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Metabolic Myopathies

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INTRODUCTION

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Background: Metabolic myopathies refer to a group of hereditary muscle disorders caused by enzymatic defects due to defective gene insult. Metabolic myopathies are heterogeneous conditions that have common abnormalities of muscle energy metabolism that result in skeletal muscle dysfunction. Most recognized metabolic myopathies are considered primary inborn errors of metabolism and are associated with known or postulated enzymatic defects that affect the ability of muscle fibers to maintain adequate adenosine triphosphate (ATP) concentrations. Traditionally, these diseases are grouped into abnormalities of glycogen, lipid, purine, or mitochondrial biochemistry.

Metabolic myopathies are rare but potentially treatable disorders. Metabolic myopathies are the most clearly defined and etiologically understood muscle disorders, because their fundamental biochemical defects are known through recent developments in molecular biology and biochemistry. Also, many of the genetic defects have been characterized, and genetic counseling is now possible.

Metabolic myopathies are important disorders, since they mimic other more commonly encountered neurological diseases. The diagnosis depends on a high index of suspicion and involves correlating certain clinical manifestations to specific metabolic defects. Finally, understanding these muscle disorders enables a better understanding of the dynamics of muscle and body metabolism.

Pathophysiology: Understanding energy metabolism in exercising muscles is a prerequisite to the study of metabolic myopathies. Muscle contraction depends on the chemical energy of ATP. Many processes within the muscle cell maintain a supply of ATP to support muscle contraction. The 3 major pathways that supply ATP to meet the energy demands of exercising muscle are as follows:

- Glycogen metabolism: Aerobic exercise is essential for intermittent or submaximal contraction. Anaerobic exercise may be substituted for high-intensity muscular activity, particularly when blood flow is reduced and oxygen availability is limited.
- Lipid metabolism: Lipid is an important source of energy in sustained submaximal exercise (ie, exercise lasting longer than 40 min).
- Phosphocreatine stores: These stores, consumed in the purine nucleotide cycle, are vital for very high-intensity exercise of short duration, as other stores are depleted early.

The pathophysiological principles of metabolic myopathies may be simplified into a logical biochemical cascade. For example, presume that a series of reactions proceed forward (from substrate A to H) through stepwise enzymatic reactions (ie, enzymes 1-7) as follows:

A -(1)® B -(2)® C -(3)® D -(4)® E -(5)® F -(6)® G -(7)® H

If enzyme 3 is absent (or deficient), some possible results may be as follows:

- Accumulation of substrate C
- Absence (or decrease) in the subsequent substrates (ie, D, E, and so on) needed for metabolism
- Potential disruption in the feedback or rate-limiting effect of one or more of the absent (or deficient) substrate

products

- Potential defect in transportation of substrate into its target destination

Traditionally, the metabolic myopathies are divided into 3 categories, as follows.

Glycogen storage diseases

Muscle cells transport glucose from the circulating blood, synthesize glycogen, and then degrade it when energy demands increase. Muscle cell membrane (ie, sarcolemma) is not freely permeable to glucose; therefore, utilization of circulating glucose is limited by its rate of transportation through the sarcolemma. Glycogen is the main form of carbohydrate storage in the muscle. When energy is required for muscle contraction, glycogen is degraded to glucose and provides the energy required for muscle work. Any disturbance in either the synthesis or the degradation of glycogen could result in glycogen storage disease (ie, glycogenoses).

Lipid storage diseases

Long-chain fatty acids are the major source of energy for the skeletal muscle during sustained exercise and fasting. The passage of these fatty acids through the mitochondrial membrane, for beta-oxidation, requires their binding with carnitine. Carnitine is synthesized mainly in the liver and actively transported into the muscle against a concentration gradient. Free fatty acids are first converted to acyl coenzyme A (CoA) compounds by the action of fatty acyl CoA synthetases. Then, the long-chain acyl CoA is bound to carnitine by acylcarnitine transferases, such as carnitine palmitoyltransferase I (CPT I). This occurs on the outer mitochondrial membrane.

The new compound passes through the inner mitochondrial membrane by the action of acylcarnitine translocase. Within the mitochondrial matrix, carnitine palmitoyltransferase II (CPT II) splits the transferred compound to free fatty acids and carnitine. In the mitochondria, beta-oxidation of the long-chain fatty acids is then carried out. Carnitine deficiency, deficiency of carnitine palmitoyltransferases, or a defect in beta-oxidation of these fatty acids may lead to myopathies.

Disorders of purine nucleotide metabolism

Adenylate deaminase is an enzyme that catalyses transformation of adenosine monophosphate (AMP) to inosine monophosphate (IMP) and ammonia. This reaction mainly occurs during anaerobic exercise to replenish ATP, which is an essential source of energy for the muscles. Myoadenylate deaminase deficiency is the result of a relatively common mutant allele with a heterogeneous clinical presentation.

Mitochondrial disorders

Mitochondrial disorders encompass a group of disorders resulting from abnormalities of the respiratory chain. These are discussed in a separate article.

Frequency: The exact incidence and prevalence of metabolic myopathies is uncertain. They are considered relatively rare and are much less common than most of the muscular dystrophies. However, increased awareness and improved diagnostic capabilities have resulted in increasing number of patients diagnosed with metabolic myopathies. Additionally, the presence of an abnormal allele in some patients, such as with myoadenylate deaminase deficiency, does not result in a specific disorder.

Approximately 2% of the population is homozygous for mutant alleles of myoadenylate deaminase, although not all have clinical symptoms. Acid maltase deficiency (Pompe disease) is seen in approximately 1 in 40,000 people. McArdle disease affects approximately 1 of 100,000 people. Carnitine palmitoyl transferase deficiency is the most commonly identified metabolic cause of recurrent myoglobulinemia in adults, and it has been reported in more than 150 patients. Other forms of metabolic myopathies are much less common.

Mortality/Morbidity: Mortality and morbidity rates vary depending on the specific disorder and the extent of enzymatic defect (ie, complete or partial).

- Mortality rate is high in infantile acid maltase deficiency (AMD; Pompe disease). Invariably, the disease is progressive, leading to death within 1-2 years.
- The childhood form of AMD is less severe, and most children die by the end of the second decade of life from respiratory complications.
- In contrast, patients with the adult form of AMD often present with slowly progressive limb-girdle weakness, but

some develop early respiratory failure secondary to involvement of intercostal muscles. The mortality rate of the adult form of AMD is much lower and the morbidity much less severe than those of the other 2 forms, due to the only partial deficiency of the enzyme.

Age: Metabolic myopathies have a wide age range of symptom onset. Most patients, however, present early in life (ie, infancy, childhood, young adulthood).

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TYPES OF MYOPATHIES

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Clinical features of metabolic myopathies usually include the following:

- Metabolic myopathies presenting with exercise intolerance, cramps, and myoglobinuria
  - Cramps and myalgia may occur after brief exercise or after prolonged physical activity.
  - Glycogen is the main source of energy during brief exercise, while free fatty acids are the most important source of fuel during prolonged exercise. Accordingly, cramps are the hallmark of glycogen storage diseases (eg, McArdle disease). However, in lipid storage disease (eg, CPT deficiency), muscle cramps and exercise intolerance occur only after prolonged exercise and are worse during fasting.
- Metabolic myopathies presenting with progressive muscle weakness
  - These metabolic myopathies may mimic limb-girdle muscular dystrophy or polymyositis.
  - They are a common presentation of deficiencies of acid maltase, debrancher enzyme, and carnitine.
- Glycogen storage diseases (glycogenoses) are named according to their specific defective enzyme function, an eponym, or by Roman numerals that correlate to the time of their discovery (see Table 1). They are as follows:
  - Glycogenosis type I - Glucose-6-phosphatase deficiency
  - Glycogenosis type II - Acid maltase deficiency (AMD); Pompe disease in infants; autosomal recessive (17q23)
  - Glycogenosis type III - Debrancher enzyme deficiency; Cori-Forbes disease; autosomal recessive (1p21)
  - Glycogenosis type IV - Brancher enzyme deficiency; Andersen disease; autosomal recessive (3p12)
  - Glycogenosis type V - Muscle phosphorylase deficiency; McArdle disease; autosomal recessive (11q13)
  - Glycogenosis type VI - Liver phosphorylase deficiency
  - Glycogenosis type VII - Phosphofructokinase deficiency; Tarui disease; autosomal recessive (12q13.3)
  - Glycogenosis type VIII - Phosphorylase b kinase deficiency; X-linked recessive (Xq12)
  - Glycogenosis type IX - Phosphoglycerate kinase deficiency; X-linked recessive (Xq13)
  - Glycogenosis type X - Phosphoglycerate mutase deficiency; autosomal recessive (7p12-p13)
  - Glycogenosis type XI - Lactate dehydrogenase deficiency; autosomal recessive (11p15.4) (isozyme LDH-M on chromosome 11/ LDH-H on chromosome 12)

- Glycogenosis type XII - Aldolase A deficiency; autosomal recessive (16q22-q24)

The following is a discussion of the two most common glycogen storage diseases, followed by Table 1, which summarizes some of the other rare forms of glycogen storage disease.

Acid maltase deficiency (Pompe disease; glycogen storage disease II)

Pompe disease is a rare, autosomal-recessive, progressive metabolic myopathy caused by a deficiency of the intralysosomal enzyme alpha-glucosidase (GAA), that cleaves 1,4- and 1,6-alpha-glycosidic linkages. The GAA gene is linked on the long arm of Chromosome 17 with more than 150 mutations has been identified. These multiple genetic mutations may account for the variability of age of presentation and mode of expression. Pompe disease is commonly divided into infantile form, childhood form, and adult form. The level of residual activity of the enzyme seen with biochemical analysis correlates with the severity of the disease. The overall incidence is approximately 1 in 40,000-50,000 live births, with a prevalence of 5,000-10,000 cases worldwide.

Infantile acid maltase deficiency

Infants with AMD often present within the first few months of life with hypotonia, weak bulky muscles, macroglossia, hepatomegaly, cardiomegaly, and congestive heart failure. Infantile AMD is a progressive systemic disease that culminates in death within 1-2 years. Respiratory failure and feeding difficulties are common, and death usually is caused by cardiorespiratory failure before the child reaches age 2 years.

ECG shows short PR interval, high QRS voltage, and left ventricular hypertrophy. Echocardiography demonstrates marked thickening of the interventricular septum and posterior left ventricular wall, left ventricular outflow obstruction, and trabecular hypertrophy.

Pathological studies reveal massive accumulation of glycogen in liver, heart, and skeletal muscles. Microscopic examination shows more glycogen deposition in smooth muscle, endothelial cells, lymphocytes, all cellular components of the eye (except the pigmentary epithelium of the iris and retina), and renal glomerular and interstitial cells (sparing the distal tubular cells). Most cells of the brain and spinal cord are affected, but cerebellar and cortical neurons are spared. Motor neurons of the brain stem and spinal cord are most severely involved. Glycogen also accumulates in Schwann cells in the peripheral nerves.

Appropriate biochemical studies establish the correct diagnosis. Acid maltase is deficient in muscle, liver, heart, leukocytes, and cultured fibroblasts.

Disorders with similar clinical presentations should be considered in the differential diagnosis, including the following:

- Cytochrome c oxidase enzyme deficiency syndromes
- Debranching enzyme deficiency
- Congenital myopathies (nemaline, centronuclear, central core)
- Inflammatory myopathies (polymyositis)
- Secondary carnitine deficiency syndromes associated with organic acidurias
- Fatal infantile cardioskeletal myopathy without AMD

Childhood acid maltase deficiency

Childhood AMD presents in late infancy or early childhood. Motor milestones are delayed, and the weakness usually is greater in proximal than distal muscles. Respiratory muscles tend to be involved selectively early in the course of the disease. Enlargement of calf muscles may occur, thereby confusing the presentation with muscular dystrophies. Sometimes, liver, tongue, or heart enlargement also may occur. AMD has been reported to be associated with basilar artery aneurysm, which may lead to subarachnoid hemorrhage.

The disease progresses slowly, and the usual cause of death is respiratory failure in the second decade of life. However, patients surviving longer than 20 years have been reported.

Pathological studies reveal that glycogen excess in muscle is relatively less marked than in infantile AMD. Autopsy studies show little, if any, increase in glycogen in liver, heart, skin, and nervous system. Autopsies of patients who died of subarachnoid hemorrhage show abnormal lysosomal storage material in the smooth muscle fibers of the arterial vessel wall.

Biochemical testing confirms deficiency of acid maltase enzyme in skeletal muscle, heart, liver, and cultured fibroblasts. Sometimes, residual enzyme activity is detected.

Adult acid maltase deficiency

Adult AMD presents after age 20 years, either as a slowly progressive myopathy, which clinically mimics polymyositis or limb-girdle muscular dystrophy, or with symptoms of respiratory failure, or both. Weakness affects the proximal muscles more than the distal muscles. Selective muscle weakness is not uncommon, eg, the sternal head of pectoralis major often is affected more than the clavicular head and the thigh adductors are affected more severely than other lower limb muscles. Scoliosis affects about 10% of patients. Atrophy of muscles, when present, is proportionate to the weakness. The deep tendon reflexes diminish and disappear with the progression of weakness. About 30% of patients present with respiratory failure. An increased association with basilar artery aneurysms exists.

Diagnosis of acid maltase deficiency

Laboratory values of creatine kinase (CK) are elevated in 95% of patients, highest in the infantile form, usually 10 times normal.

Usually, nerve conduction study findings are normal. Needle electromyography (EMG) may reveal increased insertional activity and/or myotonic discharges without clinical myotonia. Short-duration, low-amplitude motor unit potentials may be detected in proximal muscles.

Pathologic examination reveals vacuolar myopathy with an increased amount of glycogen and increased activity of acid phosphatase within these vacuoles. However, a normal muscle biopsy has been reported in up 1/4 of cases with Pompe disease.

The diagnosis is confirmed through biochemical analysis of GAA enzyme activity. This could be performed on lymphocytes, skin fibroblasts, muscle tissue, or a dried blood spot.

Differential diagnosis of childhood and adult acid maltase deficiency

Late-onset AMD may be confused with the following because of the proximal weakness:

- Polymyositis or limb-girdle muscular dystrophy
- Becker muscular dystrophy because of calf muscle enlargement
- Myotonic dystrophy because of myotonic discharges on needle EMG
- Motor neuron disease because of respiratory failure as an initial presentation

Important clinical clues that direct attention to the diagnosis of AMD are as follows:

- Muscle weakness with firm consistency of the muscle on palpation
- Selective involvement of the respiratory muscles and diaphragm

- Myotonic discharges on needle EMG without clinical myotonia
- Organomegaly, especially in children

Therapy

Recently, intravenous recombinant acid alpha-glucosidase (rhGAA) was used in a phase II clinical trial to treat the classic infantile form of the deficiency (Pompe disease). The rhGAA was obtained from the milk of transgenic rabbits and delivered intravenously to 2 patients over 48 weeks. An improvement in left ventricular mass, cardiac function, skeletal muscle function, and histological appearance of skeletal muscle was noted. These findings point the way for further enzymatic treatments of these patients. The US Food and Drug Administration has now designated rhGAA (Myozyme) as an orphan drug.

McArdle disease (myophosphorylase deficiency; glycogenosis type V)

McArdle disease usually begins in childhood or early adolescence, typically with attacks of muscle cramps and pain and, in 50% of patients, myoglobinuria. Many patients with exercise-induced muscular pain or cramps are able to continue with their activities following a brief period of rest (ie, second-wind phenomenon). Fixed muscle weakness, usually mild, is common in older patients. Rarely, McArdle disease may present in adulthood with muscle weakness.

McArdle disease usually is inherited as an autosomal recessive disorder but sometimes as a dominant trait. It is encoded by a gene on chromosome band 11q13. More than 30 different mutations have been identified to date.

Levels of CK at rest are almost always elevated in McArdle disease. Patients may have an elevated potassium level during exercise. However, a key diagnostic feature is the absence of a rise in serum venous lactate during the Forearm ischemic exercise test in Workup. Also, the cramp, when recorded by needle EMG, is silent (contracture). Definitive diagnosis requires biochemical testing showing the enzyme deficiency in muscle.

McArdle disease is a common cause of recurrent rhabdomyolysis and myoglobinuria, second only to CPT deficiency. However, differentiating these 2 disorders requires a detailed history of the characteristics of exercise intolerance (see Table 2).

Specific effective treatment is not available. Situations that precipitate myoglobinuria, such as vigorous exercise, should be avoided. Occasionally, a high-protein diet is helpful, on the basis of the theory that branched-chain amino acids may be used as a fuel alternative to glycogen. However, the branched amino acids lower the levels of free fatty acids; therefore, some patients express exercise impairment rather than improvement. Vitamin B-6 has been used since it is deficient in some patients, with questionable results. Paradoxically, regular moderate exercise has been proposed to prevent deconditioning and to promote overall cardiovascular health and the circulatory capacity of blood-borne fuels that may promote an increase in mitochondrial biogenesis.

Recently, a placebo-controlled study evaluating the administration of the dietary supplement carnitine has shown a significant increase in ischemic, isometric forearm exercise capacity. However, no improvement occurred in the nonischemic isometric exercise or in cycle exercise. These results are encouraging for those studying other possible treatments.

Table 1. Other Less Common Glycogenoses

Condition	Clinical Features	Laboratory Findings	Genetics
Phosphofructokinase (PFK) deficiency (glycogenosis VII, Tarui disease)	Exercise intolerance Myoglobinuria Mild hemolytic anemia Indistinguishable clinically from McArdle disease, except by enzyme assay Normal muscle strength, except in old age	Hemolytic anemia CK elevated Forearm exercise test - No rise in lactate PFK absent in muscles	Autosomal recessive trait Gene location - Band 1cenq32 Male predominance (unexplained) in Ashkenazi Jews
		CK level elevated Forearm ischemic	Autosomal

Phosphoglycerate mutase deficiency (glycogenosis X)	Exercise intolerance Myoglobinuria Normal muscle strength	Forearm ischemic exercise test - Reduced (not absent) rise in lactate Enzyme - Reduced in muscles	recessive trait Gene location - Band 7p12-13 Predominantly African American
Lactate dehydrogenase deficiency (LDH) (glycogenosis XI)	Excessive fatigue and exercise intolerance, especially for maximal exercise Myoglobinuria Normal muscle strength	CK level elevated (with normal serum LDH) Forearm ischemic exercise test - No rise in lactate Normal rise in pyruvate Absent or reduced LDH in muscles and RBCs	Autosomal recessive trait Gene location - Band 11p15.4
Phosphoglycerate kinase (glycogenosis IX)	Two forms: (1) seizure, mental retardation, and (2) exercise intolerance and myoglobinuria with slowly progressive weakness	Hemolytic anemia CK level elevated Forearm ischemic exercise test - No rise in lactate level EMG usually normal Absent or reduced enzyme in muscles	X-linked recessive trait Gene location - Band Xq13

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OTHER DISORDERS

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Carnitine deficiency

Whether carnitine deficiency manifests as a spectrum of disorders or is 2 separate entities remains a matter of debate. However, most clinical cases of the deficiency are ascribed to one of the following 2 types of carnitine deficiencies:

Myopathic carnitine deficiency

Myopathic carnitine deficiency is attributed to impairment in the active transportation of carnitine from the plasma into muscle cells. Hence, carnitine level is reduced in muscles and is normal or slightly decreased in plasma and liver.

Clinically, carnitine deficiency manifests during childhood or early adult life as progressive proximal muscle weakness, exertional myalgias, or, rarely, myoglobinuria.

Pathologically, the muscle shows an increased number of lipid droplets, especially in type I muscle fibers. Electron microscopy often confirms the abnormal lipid accumulation with minimal or no increase of mitochondria.

Systemic carnitine deficiency

Systemic carnitine deficiency is attributed to impaired hepatic biosynthesis and/or excessive renal excretion of carnitine. Plasma, liver, and muscle carnitine levels are reduced.

The disorder usually manifests in infancy or childhood as progressive muscle weakness or episodes of hepatic and cerebral dysfunction precipitated by sustained exercise or fasting. This often simulates Reye syndrome. Cardiomyopathy and congestive heart failure are common and may be the direct cause of death.

Pathologically, the muscle shows marked increase in the number of lipid droplets, mainly in type I muscle fibers.

Carnitine deficiency in muscle and plasma is not specific for carnitine deficiency disorders. It may be encountered in genetic diseases (eg, mitochondrial myopathies, advanced cases of X-linked muscular dystrophies) or acquired disorders (eg, patients on hemodialysis or valproate therapy).

Carnitine palmitoyltransferase deficiency

CPT deficiency is the most commonly identified metabolic cause of recurrent myoglobinuria in adults. Men are affected more than women.

Symptoms start soon after puberty, but often patients come to medical attention following an attack of rhabdomyolysis and myoglobinuria. Patients often have episodes of muscle pain, stiffness, and tenderness, usually without frank cramps. The attacks are triggered by prolonged exercise, especially in fasting conditions.

Patients with CPT deficiency often have history of recurrent episodes of rhabdomyolysis and myoglobinuria dating back to childhood. When severe, myoglobinuria may result in acute renal failure. Most of the episodes of rhabdomyolysis are precipitated by prolonged exercise, especially when combined with exposure to cold weather or fasting. Some episodes are precipitated by concurrent infection. The patients usually have no warning signs, like cramps, as in glycogenoses. Rhabdomyolysis results in marked elevation of serum CK and the release of myoglobin into the plasma. When myoglobin is excreted through kidneys, it gives the urine a distinct dark color (cola color), which is characteristic of myoglobinuria.

As outlined above, 2 CPT enzymes, CPT I and CPT II, exist. Both are essential in the transport of long-chain fatty acids from the cytosol to the mitochondria. CPT II deficiency is more common and is inherited as an autosomal recessive trait (gene is located on band 1p32).

In addition to the adult muscular form, CPT I or CPT II deficiency may cause a rare but severe and fatal disease in the neonatal period and during early infancy. This is characterized by hypoketotic hypoglycemia and multiple organ malformations (eg, microgyria, neuronal heterotopia, renal cystic dysplasia, facial dysmorphism). Another rare disorder linked to CPT II deficiency is manifest in infancy as hypoketotic hypoglycemia, hepatomegaly and hepatic failure, cardiomegaly and arrhythmias, lethargy, seizure, and coma.

A more severe CPT deficiency (CPT I) is related to a separate gene that has been mapped to human chromosome band 1p32 by Gellera et al.

Diagnosis of carnitine palmitoyltransferase deficiency

Usually, the diagnosis is suggested by the typical history of exercise-induced myalgia (the most common symptom), with recurrent myoglobinuria, and is supported by a normal ischemic exercise test result. However, myoglobinuria has been reported to be missing in 21% of patients, so it is not essential for the diagnosis. Usually, CK level is normal between attacks. Plasma carnitine level may be increased in CPT I deficiency, but it is usually normal in CPT-II. Patients will have a high ratio of palmitoylcarnitine + oleocarnitine/acetylcarnitine. Findings of electrodiagnostic studies, including needle EMG, as well as the morphological and histochemical studies on muscle biopsy, may be normal, which does not exclude the diagnosis of CPT deficiency. CPT deficiency should be differentiated from glycogen storage diseases, particularly McArdle disease (Table 2).

The final diagnosis usually is established through biochemical demonstration of CPT deficiency in the muscle or by identification of the genetic defect. Earlier studies suggested that a decrease of CPT level in cultured fibroblasts was a diagnostic test. However, recent advances have discovered that cultured fibroblasts harbor the liver isoform but not the muscle isoform of CPT.

Therapy

No specific treatment for CPT deficiency exists. However, preventive measures, such as high-carbohydrate and low-fat diet and frequent small meals, may be helpful in alleviating muscle pain. Carbohydrate supplements also are advised before and during anticipated exercise. Prolonged exercise should be avoided to prevent attacks of rhabdomyolysis. Recently, it has been shown that a diet that is rich in polysaccharides (although not glucose) can improve exercise intolerance in those with CPT II.

Table 2. Differences Between McArdle Disease and CPT Deficiency

	McArdle Disease (glycogenosis V)	CPT Deficiency

Metabolic defect	Glycogen storage	Lipid storage
Exercise	Usually cramps with short strenuous exercise	Usually myalgia and tenderness (without cramps) with prolonged exercise, worse with fasting
Second-wind phenomenon	Present	Absent
Recurrent myoglobinuria	Less frequent (50% of patients)	Common
CK at rest	Increased	Normal
Ischemic forearm exercise test	Absence of normal increase in lactate level	Normal
Muscle biopsy	Usually shows glycogen accumulation	May be normal
Gene location	Band 11q13	Band 1p32 (CPT II)

Myoadenylate deaminase deficiency

Most subjects with myoadenylate deaminase (MAD) deficiency are asymptomatic. The most commonly reported complaints are muscle cramps, exercise intolerance, fatigue, stiffness, and pain after exercise. It is not clear whether this deficiency is clinically significant or is an epiphenomenon, since approximately 3% of muscle biopsies studied have MAD deficiency. Many of these biopsies were performed on patients with specific neuromuscular disorders and symptoms not consistent with MAD deficiency.

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DIFFERENTIAL DIAGNOSES

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Dermatomyositis
Polymyositis
Limb-girdle muscular dystrophy

Other problems to be considered

Becker muscular dystrophy
Myotonic dystrophy
Motor neuron disease
In infants with acid maltase deficiency, the following:

- Cytochrome c oxidase enzyme deficiency syndromes
- Debranching enzyme deficiency

- Secondary carnitine deficiency syndromes associated with organic acidurias
- Fatal infantile cardioskeletal myopathy without acid maltase deficiency

Lab studies

- Serum CK level may be elevated modestly in metabolic myopathies, and the level may fluctuate significantly in patients prone to rhabdomyolysis.
- CBC and reticulocyte count may reveal signs of hemolytic anemia in patients with phosphofructokinase deficiency.
- Needle EMG may show myotonic discharges in AMD, a relatively specific finding in patients with suspected metabolic myopathy. In general, needle EMG may reveal short-duration, low-amplitude motor unit action potentials. However, EMG readings may be normal in many metabolic myopathies.
- Forearm ischemic exercise test: McArdle introduced this test in 1951. It is a useful screen to detect a possible enzymatic defect in the glycogenolytic and glycolysis pathways.
    - Technique
        - Insert an indwelling catheter in a superficial antecubital vein.
        - Draw blood for lactate and ammonia as baseline samples.
        - Apply a sphygmomanometer on the arm to be tested and raise its pressure slightly above the systolic blood pressure.
        - Ask the patient to exercise repetitively for 1 minute by using an ergometer or by making a hard fist around a rolled-up sphygmomanometer cuff.
        - Assess the power generated by the patient by checking the ergometer or noting the rise in the

mercury column.

- Stop exercise, deflate the sphygmomanometer, and draw blood samples at 1, 3, 6, and 10 minutes after 1 minute of exercise for lactate and ammonia.

- Remarks
  - Some clinicians prefer to perform the test without producing ischemia (ie, do not apply sphygmomanometer cuff on the arm). This renders the test less painful with less potential for cramps. Advocates of the test have claimed positive results without producing ischemia in patients with glycogenoses.
  - In a series of patients with suspected glycogenosis, applying pressure almost equal to the systolic pressure resulted in the test being less painful with reliable results in all the tested children except 2 who were younger and less cooperative.
- Findings
  - In healthy subjects, lactate level should increase to 3-5 times the basal level in the first 2 samples after exercise and then decrease gradually to the baseline.
  - Ammonia level also should increase after exercise. Ammonia level is useful not only as a monitor of sufficient exercise but also as a test for myoadenylate deaminase deficiency (MAD).
  - In glycogen storage diseases, such as McArdle disease, serum lactate levels do not increase after exercise (ie, flat lactate curve), while in lipid storage diseases, both lactate and ammonia levels increase in a normal fashion.
  - In MAD deficiency, ammonia does not increase (ie, flat ammonia curve).
  - On rare occasions, 2 enzyme defects are found in the same patient, such as myophosphorylase or phosphofructokinase defect along with adenylate deaminase defect. The latter usually is due to poor effort during exercise.

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