vesicle transport and repair of cell membrane after injury.

Other X-Linked and Autosomal Muscular Dystrophies

- *Emery-Dreifuss muscular dystrophy (EMD)* is a genetically heterogeneous disorder caused by mutations affecting structural proteins found in the nucleus. An X-linked form results from mutations in the gene encoding the protein emerin, whereas an autosomal dominant form is caused by mutations in the gene encoding lamin A/C.
- *Facioscapulohumeral dystrophy* is an autosomal dominant form of muscular dystrophy that is caused by complex genetic changes that allow expression of the transcription factor DUX4 that is normally repressed in mature tissues. It is thought that the disease is caused by over expression of DUX4 target genes, many of which are involved in the normal function of skeletal muscles.

Channelopathies

- *Ion channel myopathies* are a group of familial disorders caused by inherited defects in ion channels that are characterized by myotonia, relapsing episodes of hypotonic paralysis associated with abnormal serum potassium levels, or both. Hyperkalemic periodic paralysis results from mutations in the gene encoding the skeletal muscle sodium channel SCN4A, which regulates sodium entry during contraction. Malignant hyperthermia is a rare syndrome characterized by tachycardia, tachypnea, muscle spasms, and hyperpyrexia.

Metabolic Myopathies

- *Myopathies due to inborn errors of metabolism* include disorders of glycogen synthesis and degradation and lipid handling. The latter include disorders of the carnitine transport system and deficiencies of the mitochondrial dehydrogenase enzyme system, both of which can lead to accumulation of lipid in myocytes (lipid myopathies).

Mitochondrial Myopathies

- *Mitochondrial myopathies* can stem from mutations in either the mitochondrial or nuclear genomes because both encode proteins and RNAs that are critical for mitochondrial function. Mitochondrial myopathies usually manifest in early adulthood with proximal muscle weakness and sometimes with severe involvement of the ocular musculature (external ophthalmoplegia). There may also be neurologic signs and symptoms, lactic acidosis, endocrinopathy, peripheral neuropathy, and cardiomyopathy. Some mitochondrial diseases are associated with normal muscle morphology, whereas others show aggregates of abnormal mitochondria; the latter impart a blotchy red appearance in special stains - hence the term ragged red fibers.

Acquired Disorders of Skeletal Muscle

Inflammatory Myopathies

- *Polymyositis* is an autoimmune disorder associated with increased expression of MHC class I molecules on myofibers and predominantly endomysial inflammatory infiltrates containing CD8+ cytotoxic T-cells. The autoimmune attack leads to myofiber necrosis and subsequent regeneration.
- *Dermatomyositis* is the most common inflammatory myopathy in children, in whom it appears as an isolated entity. In adults, it often manifests as a paraneoplastic disorder. In both contexts, it is believed to have an autoimmune basis. The disease is typically associated with skin manifestations, as implied by the name, and may also have systemic manifestations such as interstitial lung disease.

Inflammatory Myopathies

- *Inclusion body myositis* is the most common inflammatory myopathy in patients older than 60 years of age. It is grouped with other forms of myositis, but it has yet to be determined whether inflammation is a cause or an effect in this disorder. The morphologic hallmark of inclusion body myositis is the presence of rimmed vacuoles that contain aggregates of the same proteins that accumulate in the brains of patients with neurodegenerative diseases-hyperphosphorylated tau, amyloid derived from β-amyloid precursor protein, and TDP-43-leading some to speculate that this is a degenerative disorder of aging.

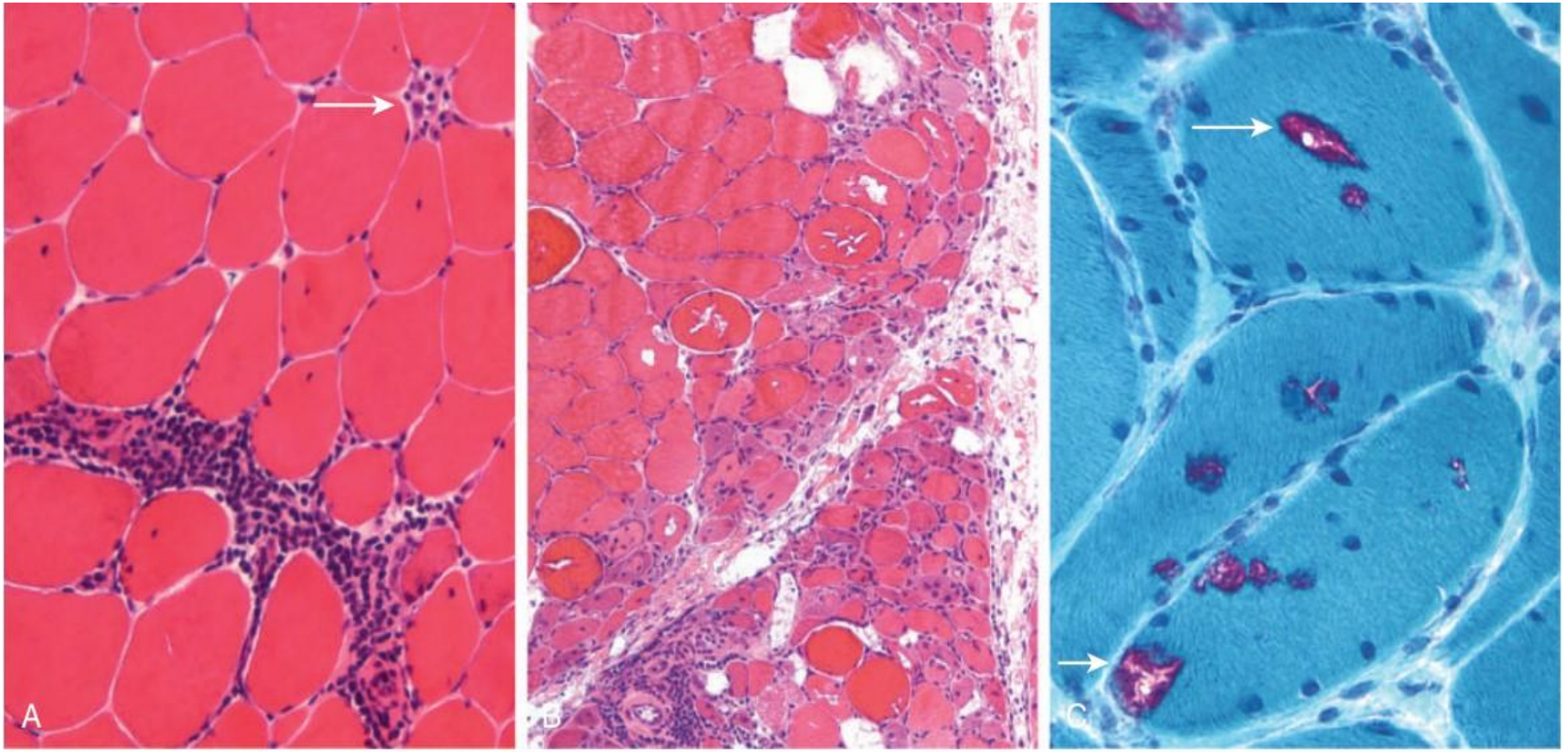


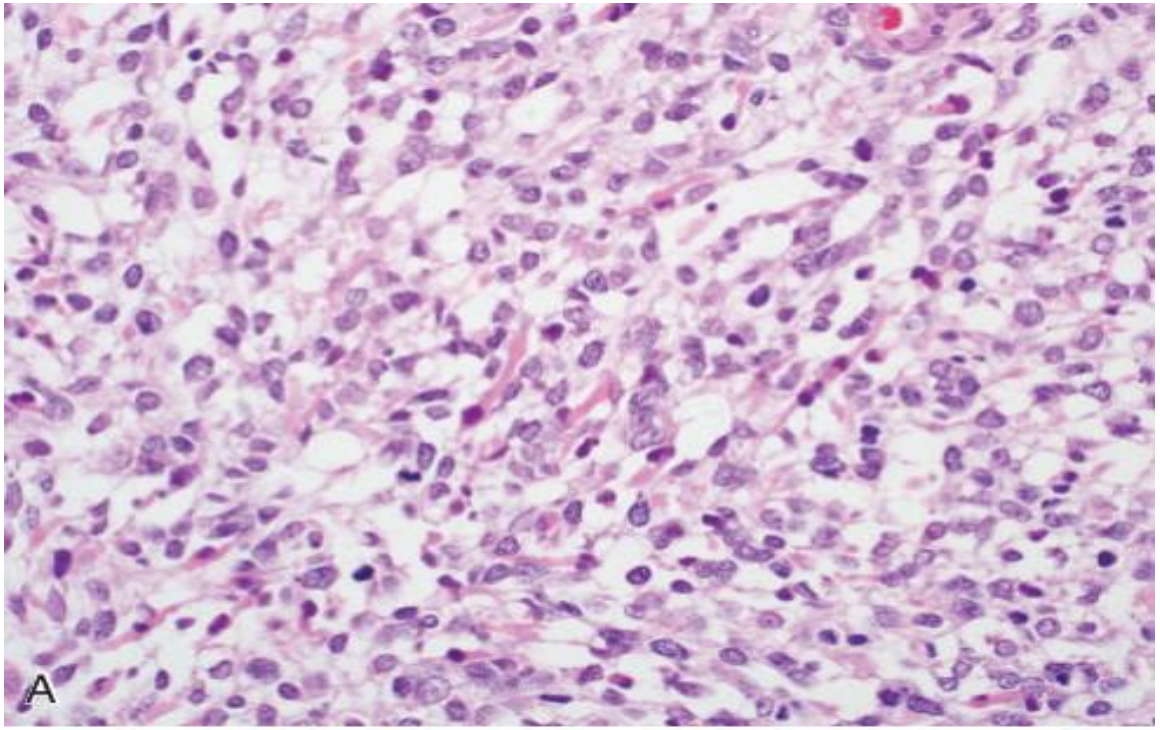
Fig. 22.6 Inflammatory myopathies. (A) Polymyositis is characterized by endomysial inflammatory infiltrates and myofiber necrosis *(arrow)*. (B) Dermatomyositis often shows prominent perifascicular and paraseptal atrophy. (C) Inclusion body myositis, showing myofibers containing rimmed vacuoles *(arrows)*. Modified Gomori trichrome stain.

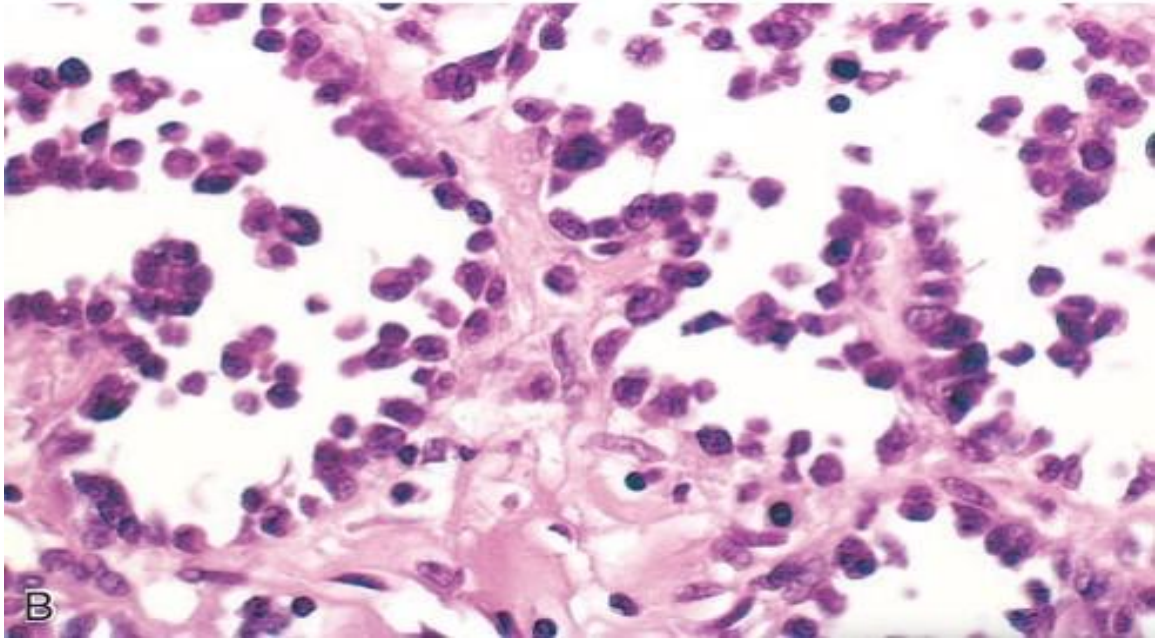
Toxic Myopathies

- *Thyrotoxic myopathy* may take the form either of acute or chronic proximal muscle weakness, and it can be the first indication of thyrotoxicosis. Histologic findings include myofiber necrosis and regeneration.
- *Ethanol myopathy* occurs after an episode of binge drinking. The degree of rhabdomyolysis may be severe, sometimes leading to acute renal failure secondary to myoglobinuria.
- *Drug myopathy* can be produced by a variety of agents. For example, myopathy is the most common complication of statins (e.g., atorvastatin, simvastatin, pravastatin), occurring in approximately 1.5% of users. Two forms of statin associated myopathy are recognized: (1) toxicity of the drug and (2) statin-induced HMG-CoA reductase autoantibodies causing an immune mediated myopathy.

Tumors of Skeletal Muscles

- *Rhabdomyosarcoma* is a malignant mesenchymal tumor with skeletal muscle differentiation. Three main subtypes are recognized: alveolar (20%), embryonal (60%), and pleomorphic (20%). Rhabdomyosarcoma (alveolar and embryonal) is the most common soft tissue sarcoma of childhood and adolescence, usually appearing before age 20. Pleomorphic rhabdomyosarcoma is seen predominantly in adults. The pediatric forms often arise in the sinuses, head and neck, and genitourinary tract, locations that do not normally contain much skeletal muscle.





A – embryonal subtype
B – alveolar subtype

Tumors of Skeletal Muscles

- *Leiomyoma,* a benign tumor of smooth muscle, is most common in the uterus but can arise in any soft tissue site. Uterine leiomyomas are common and may cause a variety of symptoms including infertility and menorrhagia. Leiomyomas also may arise from the erector pili muscles (pilar leiomyomas) in the skin and rarely in the deep somatic soft tissues or gastrointestinal tract.

Tumors of Skeletal Muscles

- Soft tissue *leiomyosarcoma* accounts for 10% to 20% of soft tissue sarcomas. They occur in adults and affect women more frequently than men. Most develop in the deep soft tissues of the extremities and retroperitoneum or arise from the great vessels. Leiomyosarcomas have complex genotypes that stem from acquired defects that lead to profound genomic instability.

Summary

- Skeletal muscle function can be impaired by a primary (inherited or acquired) myopathy or secondarily because of problems with muscle innervation.
- The genetic forms of myopathy fall into several fairly distinct clinical phenotypes, including muscular dystrophy, congenital myopathy, and congenital muscular dystrophy.
- Dystrophinopathies are X-linked disorders caused by mutations in the dystrophin gene and disruption of the dystrophin-glycoprotein complex. Depending on the type of mutation, the disease may be severe, such as DMD, or mild (e.g., Becker dystrophy).
- Acquired myopathies have diverse causes, including inflammation and toxic exposures.

THANK YOU FOR YOUR ATTENTION

ANY QUESTIONS?