Facioscapulohumeral Muscular Dystrophy

Definition and Epidemiology

The majority of patients with facioscapulohumeral muscular dystrophy (FSHD) have disease inherited in an autosomal dominant fashion due to a deletion of a large repetitive element on chromosome 4 (FSHD-1). An additional 5% of patients (FSHD-2) will have disease with digenic inheritance, which occurs through a deletion-independent pathway. The prevalence of FSHD is 1 : 15,000.

Pathology

Both forms of FSHD lead to changes in methylation on chromosome 4 leading to the de-repression of the gene, *DUX4*, which is typically silenced in adult muscle; it is believed to cause disease in a toxic gain-of-function fashion. Muscle biopsy is typically not required for the diagnosis, but shows nonspecific myopathic changes. Up to 30% of biopsies can show inflammatory infiltrates.

Clinical Presentation

Patients typically present in their late teens or early twenties with weakness in a characteristic pattern, often with dramatic side-to-side asymmetry: typically first in the face, shoulders, and arms, later involving the trunk and distal lower extremities. Patients are unable to squeeze their eyes shut, have a transverse smile, scapular winging, loss of proximal muscle mass with often preserved forearm muscles, and a positive Beevor's sign (movement of the umbilicus up or down when asked to tense the abdominal muscles). Extramuscular manifestations of FSHD are rare: retinal vascular changes, which can occasionally lead to symptomatic retinal vasculopathy termed Coat's syndrome, high frequency hearing loss, and often asymptomatic atrial arrhythmias.

Diagnosis and Differential Diagnosis

Diagnosis is based on clinical examination, family history, and is confirmed by genetic testing. The differential diagnosis includes other myopathies or neuropathies with a scapuloperoneal pattern of weakness.

Treatment

There is no treatment for the weakness of FSHD. A dilated eye examination is indicated at the time of diagnosis, and surveillance for respiratory involvement for patients with pelvic girdle weakness or who are confined to wheelchair.

Prognosis

FSHD is not life limiting, but approximately 20% over the age of 50 will require a wheelchair.

CONGENITAL MYOPATHIES

Congenital myopathies are defined by their appearance on biopsy (see E-Table 122-2; Fig. 122-1C), and have a large number of genetic mutations associated with them. They are usually present at birth with hypotonia and subsequent delayed motor development. If the child survives the perinatal period, most congenital myopathies are relatively nonprogressive and may not be diagnosed until the second or third decade. Clinical findings common in the congenital myopathies are reduced muscle bulk, slender body build, a long and narrow face, skeletal abnormalities (high-arched palate, pectus excavatum, kyphoscoliosis, dislocated hips, and pes cavus), and absent or reduced muscle stretch reflexes.

METABOLIC MYOPATHIES

Metabolic myopathies are muscle diseases due to mutations in enzymes responsible for energy production including glycogen, lipid, and mitochondrial metabolism (see E-Table 122-3). Classically, these disorders present in older children or adults with episodes of exercise intolerance, muscle cramping, or pain associated with myoglobinuria. Newborn and infants present with severe multisystem disorders that are often fatal.

Glucose and Glycogen Metabolism Disorders

Definition and Epidemiology

Glucose, and its storage form glycogen, is essential for the short-term, predominantly anaerobic energy requirements of muscle (see E-Table 122-3). Disorders of glucose and glycogen metabolism (called glycogenesis) have two distinct syndromes: static symptoms of fixed weakness without exercise intolerance or myoglobinuria, and dynamic symptoms of exercise intolerance, pain, cramps, and myoglobinuria. Acid maltase deficiency (Pompe disease) is an example of the first and is notable for enzyme replacement therapy, which is life extending for the childhood variant. McArdle's disease is an example of the second. These are rare disorders with incidence rates for the individual disorders of around 1 : 100,000. The incidence varies between region and ethnic group. For example, acid maltase deficiency has an incidence as high as 1 : 14,000 in African Americans. The prevalence of McArdle's disease is approximately 1 : 100,000.

Pathology

All are due to mutations in enzymes responsible for glucose or glycogen metabolism. Muscle biopsies usually show subsarcolemmal accumulation of glycogen.

Clinical Presentation

Acid maltase disease typically has a severe infantile form with respiratory and cardiac involvement and a slowly progressive adult myopathy, which can affect the diaphragm, so surveillance for respiratory involvement is important. However, McArdle's disease presents with severe episodes of muscle cramping and contractures associated with exercise and a fixed myopathy later in life. Many patients note a "second wind" phenomenon after a period of brief rest so that they can continue the exercise at the previous level of activity.

Diagnosis and Differential Diagnosis

Diagnosis is made by characteristic appearance on muscle biopsy with subsequent study of the enzyme activity or by searching for specific genetic mutations. The differential diagnosis includes other glycogen storage disorders, disorders of lipid metabolism, or mitochondrial disorders.