CHAPTER 19

Metabolic Myopathies

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- The metabolic myopathies are a heterogeneous group of diseases characterized by impaired skeletal muscle energy production.
- Primary metabolic myopathies are associated with genetic defects in glycogen and lipid metabolism.
- Secondary types occur with abnormal production of parathyroid, thyroid, and cortisol production and vitamin D deficiency.
- Symptoms occur mainly during or shortly after exercise and include pain, weakness, and cramping, and can result in myoglobinuria due to muscle necrosis.

The metabolic myopathies are a heterogeneous group of diseases characterized by impaired skeletal muscle energy production. Primary metabolic myopathies are associated with genetically determined defects in glycogen and lipid metabolism and in mitochondrial oxidative phosphorylation. These include the muscle glycogenoses and the lipid and mitochondrial myopathies. Other metabolic myopathies arise from endocrine or electrolyte abnormalities and therapy with specific drugs. A classification of the primary metabolic myopathies is presented in Table 19-1.

The symptoms of a metabolic myopathy develop predominantly during or shortly after muscle exertion, and include muscle weakness, pain, stiffness, and cramping, sometimes culminating in myoglobinuria due to muscle fiber necrosis. Patients with metabolic myopathies may also develop fixed proximal muscle weakness, generally mild in severity, and be misdiagnosed as having polymyositis. While the symptoms of a metabolic myopathy are usually first experienced in childhood or early adulthood, they may also develop later in adult life.

The type of exercise intolerance varies in relation to the defect in muscle bioenergetics (Figure 19-1). Patients with muscle glycogenoses develop muscle pain and cramps early during strenuous exertion, at a time when muscle energy is derived from glycogen. Patients with defects of lipid metabolism experience similar muscle symptoms during or shortly after prolonged lower-intensity exercise or during fasting, reflecting the dependence of muscle on free fatty acids as their primary energy source during these conditions. Patients with mitochondrial myopathies have impaired muscle oxygen utilization, as a result of defects in oxidative phosphorylation. With exercise, there is an exaggerated circulatory and ventilatory response to overcome the block in muscle oxygen utilization. As a result, patients note undue fatigue and dyspnea during low levels of exertion, including moderate activities of daily living.

The diagnosis of a metabolic myopathy should be suspected in a patient with muscle symptoms that develop during or after exercise, particularly if associated with myoglobinuria. These diseases should also be included in the differential diagnosis of slowly progressive proximal or truncal muscle weakness. Support for the diagnosis of certain metabolic myopathies can be gained from the measurement of organic and amino acids in the blood and urine and exercise testing, including the ischemic forearm exercise test and cycle ergometry (Table 19-1). Confirmation of the diagnosis usually requires muscle biopsy and/or molecular genetic testing (1).

PRIMARY METABOLIC MYOPATHIES

Muscle Glycogenoses

The glycogen storage diseases arise from inherited defects in glycogen degradation, glycogen synthesis, or glycolysis. Eleven defects in glycogen metabolism affect skeletal muscle, either alone or together with other organs and are known as muscle glycogenoses (2). The classic clinical manifestation of a muscle glycogenosis is exercise intolerance. Patients develop painful cramps and swelling of the exercising muscles, sometimes associated with myoglobinuria. The symptoms are relieved by rest. In some muscle glycogenoses, progressive muscle weakness is the predominant clinical presentation (Table 19-1).

The most common muscle glycogenosis is myophosphorylase deficiency (McArdle's disease), with an

TABLE 19-1. KEY FEATURES OF THE PRIMARY METABOLIC MYOPATHIES.

BIOCHEMICAL CLASS	ENZYME OR BIOCHEMICAL DEFECT	GENETICS	MUSCLE SYMPTOMS	OTHER CLINICAL FEATURES	LABORATORY FEATURES	DIAGNOSTIC TESTING
Defects in glycogenolysis or glycolysis (glycogenoses)	Myophosphorylase	AR	Exercise intolerance	Second wind phenomenon	Variable ↑ serum CK	Abnormal FIET
	Phosphofructokinase	AR	Exercise intolerance; proximal myopathy (late onset)	Out of wind phenomenon Hemolytic anemia, Gout	↑ serum CK, uric acid	Abnormal FIET
	Phosphorylase b kinase	AR	Myopathy in childhood	Hepatomegaly, Fasting hypoglycemia	↑ serum CK	
		AR(?XR)	Exercise intolerance, myoglobinuria		↑ serum CK	
	Phosphoglycerate mutase	AR	Exercise intolerance, myoglobinuria	Most often in African Americans	↑ serum CK	Abnormal FIET
	Lactate dehydrogenase	AR	Exercise intolerance, myoglobinuria		LDH does not rise in proportion to serum CK	Abnormal FIET with elevated pyruvate/ lactate ratio
	Phosphoglycerate kinase	XR	Exercise intolerance, myoglobinuria	Hemolytic anemia CNS dysfunction	Variable ↑ serum CK	Abnormal FIET
	Debrancher (adult patients)	AR	Generalized or distal weakness	Hepatomegaly, Left or biventricular hypertrophy		
	Brancher	AR	Progressive myopthy	Cardiomyopathy, Hepatomegaly		
	Aldolase	AR	Exercise intolerance Weakness	Hemolytic anemia		
	Acid maltase (nonclassical forms)	AR	Progressive myopathy	Respiratory insufficiency	Deficient alpha-glucosidase in leucocytes and muscle	Myotonic discharges on EMG

Defects in fatty acid transport	Carnitine deficiency (primary systemic)	AR	Facial and proximal myopathy	Hypoketotic hypoglycemia, Encephalopathy, Cardiomyopathy	Total serum carnitine <5% normal	Reduced muscle carnitine
	Carnitine deficiency (primary myopathic)	AR	Progressive myopathy		Normal serum carnitine levels; variable ↑ serum CK	Muscle carnitine levels <25% normal
	Carnitine palmitoyltransferase II	AR	Exercise intolerance, myoglobinuria		Serum CK normal between attacks	
Defects in fatty acid beta-oxidation	Multiple acyl coA dehydrogenase		Progressive myopathy		Increased urinary glutaric acid Increased plasma acyl-carnitine	
	Very-long-chain acyl coA dehydrogenase (adult phenotype)		Exercise intolerance, myoglobinuria			
	Trifunctional protein enzyme		Myoglobinuria	Peripheral neuropathy	Increased urinary DCAs	
Defects in respiratory chain function (mitochondrial myopathy)	Mutations in mtDNA or nDNA genes that determine mitochondrial respiratory chain function	Maternal Mendelian Sporadic	Exercise intolerance, ptosis, external ophthalmoplegia	Axonal neuropathy, Ataxia Seizures, Pigmentary retinopathy, Sensorineural hearing loss	Elevation of resting, fasting blood lactate	Abnormal cycle ergometry
Defects in purine nucleotide cycle	Myoadenylate deaminase	AR			None	Abnormal FIET

SOURCE: Data from References 1, 2, 12, 14, 15, 16.
ABBREVIATIONS: CK, creatine kinase; FIET, forearm ischemic exercise test; AR, autosomal recessive; XR, X-linked recessive; DCA, dicarboxylic acid; EMG, electromyography; mtDNA, mitochondrial DNA; nDNA, nuclear DNA.

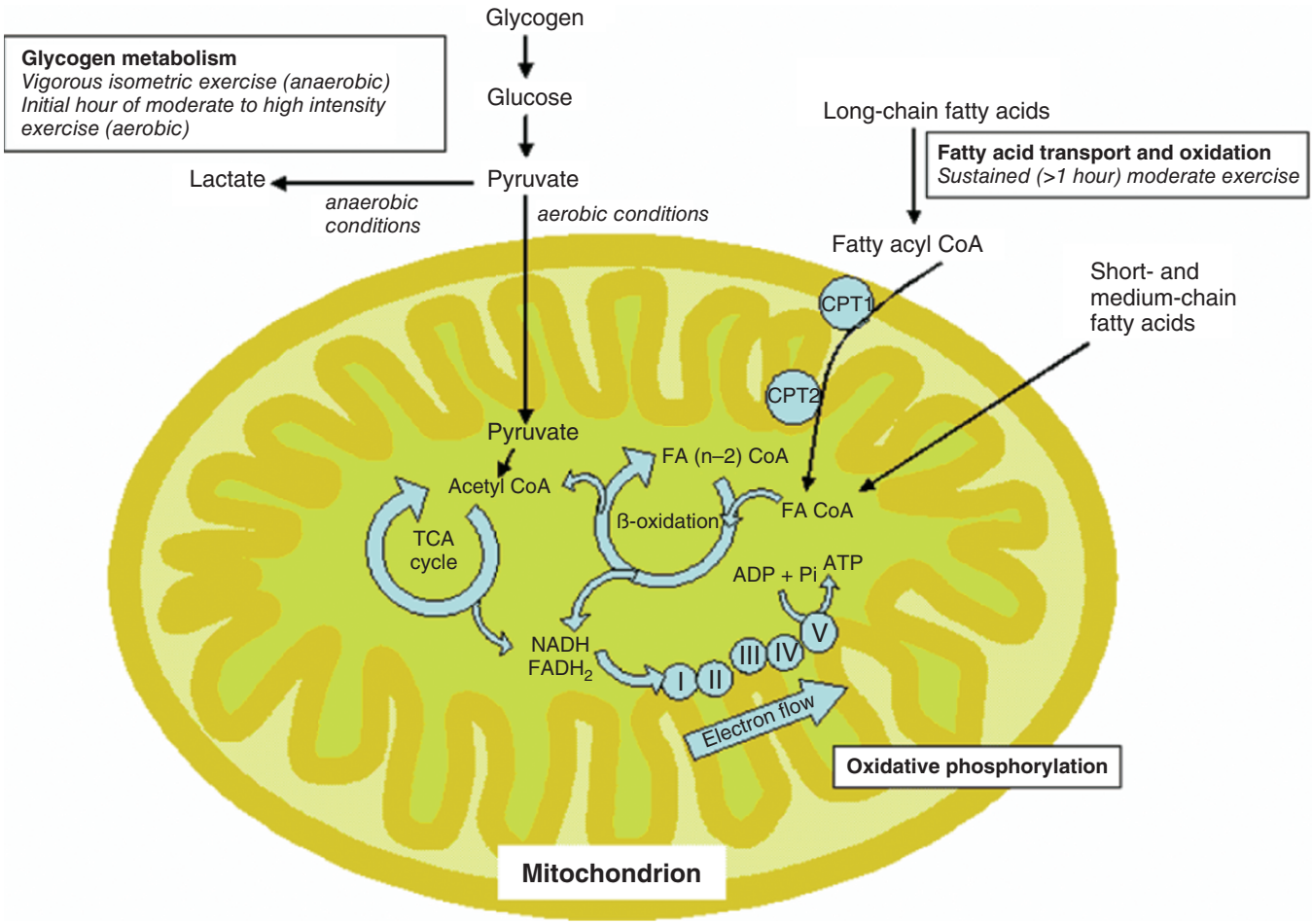

FIGURE 19-1

Skeletal muscle bioenergetics. The primary muscle fuels are glucose and free fatty acids. At rest, muscle utilizes predominantly fatty acids. During a sudden, vigorous bout of exertion, energy is derived from anaerobic glycolysis. Glucose, derived primarily from the breakdown of muscle glycogen, is metabolized by the glycolytic pathway to yield pyruvate. In anaerobic conditions, the pyruvate is converted to lactate. During submaximal exercise, the utilization of muscle fuels depends on its relative intensity and duration. At higher intensities, aerobic metabolism of glycogen is an important source of energy. Pyruvate derived from glycolysis enters mitochondria and is metabolized by the tricarboxylic acid (TCA) cycle. At lower intensities, muscle energy is derived from both blood glucose and free fatty acids. With longer durations of low intensity exercise, free fatty acids become the primary fuel source. The free fatty acids enter the mitochondria, either via the carnitine shuttle (long-chain fatty acids) or by passive diffusion (short and medium chain fatty acids). The carnitine shuttle transports fatty acids into mitochondria as their acylcarnitine derivatives and involves the enzymatic activities of the carnitine palmitoyltransferases, CPT1 and CPT2. Within the mitochondria, the fatty acids are converted to their coenzyme A (CoA) derivative and then undergo successive cycles of beta-oxidation, their acyl chains shortening by two carbons with each cycle. Acetyl CoA, NADH, and $FADH_2$ are produced during each cycle of beta-oxidation; the acetyl CoA is then metabolized in the TCA cycle, yielding additional molecules of NADH and $FADH_2$. Electrons derived from these reduced flavoproteins are passed along the respiratory chain, releasing energy that is stored as a proton gradient across the mitochondrial inner membrane. This energy is used by the last component of the respiratory chain, adenosine triphosphate (ATP) synthase, to produce ATP from adenosine diphosphate (ADP) and phosphate.

estimated prevalence of 1 case per 100,000 persons (3). Symptoms develop during intense isometric exercise, such as weight lifting, and during the initial minutes of moderately intense exertion, such as walking uphill (2). Most affected persons are well at rest and can function without difficulty at low levels of exertion. Symptoms often begin during childhood, but significant problems, such as severe cramping or exercise-induced rhabdomyolysis, may not develop until the teenage years. Patients with myophosphorylase deficiency may first present in mid-adult life with a history of slowly progressive proximal muscle weakness. Patients commonly describe a "second wind" phenomenon. With the initial onset of exercise-induced symptoms, they must stop or reduce the level of exercise, but are often able to resume the same level of exercise with better endurance after a few minutes of rest. The second wind occurs as a result of increased availability of blood glucose and free fatty acids derived from nonmuscle sources.

Serum creatine kinase (CK) levels are commonly increased in the muscle glycogenoses. Electromyography (EMG) may be normal or show nonspecific myopathic changes. The forearm ischemic exercise test is a useful screening test for most of these disorders (4). In one version of the test, the patient squeezes a ball repeatedly for 2 minutes or to the point of exhaustion while arterial blood flow to the exercising arm is occluded by a blood pressure cuff inflated to above systolic blood pressure (5). The blood pressure cuff is then released. Levels of lactate and ammonia are measured in blood obtained from the antecubital vein of the exercising arm, both at baseline and then 2 minutes after the cessation of the anaerobic exercise. In individuals with a muscle glycogenosis (except in those with acid maltase, brancher enzyme, or phosphorylase b kinase deficiencies), plasma levels of ammonia increase at least threefold while those of lactate do not rise. False-positive results may result if the patient does not exercise with sufficient vigor to increase lactate production. The characteristic abnormality on muscle biopsy is PAS (periodic acid Schiff)-positive deposits of glycogen in the periphery of muscle fibers. The putative diagnosis can be confirmed by specific enzyme analysis of muscle tissue whenever it is suspected based on histology or ischemic exercise testing. Molecular genetic tests for the mutations that account for up to 90% of cases of myophosphorylase deficiency can also be performed using whole blood, thereby obviating the need for muscle biopsy (6).

Adult-onset myopathies may occur in debrancher deficiency. Four different clinical phenotypes are recognized: a generalized myopathy that may resemble polymyositis, a distal myopathy involving calves and peroneal muscles, a selective myopathy of respiratory muscles, and mild weakness accompanying severe liver involvement (7). Childhood hepatomegaly is an important historical feature.

Acid maltase (lysosomal alpha-1,4-glucosidase) deficiency has three modes of clinical presentation (8). The classic form, known as Pompe's disease, is characterized by a hypertrophic cardiomyopathy, progressive myopathy, and death by the age of 2 years. The nonclassic forms are dominated by skeletal muscle involvement (9). A childhood variant is characterized by severe proximal, truncal, and respiratory muscle weakness. Affected individuals usually die of respiratory insufficiency in their second or third decade of life. Acid maltase deficiency may also present in young adults with slowly progressive proximal muscle weakness, simulating polymyositis and limb-girdle muscular dystrophy. In contrast to other muscle glycogenoses, there are no exercise-related muscle symptoms. A minority of adult patients presents with respiratory insufficiency, manifested by dyspnea on exertion, excessive daytime somnolence, or morning headaches. Respiratory involvement eventually occurs in all adults and is the usual cause of death. CK levels are usually elevated. Adult acid maltase deficiency causes characteristic electromyographic changes of intense electrical irritability and myotoniclike discharges in the absence of clinical myotonia. Muscle biopsy shows a glycogen storage vacuolar myopathy. The diagnosis can be confirmed by demonstrating deficient alpha-glucosidase activity in muscle, leucocytes, or fibroblasts.

Management of patients with a muscle glycogenosis includes modification of their exercise and dietary regimens. A high-protein, low-carbohydrate diet is generally recommended for patients with myophosphorylase deficiency because branched chain amino acids may be an alternative to glycogen as a fuel source. Ingestion of sucrose before exercise can markedly improve exercise tolerance (3). Vitamin B_6 and creatine supplementation may also be beneficial. Patients with phosphofructokinase deficiency should avoid high-carbohydrate diets because these may provoke decreased exercise capacity, the so-called out-of-wind phenomenon (10).

Disorders of Lipid Metabolism

The disorders of lipid metabolism in muscle result from various biochemical defects in mitochondria. Some are caused by defective transport of fatty acids into the mitochondria and others by defects in their subsequent beta-oxidation. The mitochondrial myopathies result from defects in oxidative phosphorylation. Disorders of fatty acid transport and oxidation share common features. They present most commonly in the neonatal period or infancy with hypoketotic hypoglycemia and liver dysfunction. Older children and young adults typically present with exercise intolerance and myoglobinuria.

Carnitine is an amino acid that is required for the transport of long-chain fatty acids into mitochondria.

Carnitine deficiency causes a lipid storage myopathy. Primary and secondary types are distinguished. One primary form, inherited as an autosomal recessive trait, is related to mutations in OCTN2, an organic cation transporter (11). It affects multiple tissues and usually presents with a progressive cardiomyopathy in children between the ages of 2 and 4 years, with or without skeletal muscle weakness. Some affected children present at a younger age with recurrent episodes of hypoketotic hypoglycemia and hepatic encephalopathy, resembling Reye's syndrome. Another primary form affects skeletal muscle only (12). It presents in late childhood and through the early adult years as a progressive myopathy affecting the proximal limbs and occasionally the facial and respiratory muscles. The molecular basis for this form has not been defined. Carnitine deficiency may also occur in the setting of other metabolic disorders (fatty acid oxidation disorders, organic acidemias), pregnancy, long-term hemodialysis, end-stage cirrhosis, myxedema, adrenal insufficiency, and chronic treatment with valproate or pivampicillin.

Carnitine deficiency may be confused with polymyositis because serum CK concentrations may be increased and EMG may reveal myopathic changes. Measurement of carnitine levels in muscle and plasma is required to establish the diagnosis. In the systemic form of primary carnitine deficiency, both plasma and tissue carnitine levels are markedly reduced, while in the myopathic form, only carnitine levels in the muscle are reduced. The carnitine deficiency syndromes can be treated effectively with pharmacologic doses of oral carnitine.

Two distinct carnitine palmitoyltransferases (CPT) serve to transport long-chain fatty acids into mitochondria. CPT1 is located on the inner surface of the outer mitochondrial membrane and CPT2 is located on the inner side of the inner mitochondrial membrane. Deficiencies of both CPT1 and CPT2 occur, but muscle disease is confined to the latter. CPT2 deficiency is an autosomal recessive disorder with clinical presentations in juvenile or adult life (myopathic form), in infancy (hepato-cardio-muscular form) and at birth (hepatic form) (13). The myopathic form of CPT2 deficiency is the most common cause of hereditary recurrent myoglobinuria. It occurs most often in young men aged 15 to 30 years. Women are affected far less frequently, usually later in life and with a milder form of the disease. Paroxysmal rhabdomyolysis is the primary clinical feature of CPT2 deficiency and is usually precipitated by sustained exercise, ranging in vigor from strolling to mountain hiking (13). Other precipitants include fasting, infection, or exposure to cold. Stiffness, pain, and weakness of the exercising muscles are commonly experienced following prolonged exercise. True cramps do not occur. Muscle weakness is not present between attacks. Serum CK concentrations, EMG, and muscle histology are normal, except during episodes of symptomatic rhabdomyolysis or, often, after prolonged exercise or fasting. Molecular genetic testing, using whole blood, can detect known mutant alleles in approximately 80% of affected patients (1). The diagnosis may also be established by assaying muscle tissue for enzyme activity. Management of CPT2 deficiency includes avoidance of prolonged fasting and of exercise lasting more than 30 minutes. Consumption of small low-fat, high-carbohydrate meals throughout the day may reduce the frequency of attacks. If sustained exercise is anticipated, carbohydrate loading may prevent attacks. Dietary supplementation with medium chain triglycerides may be beneficial.

Defects in fatty acid beta-oxidation are rare causes of myopathies. Late-onset forms of very-long-chain acyl-coenzyme A dehydrogenase deficiencies may share the same clinical features as CPT2 deficiency (14). The multiple acyl-coenzyme A dehydrogenase deficiencies may present in late childhood or adulthood as lipid storage myopathies. One form, responsive to riboflavin supplementation, is characterized predominantly by respiratory and neck muscle weakness (14). Patients with mitochondrial trifunctional protein enzyme deficiency typically have episodic rhabdomyolysis and a peripheral neuropathy.

Mitochondrial Myopathies

The mitochondrial myopathies are a clinically heterogenous group of disorders that arise due to defects in mitochondrial respiratory chain function. Their varied clinical features and multisystemic nature reflect dysfunction of organs that are highly dependent on oxidative metabolism, such as skeletal muscle, brain, peripheral nerve, organ of Corti, heart, retina, endocrine glands, and renal tubules. Clinical features of these disorders include a proximal myopathy, strokelike episodes, seizures, ataxia, cognitive decline, axonal neuropathy, sensorineural hearing loss, hypertrophic cardiomyopathy, pigmentary retinopathy, diabetes mellitus, short stature, and renal tubular acidosis. A number of diverse syndromes are characterized by specific combinations of these clinical features (15). Predominant involvement of one organ system can also occur. The age at onset of symptoms ranges from birth to late life, but is usually childhood or early adult life (16). Most mitochondrial myopathies are caused by mutations in mitochondrial DNA (mtDNA) genes that encode polypeptide subunits of the respiratory chain or transfer or ribosomal RNAs that mediate the synthesis of entire mitochondrial proteins (15). These mtDNA mutations are usually inherited through maternal transmission and are thus expressed in a heteroplasmic fashion in cells and tissues. A minority of mitochondrial myopathies are caused by mutations of genes in the nuclear DNA that encode functional subunits or ancillary proteins of

the respiratory chain, as well as factors involved in intergenomic communication. These nuclear DNA defects are inherited as autosomal recessive or dominant traits. Mitochondrial diseases have an estimated prevalence of 10 to 15 cases per 100,000 persons (15).

Muscle involvement is present in the majority of mitochondrial diseases and varied in its clinical presentation. Chronic progressive external ophthalmoplegia and eyelid ptosis often precede or accompany the skeletal muscle disease (16). Mild weakness of the proximal limb musculature is usually present and is made worse by exertion. Patients often note myalgias and premature fatigue during exercise. Headache and nausea may occur during strenuous activity. More severe defects of oxidative phosphorylation result in a disparity between oxygen delivery and oxygen utilization and a hyperdynamic cardiopulmonary response to exercise (17). Patients thus experience marked tachycardia and exertional dyspnea when they engage in submaximal exercise.

Serum CK levels are normal or only mildly elevated. Electromyography usually shows mild myopathic or neuropathic changes, or a combination of both. An elevated resting and fasting lactate level (>2.5 mmol/L) in the blood has high specificity but only modest sensitivity for the diagnosis (18). Exercise testing using a cycle ergometer typically shows a reduction in maximal whole body oxygen consumption due to a reduction in peripheral oxygen extraction and a disproportionately greater production of carbon dioxide relative to oxygen consumption (18). Muscle biopsy is required for specific diagnosis. The characteristic findings include ragged red fibers, evident with the modified Gomori trichrome stain, and/or muscle fibers with reduced or absent cytochrome c oxidase activity. Electron microscopy may also show mitochondria in increased numbers or with abnormal morphology or inclusions. Identification of the responsible mitochondrial defect requires biochemical assessment of respiratory chain function in muscle tissue, often coupled with molecular genetic studies (19).

Myoadenylate Deaminase Deficiency

Myoadenylate deaminase deficiency is the most common genetic abnormalitiy of skeletal muscle, affecting up to 2% of the population. The affected biochemical pathway normally metabolizes adenosine monophosphate (AMP), generated via the adenylate kinase reaction, to inosine monophosphate and ammonia. This serves to buffer increases in AMP that occur during strenuous exertion. Individuals with this deficiency do not have a measurable impairment in exercise energy metabolism (20) and are almost always asymptomatic. If an individual with this deficiency has muscle weakness, myalgia, or fatigue, another diagnosis should be sought to explain these symptoms. Patients with primary myoadenylate deaminase deficiency have normal serum CK concentrations, EMG, and muscle histology. However, the forearm ischemic exercise test is abnormal. In contrast to the muscle glycogenoses, levels of lactate, but not those of ammonia, increase several-fold in the blood after ischemic exercise.

SECONDARY METABOLIC MYOPATHIES

Proximal muscle weakness is the primary feature of the myopathies that may accompany Cushing's syndrome, hypothyroidism, hyperthyroidism, vitamin D deficiency, acromegaly, and hyperparathyroidism. Hypothyroidism may be associated with elevation of the serum CK and be misdiagnosed as polymyositis. Disorders that cause abnormally high or low concentrations of sodium, potassium, calcium, magnesium, or phosphorus can also cause weakness, fatigue, myalgias, or cramps. Zidovudine may induce a mitochondrial myopathy.

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