Treatment

The only glycogen storage disorder with a therapy approved by the U.S. Federal Drug Administration is enzyme replacement for infantile or adult-onset acid maltase deficiency. Treatment for the other glycogen storage disorders is supportive.

Prognosis

Severe infantile forms of most these disorders can often involve multiple organs and be fatal. A less severe adult myopathic phenotype is also common.

DISORDERS OF FATTY ACID METABOLISM

Disorders of lipid metabolism differ from glucose and glycogen disorders in that the metabolic derangement is in the enzymatic breakdown of fatty acids (see E-Table 122-3). Many present in childhood with episodes of encephalopathy precipitated by fasting with hypoketotic hypoglycemia. Serum fatty acid profiles often show reduced carnitine and increased longer chain fractions, depending on whether the mutation is in very long chain, long chain, or medium chain fatty acid metabolism. Adults typically show exercise intolerance and myoglobinuria and may developed a mild limb-girdle pattern myopathy. The most prevalent disorder of fatty acid metabolism is carnitine palmitoyltransferase II deficiency. This disease ranges from a lethal neonatal form to an adult form with muscle pain and recurrent myoglobinuria, often precipitated by intense exercise, febrile illness, or fasting. The diagnosis is usually made by detection of reduced carnatine palmitoyltransferase enzyme activity in skeletal muscle.

Mitochondrial Myopathies

Definition and Epidemiology

Mitochondrial myopathies can present at any age, with varying degrees of severity or weakness, affect multiple organ systems, and have any pattern of inheritance (see E-Table 122-3). Mutations affect enzymes necessary for normal mitochondrial function, and can be mitochondrial or nuclear. The overall prevalence for mitochondrial disorders is thought to be approximately 1 : 8500; however, the prevalence of individual mitochondrial syndromes is much lower and ranges from just a handful of cases, to 1to 6 per 100,000.

Pathology

Mutations can occur in both mitochondrial DNA (in which case inheritance is maternal) and nuclear DNA (autosomal dominant, recessive, or x-linked). Mitochondrial disorders produce biochemical defects proximal to the respiratory chain (involving substrate transport and usage) or within the respiratory chain. On muscle biopsy, muscle fibers contain abnormal mitochondria. Pathologically these fibers have a "ragged red" appearance on biopsy stains (trichrome) and may fail to react for cytochrome c oxidase.

Clinical Presentation

Despite the diversity, there are certain patterns that are characteristic for mitochondrial disorders, including slowly progressive myopathy and myalgias, which worsen with exertion or illness, and ptosis and/or ophthalmoplegia. E-Table 122-3 lists common clinical mitochondrial syndromes.

Diagnosis and Differential Diagnosis

The diagnosis is based on clinical history, serum lactate levels, which are often elevated at rest, and characteristic findings on muscle biopsy. Diagnosis is confirmed by mitochondrial or nuclear genetic testing.

Treatment

Treatment is largely supportive, and includes identification of other multisystem involvement, including diabetes, cardiac and ophthalmological involvement, and hearing loss. Many agents have been tried in mitochondrial diseases, including coenzyme Q10, creatine, and carnitine; however, a meta-analysis showed no clear evidence for benefit for any treatment. Aerobic exercise may reduce fatigue and improve muscle function, although there are no large trials of efficacy.

Prognosis

The severity and prognosis depends partially on the load of abnormal mitochondrial DNA as well as the degree of multisystem involvement. Certain clinical syndromes with more predictable prognosis have been described (see E-Table 122-3).

MUSCLE CHANNELOPATHIES

The muscle channelopathies are a spectrum of disorders due to mutations in muscle ion channels commonly divided into the nondystrophic myotonias and periodic paralyses. Most are inherited in an autosomal dominant fashion, with episodic symptoms, often triggered by temperature or certain foods.

Nondystrophic Myotonias

Definition and Epidemiology

Nondystrophic myotonias are due to mutations in muscle chloride (CLCN1 on chromosome 7) or sodium (SCN4A on chromosome 17) channels resulting in hyperexcitable muscle and myotonia. The overall worldwide prevalence for nondystrophic myotonias is 1 : 100,000.

Pathology

Mutations in chloride channels cause a loss of function. Loss of hyperpolarizing chloride conductance cannot counteract a buildup of potassium in the t-tubule system during repetitive contractions, which results in a depolarized sarcolemma. Sodium mutations, on the other hand, cause anomalous depolarizing sodium currents due to alterations in fast or slow channel inactivation, or hyperpolarizing shifts in channel activation curves.

Clinical presentation

The nondystrophic myotonias have myotonia in common; on examination this can be seen as delayed muscle relaxation after contraction. Patients have trouble opening their eyes or fist when instructed to squeeze them shut. On percussion of the thenar eminence or wrist extensors there is a catch then delay in the relaxation phase. Electromyography shows a characteristic waxing and waning motor unit amplitude and frequency that