

# Metabolic Myopathies

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The term metabolic myopathy is applied to a heterogeneous group of disorders that result from the inability of skeletal muscle to produce or maintain adequate levels of energy (ATP). The clinical features of the metabolic myopathies vary widely, but generally include fixed, progressive muscle weakness; premature fatigue; episodic aches, cramps and pains; and occasionally extensive rhabdomyolysis with myoglobinuria. The metabolic myopathies are generally classified according to the altered area of metabolism and can be divided into muscle glycogenoses, disorders of lipid metabolism and mitochondrial myopathies (Table 1).

## Underlying Pathophysiology

To understand this diverse group of diseases, it is helpful to understand normal muscle physiology. Both muscle contraction and relaxation are active processes and require the activities of  $\text{Na}^+\text{-K}^+$  ATPase,  $\text{Mg}^{++}$  ATPase and  $\text{Ca}^{++}$  ATPase. ATP, the substrate for these activities, is formed from carbohydrate, mostly in the form of glycogen, and lipid, primarily as free fatty acids. Glycogen is broken down and converted to pyruvate via glycolysis in the sarcoplasm. Pyruvate is then transported into mitochondria where it is decarboxylated to acetylCoA. AcetylCoA is also derived from beta-oxidation of fatty acids after they have been transported into mitochondria. Energy is generated from acetylCoA by oxidation through the Krebs (tricarboxylic acid) cycle and respiratory chain. These pathways function continuously and, in concert with the activities of the purine nucleotide cycle and creatine kinase (CK), maintain sustaining levels of energy (ATP) in muscle. The type of fuel used and the relative contribution of each particular pathway vary with the intensity and duration of exercise and with the nutritional status and degree of physical conditioning of the individual.

Any disorder that alters the electrolytes involved in these reactions or their substrate, ATP, will result in disordered muscle function and a myopathy. In fact, defects in almost every individual step of carbohydrate and lipid metabolism have been identified and are recognized to cause myopathy. Most of these defects are primary and inherited and result from point mutations or rearrangements of nuclear or mitochondrial genes. However, some are secondary or acquired.

## Clinical Features—General

The age of onset for most metabolic myopathies is childhood or teenage years, however, onset in adulthood is well recognized. Symptoms developing at age 78 years have been reported. The clinical features of the metabolic myopathies vary widely. These include premature fixed, progressive muscle weakness; fatigue; episodic aches, cramps and pains; and rhabdomyolysis with myoglobinuria; and. These clinical manifestations may occur individually or in combination. Many patients are asymptomatic most of the time and develop problems only when their level of activity or state of nutrition force their muscles to rely on the defective pathway.

Metabolic myopathies that present with fixed proximal weakness are most easily confused with inflammatory myopathy, because some patients with a metabolic myopathy satisfy criteria proposed by Bohan and Peter for the diagnosis of polymyositis. In addition to proximal weakness, they may have elevated CK levels and "myopathic changes" on electromyography (EMG) and muscle histology. However, the proximal muscle weakness of a metabolic myopathy tends to be mild and slowly progressive. Presumably this situation results from the cumulative effect of recurrent muscle damage from episodic rhabdomyolysis. There may be a

**Table 1****Muscle Glycogenoses**

Deficiency	Clinical Presentation
Acid maltase	infancy: hypotonia, weakness, cardiomegaly, death age < 1 year childhood: myopathy similar to Duchenne dystrophy, respiratory insufficiency adult: myopathy similar to limb-girdle dystrophy or polymyositis, respiratory insufficiency
debrancher enzyme	progressive weakness, hepatomegaly, fasting hypoglycemia
brancher enzyme	myopathy, hepatic cirrhosis and failure
myophosphorylase	exercise intolerance, myalgia, cramps, myoglobinuria late-onset: proximal myopathy
phosphofructokinase	exercise intolerance, myalgia, cramps, myoglobinuria with compensated hemolytic anemia late-onset: proximal myopathy
phosphorylase kinase	exercise intolerance, myoglobinuria, hepatomegaly
phosphoglycerate kinase	exercise intolerance, myoglobinuria, hemolysis, seizures, mental retardation
phosphoglycerate mutase	exercise intolerance, myoglobinuria
lactate dehydrogenase	exercise intolerance, myoglobinuria
aldolase A	exercise intolerance, weakness, nonspherocytic hemolytic anemia
beta-enolase	exercise intolerance

**Disorders of Lipid and Mitochondrial Metabolism of Adolescence and Adulthood**

Deficiency	Clinical Presentation
carnitine (primary)	cardiomyopathy, hypoketotic hypoglycemia, proximal weakness, respiratory muscle weakness
carnitine palmitoyltransferase II	exercise intolerance, myoglobinuria
very long-chain acyl-CoA dehydrogenase	exercise intolerance, myoglobinuria, with or without hypoglycemia
trifunctional protein deficiency	limb-girdle myopathy, episodic myoglobinuria, peripheral neuropathy, hypoparathyroidism
short-chain acyl-CoA dehydrogenase	chronic myopathy
complex I-IV	myopathy with limb-girdle weakness, exercise intolerance with or without progressive external ophthalmoplegia or lactic acidosis
coenzyme Q <sub>10</sub>	muscle weakness, exercise intolerance, myoglobinuria, seizures
complex V	muscle weakness, easy fatigability

predilection for the upper extremity involvement and atrophy may occur. Additional symptoms which suggest a metabolic myopathy include fatigue with repeated muscle use or exercise-induced myalgia or cramping. Furthermore, episodes of weakness may be induced by fasting, unusual exercise intensity, intercurrent infection, alcohol consumption, general anesthesia or some medications. Headache and nausea with exertional weakness or myalgia are highly suggestive of a

metabolic disorder. Finally, rhabdomyolysis with myoglobinuria is likely to portend a metabolic myopathy

**Muscle Glycogenoses**

The most common as well as prototypic muscle glycogenoses is McArdle's disease (myophosphorylase deficiency). The usual clinical picture includes exercise intolerance with myalgia,

stiffness and weakness of the exercising muscles. These symptoms are relieved by rest and, when severe, are associated with myoglobinuria. Many patients with this disease report increase exercise capacity after a brief rest following the initial symptoms of muscle dysfunction. This has been termed the "second wind" phenomenon, and is attributed to the exercise-induced mobilization and delivery of glucose and free fatty acids of non-muscle origin.

As symptoms may begin at any age, generally the disease is characterized among four types of presentation. A rapidly progressive form affects infants, causing generalized weakness, respiratory insufficiency and death. Children may manifest proximal weakness and psychomotor delay. The episodic symptoms with myoglobinuria often begin during adolescence. Some individuals do not become symptomatic until adult years and present with progressive fixed proximal muscle weakness. CK levels are elevated at rest in over 90% of patients, indicating continuous muscle damage with even low levels of physical activity.

Phosphofructokinase (PFK) deficiency (Tarui's disease) is similar to McArdle's disease. However, patients with PFK deficiency are more likely to report nausea and vomiting with myopathic spells. Because of differences in the site of the metabolic block, patients with PFK deficiency cannot use glucose for energy whereas patients with McArdle's can. This explains why high carbohydrate meals exacerbate exercise intolerance in PFK deficient individuals. This has been termed the "out of wind" phenomenon.

## Disorders of Lipid Metabolism

Fatty acid transport and beta-oxidation require the carrier molecule carnitine and the activities of carnitine acyl-carnitine translocase (CACT), carnitine palmitoyltransferase I and II (CPT I and CPT II) and fatty acid acyl-CoA dehydrogenases (CADs). One might think that defects in each of these steps would lead to a similar clinical picture. Curiously, this is not the case. The myopathic form of primary carnitine deficiency usually begins in childhood with proximal muscle weakness. Facial and pharyngeal muscles may be involved as well.

CK levels are elevated in over 50% and most have myopathic changes on electromyography (EMG). In contrast, individuals with CPT II deficiency manifest acute episodes of rhabdomyolysis with rhabdomyolysis. In between episodes, all enzyme levels and other parameters are entirely normal. And SCAD, LCAD deficiencies have been reported to cause an adult-onset chronic myopathy, and combined deficiency of short-, medium-, and long-chain activities (termed mitochondrial trifunctional protein deficiency) have been reported to cause proximal weakness associated with neck pain, elevated CPK and myopathic EMG changes in adults.

## Mitochondrial Myopathies

Most mitochondrial myopathies result from inborn defects in nuclear or mitochondrial DNA. A few defects have been identified in the Krebs (tricarboxylic acid) cycle and many defects are known in each component of the respiratory chain. The tremendous genetic heterogeneity and the rapid rate at which new mutations are being discovered suggest that more mitochondrial myopathies will be described in the future. Exercise intolerance or muscle weakness is the presenting complaint in approximately one quarter of all morphologically defined mitochondrial diseases. Myopathic symptoms, such as progressive, fixed proximal muscle weakness, may be the only manifestation. However, more commonly, additional clinical findings include external ophthalmoplegia, stroke-like episodes, seizures, myoclonus, optic neuropathy, retinopathy, sensorineural hearing loss, ataxia, dementia, myelopathy, and dystonia.

## Myoadenylate Deaminase Deficiency

Myoadenylate deaminase (MADA) is a component of the purine nucleotide cycle. Two percent of the population is homozygous for this deficiency. Some MADA-deficient individuals complain of exercise intolerance due to fatigue and postexertional cramps and myalgia. These symptoms may be triggered by fatigue, infection, anesthesia or starvation. However, the great majority of individuals with this deficiency are asymptomatic.

## Secondary Metabolic Myopathies

The most common acquired metabolic myopathies are those induced by endocrine disorders or drugs. Disorders of the thyroid, adrenal and parathyroid glands commonly cause weakness. These myopathies are due to the effects of the respective hormone on muscle tissue or the effects of drugs on metabolism or electrolyte levels. For example, glucocorticoids, either from Cushing's syndrome or therapeutic use, can induce a proximal myopathy and any factor that alters the level (either raises or lowers) of sodium, potassium, calcium, magnesium or phosphorous can lead to weakness, myalgia or cramping.

Even some mitochondrial myopathies are acquired. Both AZT (zidovudine). and clofibrate have been shown to cause mitochondrial myopathy. The HMG-CoA reductase inhibitors (statins) cause myopathy, at least in part, by inducing a coenzyme Q<sub>10</sub> deficiency. Other secondary mitochondrial abnormalities have been described in several other diseases associated with muscle weakness. These include polymyositis, inclusion body myositis, polymyalgia rheumatica, and sarcoid myopathy, facioscapulohumeral dystrophy and oculopharyngeal myopathies.

## Conclusion

The metabolic myopathies are a heterogeneous group of disorders that result mainly from inborn errors of metabolism. Most of these cause medical conditions that manifest early in life, but, more and more, presentations in teen-age years and adulthood are being recognized. The clinical manifestations of these diseases may be difficult to differentiate from those observed in polymyositis. Muscle enzymes, EMG and the forearm ischemic exercise test may be of some use in diagnosing a metabolic myopathy, but a

thorough analysis of muscle tissue including histochemical staining, electromicroscopy, assays of specific enzymes and mitochondrial DNA analysis often necessary to make the diagnosis.

### FOREARM ISCHEMIC EXERCISE TESTING

#### Method

- Venous blood is collected for measurements of lactate and ammonia are collected, preferably from the nondominant arm without using a tourniquet.
- A blood pressure cuff is inflated around the dominant upper arm and maintained at a pressure 20 to 30 mm of Hg above systolic pressure while the patient vigorously exercises the dominant forearm by squeezing a tennis ball or a rolled up, partially inflated blood pressure cuff. The cuff is kept inflated around the arm until for two minutes or until exercise cause complete exhaustion of the extremity (whichever is longer), at which point it is released.
- Two minutes later, blood is sampled for repeat lactate and ammonia levels from the dominant arm using a tourniquet.

#### Results

- Normal—at least a threefold increase over baseline in venous lactate and ammonia
- Glycogenoses (except for deficiency of acid maltase, phosphorylase b kinase, or branching enzyme)—ammonia levels increase but lactate levels remain at baseline
- Myoadenylate deaminase deficiency—lactate levels increase but ammonia levels remain at baseline.

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