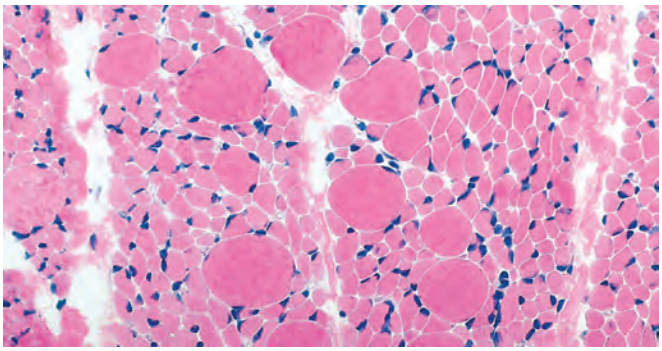

Figure 27-13 Spinal muscular atrophy with only rare hypertrophied myofibers admixed with numerous atrophic rounded myofibers. The larger fibers are those that are innervated and have undergone compensatory hypertrophy.

abnormalities of the brain (e.g. encephalopathy), and neuronopathies, of which spinal muscular atrophy is a prototypic example.

Spinal muscular atrophy is an autosomal recessive disorder with an incidence of 1 in 6,000 births, and is caused by loss-of-function mutations in the *SMN1* (survival of motor neuron-1) gene. The function of the gene is uncertain—the encoded protein may have a role in RNA splicing—but SMN1 deficiency has a dramatic effect on motor neuron survival, sometimes leading to loss of motor neurons in utero. The resulting denervation of skeletal muscle may lead to characteristic morphologic changes consisting of large zones of severely atrophic myofibers mixed with scattered normal sized or hypertrophied myofibers, found individually or in small groups (Fig. 27-13). These normal or hypertrophied fibers are those that retain innervation from remaining motor neurons.

Ion Channel Myopathies (Channelopathies)

Channelopathies are a group of inherited diseases caused by mutations affecting the function of ion channel proteins. Most channelopathies are autosomal dominant disorders with variable penetrance. Depending on the channel that is affected, clinical manifestations may include epilepsy, migraine, movement disorders with cerebellar dysfunction, peripheral nerve disease, and muscle disease.

Different ion channel myopathies may cause decreased or increased excitability resulting in hypotonia or hypertonia. Disorders associated with hypotonia can be further sub-classified based on whether symptomatic patients have elevated, depressed, or normal serum potassium levels and are called *hyperkalemic, hypokalemic,* and *normokalemic periodic paralysis*, respectively. Examples of mutated gene products that are associated with muscle dysfunction are the following:

- KCNJ2—Mutations affecting this potassium channel cause *Andersen-Twail syndrome,* an autosomal disorder associated with periodic paralysis, heart arrhythmias, and skeletal abnormalities.
- SCN4A—Mutations affecting this sodium channel cause several autosomal disorders with presentations ranging from myotonia to periodic paralysis.
- CACNA1S—Missense mutations in this protein, a subunit of a muscle calcium channel, are the most common cause of *hypokalemic paralysis*.
- CLC1—Mutations affecting this chloride channel cause myotonia congenita. As already discussed, CLC1 expression is decreased in myotonic dystrophy.
- RYR1—Mutations in the *RYR1* gene disrupt the function of the ryanodine receptor, which regulates calcium release from the sarcoplasmic reticulum. *RYR1* mutations are linked to a congenital myopathy (central core disease) and to *malignant hyperthermia*. The latter is characterized by a hypermetabolic state (tachycardia, tachypnea, muscle spasms, and later hyperpyrexia) that can be triggered by anesthetics, most commonly halogenated inhalational agents and succinylcholine. Upon exposure to anesthetic, the mutated receptor allows increased efflux of calcium from the sarcoplasmic reticulum, leading to tetany and excessive heat production.

KEY CONCEPTS

Disorders of Skeletal Muscle

- Altered muscle function may stem from neurogenic or primary myopathic processes.
- Myopathic processes are often marked by degeneration and regeneration of myofibers.
- The three main inflammatory myopathies are polymyositis, dermatomyositis, and inclusion body myositis.
  - **Inclusion body myositis** is a chronic progressive disease of older patients associated with rimmed vacuoles.
  - **Dermatomyositis** occurs in children and adults, the latter frequently as a paraneoplastic disorder. Immune damage to small blood vessels and perifascicular atrophy are common features.
  - **Polymyositis** is an adult onset myopathy caused by CD8+ T cells.
- **Muscular dystrophies** and **congenital myopathies** result from mutations that disrupt the function of proteins that are important for various aspects of muscle development, function, and regeneration. Some of these diseases present in infancy, others in adulthood. They may be relentlessly progressive or cause relatively static deficits.
- Myopathy can result from toxic injury or be the result of metabolic diseases including those of lipid metabolism, glycogen metabolism, and mitochondria.

Peripheral Nerve Sheath Tumors

A number of benign and malignant neoplasms are grouped together as peripheral nerve sheath tumors. *The vast majority of these are composed of cells that show evidence of Schwann cell differentiation.* These include the three common types, schwannoma, neurofibroma, and malignant peripheral nerve sheath tumor (MPNST). Other rare tumors arising from nerves may show evidence of perineurial cell differentiation. There is an abrupt transition between myelination by oligodendrocytes (central myelin) and myelination by Schwann cells (peripheral myelin) that occurs as nerves extend out from the substance of the brain. Thus, peripheral nerve tumors sometimes arise within the dura as well as along the distal course of peripheral nerves.

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