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Metabolic Myopathies

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ABSTRACT

Purpose of Review: Metabolic myopathies are genetic disorders that impair intermediary metabolism in skeletal muscle. Impairments in glycolysis/glycogenolysis (glycogen-storage disease), fatty acid transport and oxidation (fatty acid oxidation defects), and the mitochondrial respiratory chain (mitochondrial myopathies) represent the majority of known defects. The purpose of this review is to develop a diagnostic and treatment algorithm for the metabolic myopathies.

Recent Findings: The metabolic myopathies can present in the neonatal and infant period as part of more systemic involvement with hypotonia, hypoglycemia, and encephalopathy; however, most cases present in childhood or in adulthood with exercise intolerance (often with rhabdomyolysis) and weakness. The glycogen-storage diseases present during brief bouts of high-intensity exercise, whereas fatty acid oxidation defects and mitochondrial myopathies present during a long-duration/low-intensity endurance-type activity or during fasting or another metabolically stressful event (eg, surgery, fever). The clinical examination is often normal between acute events, and evaluation involves exercise testing, blood testing (creatine kinase, acylcarnitine profile, lactate, amino acids), urine organic acids (ketones, dicarboxylic acids, 3-methylglutaconic acid), muscle biopsy (histology, ultrastructure, enzyme testing), MRI/spectroscopy, and targeted or untargeted genetic testing.

Summary: Accurate and early identification of metabolic myopathies can lead to therapeutic interventions with lifestyle and nutritional modification, cofactor treatment, and rapid treatment of rhabdomyolysis.

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INTRODUCTION

Metabolic myopathies are genetic skeletal muscle disorders that impact enzymes and proteins involved in intermediary metabolism of glucose and free fatty acids. Although amino acids are part of intermediary metabolism and can be oxidized to a small extent by skeletal muscle,[1] the amino acid oxidation defects do not result in myopathy but rather present with neurocognitive delay or regression in infancy or childhood. Although some experts have considered myoadenylate deaminase deficiency to be part of the group of metabolic myopathies,[2,3] it is not directly involved in intermediary metabolism, and its role in causing a metabolic defect in muscle is seriously questioned. First, the prevalence of homozygous mutations is approximately 2% in the general population,[4] muscle blood flow appears to be enhanced in myoadenylate deaminase–deficient patients with no significant lowering of power,[5] and Tarnopolsky and colleagues[6] have shown that homozygous myoadenylate deaminase–deficient individuals do not show alterations in cellular energy charge in response to high-intensity exercise nor do any of the proposed pathophysiologic mechanisms of the supposed energy deficit appear valid.[6] Consequently, myoadenylate deaminase will not be further considered in this review.

Structural myopathies such as Becker muscular dystrophy (dystrophin), limb-girdle muscular dystrophy (*SGCA, SGCB, SGCD, ANO5*, and *DYSF* mutations), and malignant hyperthermia (*RYR1* and *CACNA1S* mutations) can present with symptoms triggered by exercise and thus mimic the metabolic myopathies;

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KEY POINT

■ Anaerobic energy sources at the onset of exercise include adenylate kinase/adenosine monophosphate deaminase, creatine/phosphocreatine, and anaerobic glycogenolysis/glycolysis.

these have been referred to as the pseudometabolic myopathies.[7–9] The aforementioned myopathies often initially present with hyperCKemia and exercise-induced cramps, myalgia, or rhabdomyolysis, and may progress to a fixed muscle weakness after many years. A key to considering a pseudometabolic myopathy is the persistence of creatine kinase (CK) elevation beyond 10 days after a bout of rhabdomyolysis, although the CK often normalizes in malignant hyperthermia. Statins can also present with a pseudometabolic pattern.[10,11] For example, exercising while taking a statin leads to a greater increase in CK (likely reflective of greater muscle damage) than the same exercise in those not taking a statin.[10,11] Statins can lead to myalgia in up to 10% of individuals, and rhabdomyolysis and autoimmune myopathies may occur in a small fraction of patients treated with statins.[12–14] Statins are also contextually relevant in that they can unmask a metabolic myopathy as has been described in fatty acid oxidation defects, glycogen-storage disease, and mitochondrial cytopathies.[15]

The current review focuses on the metabolic myopathies associated with glycogen-storage diseases, fatty acid oxidation defects, and mitochondrial myopathies (**Table 4-1**).

For a true clinical understanding of the metabolic myopathies, it is first necessary to review the metabolic pathways in the context of exercise and physiologic stress.

SKELETAL MUSCLE METABOLISM

The rest-to-exercise transition initiates an immediate mass action effect of ADP + ADP > ATP + AMP through the adenylate kinase reaction, where ADP is adenosine diphosphate, ATP is adenosine triphosphate, and AMP is adenosine monophosphate. The flux is maintained in the forward direction by myoadenylate deaminase, which catalyses the deamination of AMP to inosine monophosphate, which, through a series of reactions, culminates in the enzymatic (xanthine oxidase) conversion of xanthine to uric acid under anaerobic conditions. Although this pathway is active in normal muscle contraction, it is accentuated in glycogen-storage disease (myogenic hyperuricemia) and is helpful from a diagnostic perspective.[16] Myoadenylate deaminase does not appear to be essential to muscle contraction for the reasons noted previously.

The creatine-phosphocreatine system is important in anaerobic energy metabolism, where, during the rest-to-exercise transition, the increase in ADP is rephosphorylated by phosphocreatine back to ATP through the cytosolic CK reaction. This reaction results in the consumption of a proton that is produced during anaerobic glycolysis and glycogenolysis. Phosphocreatine stores are high in skeletal muscle, brain, and nerves, and phosphocreatine is present in many other tissues. The phosphocreatine stores in skeletal muscle are depleted after approximately 8 to 10 seconds of high-intensity muscle contraction and are rephosphorylated during the rest period by aerobically derived ATP. This initial cytosolic reaction is also important in initiating mitochondrial respiration because the increase in cytosolic ADP translocates through porin (voltage-dependant anion channel) to the intermembrane space where mitochondrial CK uses aerobically derived ATP to convert creatine back to phosphocreatine. The resultant ADP crosses through the adenine nucleotide translocase to the mitochondrial matrix to stimulate mitochondrial state 3 respiration.[17]

Within the first few seconds of contraction, the activation of glycogenolysis and glycolysis leads to the generation of lactate through the lactate dehydrogenase pathway. During the first few minutes of muscle contraction, a progressive increase occurs in mitochondrial respiration and in the delivery of bloodborne substrates to skeletal muscle. As

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TABLE 4-1 Metabolic Myopathies in Skeletal Muscle

▶ **Glycogen-Storage Disease (GSD)**
McArdle disease/GSD5 (myophosphorylase deficiency)
Tarui disease/GSD7 (phosphofructokinase deficiency)
GSD9 (phosphorylase *b* kinase deficiency)
GSD10 (phosphoglycerate mutase deficiency)
GSD11 (lactate dehydrogenase deficiency)
GSD12 (aldolase A deficiency)
GSD13 (β-enolase deficiency)
Phosphoglucomutase deficiency
Phosphoglycerate kinase 1 deficiency
▶ **Fatty Acid Oxidation Defect**
Carnitine palmitoyltransferase II deficiency
Trifunctional protein deficiency
Very–long-chain acyl-coenzyme A dehydrogenase deficiency
▶ **Mitochondrial Myopathy**
Mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS)
Myoclonic epilepsy with ragged red fibers (MERRF)
Chronic progressive external ophthalmoplegia
Kearns-Sayre syndrome
Complex IV deficiency
Cytochrome *b* mutations
Cytochrome *c* oxidase mutations

KEY POINTS

- Aerobic energy is predominantly derived from muscle glycogenolysis (glucose) and lipolysis (free fatty acids) with minor contributions from amino acids. The relative proportion of free fatty acid oxidation increases with longer-duration endurance exercise and fasting.
- The specific selection of intermediary metabolites to fuel aerobic muscle contraction is a function of many factors including exercise training status, macronutrient intake (habitual and during exercise), as well as exercise intensity and duration.
- At exercise intensities below 50% VO_{2max}, most individuals will oxidize predominantly free fatty acids. The proportion of carbohydrates contributing to energy supply increases at higher exercise intensities.

mitochondrial respiration increases, an expansion of the tricarboxylic acid cycle intermediates occurs, which allows the glycolytic and glycogenolytically derived pyruvate to enter the tricarboxylic acid cycle via the pyruvate dehydrogenase pathway.[18]

The specific selection of intermediary metabolites to fuel aerobic muscle contraction is a function of many factors including exercise training status, macronutrient intake (habitual and during exercise), as well as exercise intensity and duration. Aerobic exercise intensity is usually measured as a percentage of the maximum oxygen consumption (VO_{2max}). At exercise intensities below 50% VO_{2max}, most individuals will oxidize predominantly free fatty acids. The proportion of carbohydrates contributing to energy supply increases at higher exercise intensities.[19] Most untrained individuals will reach an anaerobic threshold at about 70% of VO_{2max}, where the anaerobic system will be required and both minute ventilation and plasma lactate concentration will disproportionately increase. For well-trained athletes, the anaerobic threshold can approach 85% VO_{2max}, and the proportionate contribution of free fatty acids to energy production will also increase at any given absolute exercise intensity with endurance

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KEY POINTS

- In general, women oxidize proportionately more lipids at any relative exercise intensity as compared to men. This latter point is important in fatty acid oxidation defects where men tend to have proportionately more symptoms than women, especially in the case of carnitine palmitoyltransferase II deficiency.
- Many enzymes in the glycolytic and glycogenolytic pathway have been associated with metabolic myopathies. In general, these present with higher-intensity exercise and at the onset of exercise initiation.

exercise training.[20,21] A small proportion of exercise fuel can come from the decarboxylation of amino acids (primarily branched-chain amino acids); however, this is quantitatively less important (2% to 5% of total energy) than carbohydrates and fats.[22] In general, women oxidize proportionately more lipids at any relative exercise intensity as compared to men.[22] This latter point is important in fatty acid oxidation defects where men tend to have proportionately more symptoms than women, especially in the case of carnitine palmitoyltransferase II deficiency.

The source of carbohydrate for energy provision during exercise is predominantly intramuscular glycogen; however, with longer-duration activity when glycogen stores can become limited (approximately 2 hours), the proportion of oxidized blood-borne glucose increases. The potential energy from carbohydrates is ultimately trapped as flavin adenine dinucleotide hydrogenated ($FADH_2$) and nicotinamide adenine dinucleotide hydrogenase ($NADH + H^+$) in the tricarboxylic acid cycle, which then provides these reducing equivalents to complex I ($NADH + H^+$) and complex II ($FADH_2$), which is then used by the mitochondria to shuttle electrons to complex IV, where oxygen is reduced to water. The potential energy from these reducing equivalents is used to pump a proton from the mitochondrial matrix to the intermembrane space at complex I, III, and IV, where the resultant proton motive force leads to generation of ATP synthase at complex V. The source of lipid during exercise comes from intramyocellular lipid–derived free fatty acids and blood-borne–derived free fatty acids from peripheral lipolysis. The free fatty acids are transported into muscle through three different fatty acid transporters with CD36 being quantitatively the most important.[23] Once inside the cell, the free fatty acids are chaperoned through acyl-coenzyme A (acyl-CoA) synthetase to carnitine palmitoyltransferase I, where carnitine is added to the acyl group that is then translocated via carnitine acylcarnitine translocase to the inner mitochondrial membrane where carnitine palmitoyltransferase II removes the carnitine and adds CoA to the acyl group. The resultant acyl-CoA moiety enters the mitochondrial matrix, which leads to the production of one molecule of $FADH_2$ and one molecule of $NADH + H^+$ for every turn of β-oxidation. The reducing equivalents are then used by the mitochondria as described in the previous section. Branched-chain amino acids are first deaminated by branched-chain amino acyltransferase to a keto acid and are then decarboxylated by branched keto acid dehydrogenase to generate acetoacetate (or propionyl-CoA) and acetyl-CoA that enters the tricarboxylic acid cycle.

METABOLIC MYOPATHIES

The first metabolic myopathy to be described was a glycogen-storage disease referred to as McArdle disease in a young man with exercise-induced cramps in 1951.[24] This disorder was due to a gene mutation in the myophosphorylase gene (*PYGM*), which leads to an inability to activate glycogenolysis and significant disruption of cellular energy charge within the first 10 to 20 seconds of exercise. Many enzymes in the glycolytic and glycogenolytic pathway have been associated with metabolic myopathies (**Table 4-1**). In general, these present with higher-intensity exercise and at the onset of exercise initiation. One of the glycogen-storage diseases called Pompe disease (glycogen-storage disease type 2 [GSD2]) leads to a progressive myopathy but does not alter cellular metabolism and will not be further considered in this review.

The fatty acid oxidation defects are genetic disorders affecting free fatty acid transport (eg, carnitine palmitoyltransferase II) and β-oxidation (eg, very–long-chain acyl-CoA dehydrogenase or trifunctional protein) deficiency. Fatty acid oxidation

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defects such as medium-chain acyl-CoA dehydrogenase deficiency or glutaric aciduria type II predominantly present with central nervous system symptoms and will not be considered in this review. In general, the fatty acid oxidation defects present during longer-duration exercise, fasting, or during times of superimposed metabolic stress such as fever or infection.

The mitochondrial ''myopathies'' refer to metabolic genetic defects that affect the electron transport chain and lead to exercise intolerance with or without rhabdomyolysis or fixed weakness. Like the fatty acid oxidation defects, mitochondrial myopathies often manifest symptoms during longer-duration activity or physical activity performed during periods of metabolic stress such as fasting, superimposed fever, flu, or other illness.

The next section of this article reviews the diagnosis and treatment of the metabolic myopathies with an emphasis on the more common disorders and with a clinical emphasis. The metabolic myopathies are classified as disorders of glycolysis/glycogenolysis (glycogen-storage diseases), fatty acid oxidation defects, and mitochondrial myopathies.

Disorders of Glycolysis/ Glycogenolysis

All of the glycogen-storage diseases are autosomal recessive with the exception of phosphorylase *b* kinase deficiency (GSD9) and phosphoglycerate kinase 1 deficiency, which are X-linked recessive disorders. McArdle disease (GSD5) is the most common metabolic myopathy (approximately 1 in 100,000 individuals), and is due to heterozygous mutations in the *PYGM* gene. Myophosphorylase initiates glycogen breakdown in the rest-to-exercise transition, and as a consequence there is a huge reliance on the adenylate kinase/myoadenylate deaminase pathway and phosphocreatine hydrolysis to provide energy during the first 10 seconds of muscle contraction. Symptoms usually begin shortly after exercise initiation with muscle pain and eventually a muscle contracture (muscle contraction in the absence of electrical activity). Usually, significant muscle discomfort occurs after exercise (delayed-onset muscle soreness) and often pigmenturia.

The most common glycolytic disorder is Tarui disease, which affects the rate-limiting enzyme in the glycolytic pathway called phosphofructokinase. These patients present with symptoms very similar to patients with McArdle disease as do the other rarer forms of glycolytic disorders, which include phosphoglycerate kinase 1 deficiency, phosphoglucomutase deficiency (also known as congenital disorder of glycosylation type IA), GSD10 (phosphoglycerate mutase deficiency), GSD11 (lactate dehydrogenase deficiency), GSD12 (aldolase A deficiency), and GSD13 (β-enolase deficiency). Phosphorylase *b* kinase deficiency (GSD9) is a glycogenolytic defect that reportedly presents similarly to McArdle disease; however, evidence suggests that the phenotype may be mild or nonexistent.[25,26]

Clinical presentation. Most patients with disorders of glycolysis/glycogenolysis will present with muscle cramps induced during the first seconds to minutes of exercise (**Case 4-1**). The presentation often does not occur until the second or third decade of life but can be even later since most patients adapt to their disorder by avoiding exercise or starting off at a very low intensity of exercise and gradually increasing the intensity as aerobic metabolism becomes predominant and blood-borne substrates are delivered to muscle. Patients with McArdle disease often report a significant reduction in the perception of effort after a few minutes of activity co-temporal with the delivery of blood-borne substrates, which is referred to as the *second wind phenomenon*.[27] In contrast, patients with glycolytic defects do not experience the second wind phenomenon.[28,29]

Often, patients have a history of pigmenturia (myoglobin in the urine) due to rhabdomyolysis induced by the severe deficit in energy charge with

KEY POINTS

- In general, the fatty acid oxidation defects present during longer-duration exercise, fasting, or during times of superimposed metabolic stress such as fever or infection.
- The mitochondrial ''myopathies'' refer to metabolic genetic defects that affect the electron transport chain and lead to exercise intolerance with or without rhabdomyolysis or fixed weakness. Like the fatty acid oxidation defects, mitochondrial myopathies often manifest symptoms during longer-duration activity or physical activity performed during periods of metabolic stress such as fasting, superimposed fever, flu, or other illness.
- Glycogenolytic and glycolytic disorders usually present with muscle cramps during high-intensity activity and usually in the first few minutes of muscle contraction.
- Patients with McArdle disease often report a significant reduction in the perception of effort after a few minutes of activity co-temporal with the delivery of blood-borne substrates, which is referred to as the second wind phenomenon. In contrast, patients with glycolytic defects do not experience the second wind phenomenon.

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KEY POINTS

- Most patients with McArdle disease will have a chronic elevation in serum creatine kinase.
- The presence of pigmenturia is an important clinical feature for it can lead to acute renal failure.
- Patients with McArdle disease may report that they are less symptomatic following a high-carbohydrate meal, whereas patients with glycolytic defects often feel that their symptoms are worse after a high-carbohydrate meal and feel better after a prolonged period of fasting.

Case 4-1

A 24-year-old woman presented to the emergency department 24 hours after starting a new fitness class involving boot camp–like exercises. She had experienced painful muscle cramps starting in the first 3 minutes of the class. She had lessened the intensity of her exercise, and the cramps had eased up a bit. However, the cramps had intensified again after 20 minutes, and she had to leave the class. The patient's muscles were tight, swollen, and very sore that night, and the next morning her urine was reddish brown.

Other than pain-inhibited proximal muscle weakness, the neurologic examination was normal. Her serum creatine kinase (CK) level was 300,000 IU/L (normal being less than 220 IU/L) in the emergency department, and her urine was positive for hemoglobin but negative for red blood cells.

She was admitted to the hospital for 4 days and treated with normal saline and small amounts of added potassium on days 3 and 4. Twenty-four hours after admission, the patient's urine was clear in color, and at discharge, the CK was 40,000 IU/L and her muscle pain was markedly diminished.

During follow-up at the neuromuscular and neurometabolic clinic 2 weeks later, the patient's neurologic examination was normal, and the CK was down to 800 IU/L; however, she did recall that this was elevated in several previous routine blood tests but no further investigations had been initiated at that time. In retrospect, she had experienced muscle cramps in the first few minutes of initiating exercise for most of her life but had ''learned to live with it.'' Her symptoms had improved when she had attended college and had frequently done endurance exercise, but she had not exercised for 2 years prior to the recent event. Her family history was negative for anyone with similar symptoms. The forearm exercise test showed a 10-fold increase in ammonia and no rise in lactate, implying a defect in glycolysis or glycogenolysis. Given the history, a molecular test for five common McArdle disease genes was performed and revealed a homozygous p.Arg49X mutation.

Comment. This patient's history of rhabdomyolysis and a history of similar events in the past with a likely second wind phenomenon is very suspicious for McArdle disease. Furthermore, the chronic CK elevation is a common feature in McArdle disease. Many patients adapt their lifestyle and activities to accommodate the symptoms and often do not seek out medical attention until in their twenties or even later. Her history of being less active and then going back to a gym to rapidly get back into shape is a common scenario that initiates significant rhabdomyolysis and subsequently prompts investigations.

resultant calcium dysregulation, activation of proteolysis, and muscle fiber necrosis. Patients usually describe the urine as dark, tea colored, red, and cola-colored due to the presence of muscle-derived proteins imparting pigment (usually myoglobin). The presence of pigmenturia is an important clinical feature for it can lead to acute renal failure. Some patients experience excessive shortness of breath upon exertion, and occasionally patients can develop fixed muscle weakness, but this is usually a later manifestation of untreated disease. Patients with McArdle disease may report that they are less symptomatic following a high-carbohydrate meal, whereas patients with glycolytic defects often feel that their symptoms are worse after a high-carbohydrate meal and feel better after a prolonged period of fasting. The family history is usually negative for this condition given that these are autosomal recessive disorders.

The neurologic examination is usually completely normal between episodes

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with the exception of fixed muscle weakness in GSD12, which can also occur rarely in GSD5 and others. Routine blood chemistries between events are often normal; however, CK is chronically elevated in nearly all cases of McArdle disease. Some disorders can be associated with hemolysis/hemolytic anemia (eg, GSD7, phosphoglycerate kinase 1 deficiency, GSD12). Many of the glycogenolytic and glycolytic defects are also associated with myogenic hyperuricemia, which can lead to gout.[30] A summary of some key features in the history suggesting a diagnosis of a glycogen-storage disease is found in **Table 4-2**.

Diagnostic testing. The classic diagnostic test is the forearm exercise test. With an impairment of glycolysis or glycogenolysis, no pyruvate is produced under anaerobic conditions and consequently no lactate is produced through the lactate dehydrogenase reaction.[16] Usually, a sphygmomanometer cuff is inflated beyond arterial pressure and isometric rhythmic exercises are performed for 1 minute, followed by release of the sphygmomanometer cuff. Lactate and ammonia values are determined prior to inflating the cuff and immediately post-inflation. Normally, lactate and ammonia rise approximately threefold; however, lactate rise is markedly attenuated in the glycolytic and glycogenolytic defects. Failure of both lactate and ammonia to rise usually indicates a suboptimal performance (decreased effort); however, the coexistence of a glycolytic/glycogenolytic defect with the common polymorphism in *AMPD1* has been reported and can lead to false-negative testing by mimicking a suboptimal effort. The author of this

KEY POINT

- Routine blood chemistries between events are often normal; however, creatine kinase is chronically elevated in nearly all cases of McArdle disease.

TABLE 4-2 Clinical Features Suggesting Specific Metabolic Myopathies

History	Disorder (Descending Likelihood)
Rhabdomyolysis/pigmenturia	Glycogen-storage disease (GSD), fatty acid oxidation defects, mitochondrial myopathies
Myalgia > cramps with endurance sports	Fatty acid oxidation defects, mitochondrial myopathies
Shortness of breath with endurance sports	Mitochondrial myopathies
Myalgia/cramps with power/sprint sports	Glycogen-storage disease
Symptoms triggered by fasting or superimposed illness	Fatty acid oxidation defects, mitochondrial myopathies
Gout	Glycogen-storage disease
Nausea/vomiting with exercise	Mitochondrial myopathies, GSD7
Multiple system involvement	Mitochondrial myopathies
Family history	
X-linked	Phosphorylase *b* kinase deficiency, phosphoglycerate kinase 1 deficiency
Maternal	Mitochondrial myopathies (mitochondrial DNA only)
Autosomal recessive/consanguineous	Carnitine palmitoyltransferase II deficiency, most glycogen-storage diseases, nuclear-encoded mitochondrial myopathies

DNA = deoxyribonucleic acid.

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KEY POINT

- A forearm exercise test or aerobic cycle test showing a normal rise in serum lactate (greater than three times that of baseline) is good for ruling out nearly every genetic defect in the glycogenolytic and glycolytic pathways.

article in addition to other investigators have found that the blood pressure cuff is not necessary and that rhythmic contraction in itself is sufficient to yield optimal sensitivity and specificity.[31,32] Consequently, the author recommends the non-ischemic forearm exercise test to avoid the possibility of rhabdomyolysis and acute compartment syndrome, which is somewhat more likely if a sphygmomanometer cuff is used. Given the very high sensitivity and specificity of the forearm ischemic test and nonischemic forearm exercise test, a normal test rules out every glycolytic and glycogenolytic defect with the possible exception of phosphorylase *b* kinase deficiency,[25] which can be further evaluated with the aerobic cycling exercise test. There are many examples of aerobic cycling tests; however, a standard Bruce protocol test used for cardiac evaluation where the intensity/speed of either a cycle ergometer or treadmill is progressively increased until voluntary exhaustion with measurement of lactate and ammonia pre/post is sufficient.

Nerve conduction studies and EMG are normal in all of the glycogen-storage disease disorders except for the electrical silence during a contracture; however, an EMG is rarely necessary in the workup of glycogen-storage diseases. An extensive body of literature exists that uses exercise magnetic resonance spectroscopy (MRS) to show accentuated phosphocreatine hydrolysis and the lack of acidosis in muscle in McArdle disease as well as the increase in phosphomonoesters in distal glycolytic defects.[33] An issue with MRS is that the test is expensive and requires high technical expertise and optimization and, in the author's opinion, doesn't add much to the clinical approach described herein.

If the patient's history is highly suspicious for a glycolytic/glycogenolytic defect and the forearm exercise test is normal, the remote possibility of phosphorylase *b* kinase deficiency can be further ruled out with the aerobic exercise test previously described. If a normal lactate rise occurs with the aerobic exercise test, all of the glycolytic and glycogenolytic defects are ruled out, further genetic investigations for glycogen-storage diseases are not warranted, and clinicians should consider one of the other metabolic myopathies or a pseudometabolic myopathy. If the exercise test is positive, a targeted or untargeted genetic approach would be prudent. A variety of laboratories offer full sequencing of the coding regions and the intronic boundaries of the genes for all known glycolytic and glycogenolytic defects. With the advent of next-generation sequencing, this approach is often less expensive than doing a single targeted gene (eg, *PYGM*) using Sanger sequencing methods. However, if a laboratory does have *PYGM* sequencing available, this would be a prudent first step given that McArdle disease is the most common of the glycogen-storage diseases causing a metabolic myopathy. A muscle biopsy is not necessary in a classic case of glycolytic/glycogenolytic defect with a positive genetic result; however, a muscle biopsy would be recommended if such testing is negative with the diagnostic algorithm described previously. An advantage of the muscle biopsy is that a pattern may be seen that would target further genetic analysis such as central cores (*RYR1, CACNA1S* mutations), abnormal dystrophin staining (dystrophinopathy), ragged red fibers (mitochondrial cytopathy), or membrane-bound glycogen (Pompe disease). The other potential need for a muscle biopsy would be the finding of a genetic variant of uncertain significance in a gene of interest (eg, *PYGM*). In such cases, enzyme analysis of muscle revealing the absence of phosphorylase activity would confirm the mutation. In other rare cases, an unknown splicing variant could be further evaluated with messenger RNA (mRNA) analysis from muscle. A summary of some of the tests for the glycogen-storage diseases is presented in **Table 4-3**.

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Treatment. Many patients adjust their lifestyle activities to mitigate symptoms long before a diagnosis is made. For example, patients often avoid high-intensity activity and start off activity at a low intensity to wait for their second wind. The greatest risk for rhabdomyolysis comes with unaccustomed exercise or large increases in exercise intensity. Consequently, it is important for patients to start exercise at a lower intensity and to gradually increase the intensity and duration while self-monitoring for symptoms and reducing the intensity as needed. As expected from the well-known physiologic adaptations that occur with exercise training, regular exercise has been shown to lessen symptoms in McArdle disease.[34–36]

The consumption of simple sugars containing glucose (glucose, sucrose) shortly before exercise can bypass the glycogenolytic metabolic defects.[37,38] One study found that oral sucrose (37 g)

TABLE 4-3 Testing for Metabolic Myopathies

Disease	Testing
Glycogen-storage disease	Serum creatine kinase (CK) is chronically elevated in McArdle disease; otherwise it is usually normal in the other glycogen-storage diseases
	Serum uric acid is elevated in ~50%
	Forearm exercise test shows no lactate with high ammonia rise
	Graded exercise stress test:
	Second wind phenomenon is seen in McArdle disease
	No second wind phenomenon suggests the glycolytic defects
	EMG is often normal in cases of glycogen-storage disease
	Muscle biopsy may show high glycogen, absent phosphorylase, or absent phosphofructokinase
	Genetic testing options
	Specific mutation analysis: (R49X in ~70% of white individuals with McArdle disease)
	Next-generation sequencing panels for glycogen-storage diseases or myopathy panels with glycogen-storage disease genes or whole-exome sequencing
Fatty acid oxidation defects	Serum CK usually normal
	Serum total carnitine often normal
	Serum acylcarnitine profile often abnormal (fasted or following a graded exercise stress test)
	Urine organic acids (dicarboxylic acids) may be elevated
	Hypoketotic hypoglycemia during an event
	Skin biopsy for enzyme analysis and acylcarnitine in fibroblasts
	Specific mutation analysis (S113L in ~70%) in blood
	EMG is often normal
	Muscle biopsy may show increased lipids, but usually nonspecific findings

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TABLE 4-3 Testing for Metabolic Myopathies *Continued from page 1837*

Disease	Testing
Mitochondrial myopathy	Serum CK may be chronically elevated
	Serum lactate is elevated in ~65%
	Serum alanine is occasionally elevated
	Urine organic acids (tricarboxylic acid intermediates, 3-methylglutaconic aciduria) may be elevated
	Forearm exercise test does not lead to deoxygenation
	Graded exercise stress test is associated with low VO_{2max}, high respiratory exchange ratio
	EMG is often normal
	Muscle biopsy may show ragged red fibers, cytochrome oxidase–negative fibers, or paracrystalline inclusions (electron microscopy)
	Enzyme analysis on muscle and skin fibroblasts can show mixed or single electron transport chain defects
	Genetic testing options (usually on muscle tissue)
	Specific mutation analysis for classic features of mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) (m.3243A>G); Leber hereditary optic neuropathy (m.11778G>A, m.14484T>C, m.3460G>A); chronic progressive external ophthalmoplegia (mitochondrial DNA deletion); or myoclonic epilepsy with ragged red fibers (MERRF) (m.8363G>A)
	Mitochondrial DNA sequencing (if mitochondrial DNA mutation is suspected)
	Next-generation sequencing targeted mitochondrial panels or whole-exome sequencing (both for nuclear mutations)

DNA = deoxyribonucleic acid; EMG = electromyography.

taken 5 to 10 minutes before exercise improved exercise capacity and lessened symptoms.[37] In contrast, patients with phosphofructokinase glycolytic defects generally perform better in the fasted state and are worse off following carbohydrate ingestion because they cannot use the blood-borne glucose and because the glucose raises insulin levels that attenuates lipolysis and proteolysis that are used as alternative fuel sources.[39]

Patients with the most common McArdle disease mutation (R49X) have no protein expressed because of nonsense-mediated mRNA decay; consequently, they have a secondary deficiency of pyridoxine (vitamin B_6) because these two have a protein-protein interaction. Consequently, some have advocated the use of pyridoxine supplementation (approximately 50 mg/d) in patients with null *PYGM* mutations[40,41]; however, efficacy has not yet been confirmed in a randomized clinical trial. High-protein diets have also been advocated in an attempt to increase alternative fuel availability (amino acids); however, this has not been tested in a randomized controlled trial. Furthermore, branched-chain amino acid supplements did not

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show a benefit.[42] Creatine monohydrate in low to moderate doses (approximately 0.1 g/kg/d) did show bioenergetic improvements during exercise in patients with McArdle disease[43]; however, higher doses of creatine monohydrate led to exercise impairment.[43] Although GSD3 (debranching enzyme) is considered to be a glycogen-storage disease associated with fixed weakness, a recent study showed improvements in exercise capacity with pre-exercise fructose ingestion.[44] Finally, D-ribose, verapamil, and dantrolene were not effective in treating McArdle disease.[45] In fact, adverse events or worsening of symptoms were observed with oral D-ribose (diarrhea and hypoglycemia symptoms) and dantrolene (fatigue, vertigo, and muscle weakness).[45] One study found mild improvements in exercise capacity and improved symptoms in patients with a deletion-deletion haplotype for angiotensin-converting enzyme following treatment with 2.5 mg of ramipril.[46] In summary, studies provide some support for the use of low-dose creatine monohydrate, pre-exercise sucrose/glucose, ramipril (only in the case of the deletion-deletion polymorphism), and possibly a high-carbohydrate diet.[45] Although vitamin B_6 (pyridoxine) is not universally beneficial, a low dose may not be imprudent in patients who have null phosphorylase mutations and have relative pyridoxine deficiency (**Table 4-4**).

Fatty Acid Oxidation Defects

Fatty acids are generally categorized according to the number of carbons into short-chain (two to four), medium-chain (six to 12), long-chain (14 to 18), and very–long-chain (20 or more) fatty acids. The oxidation of long-chain and very–long-chain free fatty acids requires the carnitine palmitoyltransferase system, whereas short- and medium-chain free fatty acids can directly enter the mitochondrial matrix for β-oxidation. All of the currently known clinically relevant fatty acid oxidation defects are autosomal recessive disorders with the three most common being carnitine palmitoyltransferase II deficiency (approximately 1 in 250,000 individuals), trifunctional protein deficiency, and very–long-chain acyl-CoA dehydrogenase deficiency.

Clinical presentation. Unlike the true cramping symptoms experienced by the glycolytic/glycogenolytic defects, the fatty acid oxidation defects usually present with exercise-induced myalgia. The patients may experience pigmenturia later on in the same day or within 24 hours of exercise due to rhabdomyolysis. Most patients do have delayed-onset muscle soreness for several days following a bout of rhabdomyolysis. The symptoms are often precipitated by prolonged fasting, prolonged exercise, or superimposed illness (**Case 4-2**). Often, children have myalgia and occasionally pigmenturia during fever or vomiting (fasting) and will only notice the exercise-induced symptoms in their teenage years when they do longer-duration activities (**Table 4-2**).

Diagnostic testing. Blood testing is usually completely normal for CK, lactate, and glucose between episodes of rhabdomyolysis. During an acute bout of rhabdomyolysis, an increase in CK starts within a few hours, during which hyperkalemia and hypoketotic hypoglycemia can occur. Following a bout of rhabdomyolysis, acute renal failure can occur with elevations of potassium, creatinine, and urea. The most sensitive and specific test for a fatty acid oxidation defect is the acylcarnitine profile performed by liquid chromatography–tandem mass spectrometry. This test may be abnormal between acute events; however, a false-negative test can occur in a nonstressed situation. The author of this article usually prefers that patients come in in the fasted state in the morning, which tends to increase the diagnostic yield. Additionally, this test should be sent if a fatty acid oxidation defect is suspected during an acute metabolic crisis. Often, the specific acylcarnitine signature can target a specific

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KEY POINT

■ Unlike the true cramping symptoms experienced by the glycolytic/glycogenolytic defects, the fatty acid oxidation defects usually present with exercise-induced myalgia. The patients may experience pigmenturia later on in the same day or within 24 hours of exercise due to rhabdomyolysis.

TABLE 4-4 Metabolic Myopathy Treatments

Disease	Treatment[a]
Glycogen-storage disease	Careful and progressive exercise training
	Pre-exercise sucrose/glucose in glycogenolytic defects (eg, McArdle disease)
	Overnight fasting for glycolytic defects (eg, phosphofructokinase deficiency or Tarui disease)
	Creatine monohydrate (0.1 g/kg/d), NOT higher dose
	Consider pyridoxine 50 mg/d in patients with null phosphorylase mutations (eg, R49X mutations)
Fatty acid oxidation defects	Careful and progressive exercise training; no exercise during illness
	Avoid fasting
	L-carnitine (only if low or in SLC22A5 mutation transporter defect); start at 330 mg 2 times per day
	High-carbohydrate diet
	Carbohydrate before and during exercise
	Consider triheptanoin
Mitochondrial myopathy	Careful and progressive exercise training; no exercise during illness
	Avoid fasting
	Cocktail treatment consists of coenzyme Q_{10} or idebenone (5–15 mg/kg/d) plus α-lipoic acid (5–15 mg/kg/d) plus vitamin E (5–15 IU/kg/d) plus creatine monohydrate (0.1 g/kg/d)
	L-carnitine, only if levels are low; start at 330 mg 2 times per day and retest

[a] Start medications at the lower dose range and titrate to tolerance/clinical effect using twice daily dosing and taken with meals.

genetic mutation for subsequent gene analysis. Total and free carnitine levels may be secondarily abnormal; however, very low levels of these are usually seen in systemic carnitine deficiency due to mutations in *OCTN2/SLC22A5* genes.[47]

Urine testing during rhabdomyolysis will often show a positive hemoglobin test with negative red blood cells on microscopy that reflects the myoglobin in the urine. Urine organic acid analysis may also show an elevation of specific dicarboxylic acids in β-oxidation defects. The acylcarnitine profile can also be assessed in fibroblast culture if a fatty acid oxidation defect is suspected and if plasma acylcarnitine profiling in the fasted state is nonrevealing. If the acylcarnitine profile or history are strongly suspicious for a fatty acid oxidation defect, specific genetic testing for the defect can be carried out using Sanger sequencing of exons and intron-exon boundaries. More recently, next-generation sequencing has allowed the use of panels that cover the more common fatty acid oxidation defects leading to rhabdomyolysis (carnitine palmitoyltransferase II, trifunctional protein, very–long-chain acyl-CoA dehydrogenase) and some of the less common

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Case 4-2

A 56-year-old man presented to the neuromuscular and neurometabolic clinic with a history of Tarui disease. The patient requested exercise advice as he wanted to join a cycling club. He and his sister had been given a diagnosis of Tarui disease in South Africa decades before after each had experienced a bout of rhabdomyolysis. The diagnosis had not been confirmed genetically and appeared to be based upon the fact that they both had rhabdomyolysis with exercise and were of Ashkenazi Jewish descent. In retrospect, he did recall that as a child he could not walk to the synagogue during Yom Kippur (which includes a 25-hour fast) due to myalgia. He also noted that he could not lift weights or do chores if he was ill or fasting. He also found that if he rode his bike after eating, especially if he had eaten some honey, he felt much better.

His neurologic examination was normal. With this history, a fasting acylcarnitine profile was sent and blood was banked for DNA. The acylcarnitine profile showed a pattern of long-chain acyl-coenzyme A moieties characteristic for carnitine palmitoyltransferase II deficiency. The DNA was then sent for a 5-gene common carnitine palmitoyltransferase mutation panel, which returned positive for a homozygous p.Ser113Leu common carnitine palmitoyltransferase II mutation. After this visit, the patient continued another 15 years without any bouts of rhabdomyolysis by avoiding activity during illness and fasting and by consuming a high-carbohydrate diet. He was able to cycle with a local club up to 80 km on the weekends with a preride meal and the consumption of glucose-based gels and other carbohydrate sources during the ride.

Comment. The history of symptoms during fasting and improvements in exercise capacity with feeding and carbohydrate supplements is characteristic of a fatty acid oxidation defect and the opposite of what would be expected in a patient with Tarui disease (phosphofructokinase deficiency). Furthermore, the patient had symptoms with longer-duration exercise that would also be more characteristic of a fatty acid oxidation defect as opposed to a glycolytic or glycogenolytic disorder. Homozygosity for mutations is common in restricted populations where the possibility of remote consanguinity is higher.

KEY POINTS

- A normal serum acylcarnitine level during fasting or following an acute bout of rhabdomyolysis is a good test for ruling out a fatty acid oxidation defect, and an abnormal test pattern can often suggest a specific genetic diagnosis.
- Most patients with a fatty acid oxidation defect will have symptoms during fasting, illness or fever, or during longer-duration physical activity.

fatty acid oxidation defects associated with exercise-induced rhabdomyolysis (medium-chain acyl-CoA dehydrogenase deficiency, carnitine acylcarnitine translocase deficiency). Recurrent rhabdomyolysis in the face of fever and superimposed illness can also be seen in cases of LPIN1 deficiency (a magnesium-dependent phosphatidic acid phosphohydrolase). To date, *LPIN1* mutations have not been associated with exercise-induced rhabdomyolysis.

In cases where the fasting acylcarnitine profile is normal, the author usually carries out an aerobic exercise test on a cycle ergometer in the fasted state with pre- and postexercise lactate and postexercise acylcarnitine profiling. This is helpful in that an attenuated lactate rise would be suspicious for a glycolytic/glycogenolytic defect and the postexercise acylcarnitine profiling can sometimes reveal the specific fatty acid oxidation defect. Furthermore, high resting lactate and a low VO_{2max} with a high respiratory exchange ratio during cycle ergometry can indicate a mitochondrial myopathy. Muscle biopsy is usually not required for the workup of a suspected fatty acid oxidation defect; however, muscle tissue may show a nonspecific increase in neutral lipid, and this is felt to be quite a nonspecific and subjective impression. Nerve conduction velocity and EMG testing is often normal in fatty acid oxidation defects; however, a myopathic picture (small brief early recruiting potentials) can be seen for up

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KEY POINTS

- A high-carbohydrate diet and possibly carbohydrate consumption during exercise may attenuate symptoms of a fatty acid oxidation defect.
- Mitochondrial disorders often affect more than one tissue or organ system due to the ubiquitous distribution of the mitochondria.

to 10 days following an acute bout of rhabdomyolysis, occasionally with fibrillations, positive sharp waves, and complex repetitive discharges. A mixed axonal neuropathy can be seen in rare cases of long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (**Table 4-3**).

Treatment. Most patients avoid triggers of their disease such as exercising in the fasted state, exercising with a superimposed illness, and long-duration exercise. Most patients generally tend to choose higher-carbohydrate foods especially immediately before and during long-term endurance exercise, and a relatively low-fat (less than 30%) higher-carbohydrate diet is recommended. A carbohydrate-enriched diet improved exercise tolerance in patients with carnitine palmitoyltransferase II deficiency,[48] whereas oral glucose did not.[49] The administration of vitamin B_2 (riboflavin), medium-chain triglyceride oil, and L-carnitine has been advocated[50,51] but none have been proven in a clinical trial; however, replacement of L-carnitine would be prudent if patients are found to be deficient. The use of bezafibrate (not available in the United States) has been suggested[52]; however, Class I evidence now suggests this is not effective in carnitine palmitoyltransferase II deficiency.[53] The use of triheptanoin (odd chain free fatty acid) has been shown to improve energy production in cells from patients with fatty acid oxidation defects.[54,55] Triheptanoin has been shown to reduce hospitalizations in a retrospective study[56] and was also shown to improve exercise capacity.[55] A summary of some of the treatment options is present in **Table 4-4**.

Mitochondrial Myopathies

Mitochondrial myopathies are a diverse group of genetic disorders with a primary defect in electron transport chain function. The metabolic consequences of mitochondrial dysfunction result primarily from a decrease in aerobic energy production from fat and carbohydrate oxidation; however, the production of reactive oxygen species may play a pathogenic role. As the final common pathway for fat and carbohydrate oxidation, the symptoms of mitochondrial myopathies often manifest themselves during periods of high metabolic demand such as fasting, superimposed illness, or longer-duration exercise. Given that mitochondria are present in all tissues with the exception of red blood cells, multisystemic manifestations of the disease often occur from tissues with a high metabolic demand such as heart, brain, skeletal muscle, and nerves (especially cranial nerves II and VIII). The term mitochondrial *cytopathy* is the preferred term for patients with multisystemic clinical manifestations, and the term *mitochondrial myopathy* is used when skeletal muscle is the predominant tissue involved. Although fixed weakness can be a manifestation of a mitochondrial myopathy, the current review will focus on the metabolic function of skeletal muscle and the resultant exercise intolerance with or without rhabdomyolysis.[57–59]

Mitochondria are cellular organelles that likely evolved from photosynthetic bacteria that took on a symbiotic relationship with a proto-eukaryotic cell nearly 1.5 billion years ago. Through evolution, the DNA encoding for most of the approximately 1200 proteins required by a mitochondrion are part of the nuclear DNA and imported into the mitochondria through a transport system. The mitochondrial DNA (mtDNA) is a maternally inherited small (16,569 base pairs) circular, double-stranded molecule that resembles bacterial DNA. The mtDNA composition is highly conserved across species and encodes for two ribosomal RNAs, 22 transfer RNAs, and 13 protein encoding mRNAs. Mitochondrial replication is dependent upon many nuclear encoded proteins such as polymerase-γ (POLG1) and is not dependent upon the cell cycle. Consequently, mitochondrial biogenesis can occur in postmitotic cells such as

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skeletal muscle in response to stimuli such as exercise.

Each mitochondrion contains several mtDNA copies, and hundreds to thousands of mitochondria are present in every cell, roughly in proportion to the aerobic needs of the cell. The mtDNA is maternally inherited whilst all nuclear mitochondrial genes follow mendelian inheritance rules. The first mutations that were found in mtDNA in 1988 and 1989 were point mutations at position 3243 (m.3243A>G) and 11,778 (m.11778G>A) responsible for mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) and Leber hereditary optic neuropathy as well as a large-scale deletion seen in Kearns-Sayre syndrome.[60–62] mtDNA contains many benign polymorphisms that may contribute to evolutionary biological fitness,[63] and some define the mitochondrial haplotypes, but these can be a challenge when a variant of uncertain significance is found with mtDNA sequencing. The number of pathogenic mtDNA mutations described in the past 2 decades has been substantial. In addition, the number of nuclear encoded genes linked to mitochondrial cytopathies/myopathies has dramatically increased because of the advent of next-generation sequencing (see the MITOMAP human mitochondrial genome database at *www.mitomap.org/MITOMAP*).

Some diseases such as Leber hereditary optic neuropathy affect all copies of mtDNA and are termed homoplasmic; however, having a variable proportion of mutant to wild-type mtDNA copies within a tissue is more common, which is referred to as heteroplasmy. Because of replicative segregation that occurs within and between tissues during embryogenesis, the heteroplasmy can be very different between tissues. Furthermore, the mutant heteroplasmy does tend to be lower in tissues with rapid turnover, such as blood cells, while maintaining a constant level in more terminally differentiated tissues, such as muscle and brain. In general, a higher level of mutant heteroplasmy is associated with more severe and earlier-onset symptoms and tissue biochemical pathology.

Clinical presentation. Mitochondrial myopathies are notorious for the extreme phenotypic and genotypic heterogeneity. A classic example is MELAS syndrome, where people within the same family may present with adult-onset deafness and diabetes, while others may present with any combination of strokes, seizures, cardiomyopathy, short stature, dementia, and severe exercise intolerance. In contrast, patients with the same phenotype (eg, chronic progressive external ophthalmoplegia) may have a sporadic mtDNA deletion, a nuclear encoded mtDNA maintenance gene mutation, or a specific mtDNA point mutation.

Many patients with mitochondrial cytopathies and myopathies will have limitations in exercise capacity because of a low VO_{2max}. The protean manifestations of the disorder (eg, seizures, encephalopathy, cardiomyopathy) may overshadow exercise intolerance. For example, we found a severely reduced VO_{2max} (9.2 mL/kg/min, normal being 32 mL/kg/min) in seven patients with MELAS and yet none of them presented with exercise intolerance as the presenting symptom.[64] In retrospect, the aforementioned patients often reported that they were ''last in sports'' or ''the worst athlete in the class.'' Most patients with mitochondrial myopathies report shortness of breath and premature fatigue during exertion that is often exacerbated with superimposed infection or fasting; however, some patients may also have exertional nausea and vomiting. A few cases of temporary/partial visual loss and/or hearing loss during exertion have also been observed by the author in patients with MELAS (**Case 4-3**). In contrast to the lay perception and biological plausibility, most patients do not report symptoms of fatigue and tiredness at rest

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KEY POINTS

- A normal serum lactate level does not rule out mitochondrial disease in adults or children.
- A high serum lactate in adults is suggestive of mitochondrial disease, whereas a high lactate level in children can be a false positive due to struggling or difficulties taking the blood.

Case 4-3

A 46-year-old woman presented to the neuromuscular and neurometabolic clinic with a history of exercise-induced deafness and stomach discomfort that she had experienced for several years. The referral was also prompted by the fact that her eldest daughter underwent a heart transplant for severe hypertrophic cardiomyopathy and experienced severe postoperative lactic acidemia (up to 20 mmol/L, with the normal range being 2.2 mmol/L) with no identified cause 1 month prior to the evaluation. Her mother and her maternal grandmother had died of ''encephalitis'' in their midforties based on a history of rapid-onset seizures and strokelike episodes for which no cause had been identified. She had short stature (less than the third percentile) and her neurologic examination showed mild proximal weakness (4 out of 5) for hip flexors and shoulder abductors. Serum lactate was mildly elevated at 3.1 mmol/L (normal range being less than 2.2 mmol/L).

Muscle biopsy showed a few ragged red fibers (approximately 2%), and mitochondrial DNA (mtDNA) testing from the muscle biopsy sample using polymerase chain reaction (PCR)–restriction fragment length polymorphism for three common mutations (m.3243A>G, m.3260A>G, and m.3271T>C) revealed 86% heteroplasmy for the m.3260A>G mutation. The patient's blood heteroplasmy for m.3260A>G was 22%. Subsequent testing in her three daughters showed that blood mtDNA mutant heteroplasmy for the m.3260A>G mutation was 55%, 48%, and 60%, respectively. The patient went on to have a severe temporooccipital strokelike episode with complete homonymous hemianopsia, severe dysphasia, and acalculia 1 year after the initial diagnosis that completely resolved after 3 months.

Comment. This patient's family history was suggestive of maternal inheritance of neurologic symptoms that prompted mtDNA analysis. The exercise intolerance and exercise-induced deafness had been attributed by the patient to ''just being out of shape,'' and she did not seek medical attention for it until her daughter's postoperative course. A higher mutational heteroplasmy level in muscle-derived mtDNA versus blood-derived mtDNA is a common feature of mitochondrial disease that can lead to a missed diagnosis if mtDNA testing is only done on blood samples.

with any greater frequency than commonly seen in the general population. Unlike fatty acid oxidation defects or glycogen-storage diseases where rhabdomyolysis and pigmenturia are common, most patients with mitochondrial myopathy do not experience such events. Rhabdomyolysis has, however, been seen in cases of cytochrome *b*, cytochrome *c* oxidase, and MELAS m.3260A>G mutations.[65–67]

Other signs and symptoms often occur that suggest a mitochondrial disease diagnosis such as hypoacusis, short stature, ptosis, ophthalmoparesis, type 2 diabetes mellitus, migraine variant headaches, seizures, strokes and strokelike episodes, head and neck lipomas, peripheral neuropathy, ataxia, cardiomyopathy, cardiac conduction block, and intestinal pseudoobstruction. Fixed weakness may also be seen with or without an elevated CK that can mimic muscular dystrophy or congenital myopathy. A positive maternal family history with any number of the previously described signs and symptoms is helpful to rule in an mtDNA-based mitochondrial myopathy, but a negative family history cannot be used to rule out a mitochondrial myopathy given that many are autosomal recessive (**Table 4-2**).

Diagnostic testing. Testing for mitochondrial myopathy is complex and

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somewhat controversial; however, most experts agree that a systematic and multiple testing approach is required. Serum/plasma lactate is an important blood test for the evaluation of a suspected mitochondrial myopathy. The lactate concentration is elevated in approximately 65% of adult patients with mitochondrial myopathy (sensitivity) and normal in over 90% of people without mitochondrial myopathy (specificity).[16] It is important to take the blood to the laboratory while it is on ice and analyze promptly to avoid false-positive results. Other causes of false-positive results include diabetes mellitus, difficult blood draws (eg, struggling, prolonged tourniquet use), and if the patient has recently (within less than 1 hour) consumed a high-carbohydrate meal. Serum CK activity is often normal but will be elevated after rhabdomyolysis and in a fraction of patients in whom the elevation is usually less than three times the upper limit of normal. CK levels higher than this should prompt consideration of a muscular dystrophy. About 50% of patients with MELAS will have type 2 diabetes mellitus or impaired oral glucose tolerance. Plasma amino acid testing can reveal an elevated alanine, especially if taken after an aerobic exercise test. Urine organic acid analysis may reveal elevations of 3-methylglutaconic acid or the tricarboxylic acid intermediates (fumarate, malate, citrate).

Cycle ergometry exercise testing in mitochondrial myopathies may demonstrate a low VO_{2max}, or a high respiratory exchange ratio (indicative of early lactate production), or both.[68] The author of this article has tended to do far fewer exercise tests recently because of the large number of false-positive tests that are due to physical inactivity associated loss of mitochondrial enzyme activity.[69] Hypodynamia is a secondary manifestation of nearly every myopathy seen in the clinic but is also a very common consequence of many common disorders (eg, immobilization, chronic fatigue syndrome, fibromyalgia). Forearm nonischemic testing linked with near infrared spectroscopy or venous blood gas measurements has been used to demonstrate the failure of deoxygenation secondary to a mitochondrial defect.[70,71] For example, the venous blood oxygen content at rest is usually 28 mm Hg to 48 mm Hg, and this drops after exercise because of deoxygenation, which imparts a dark purple/black color to the blood in healthy people; in contrast, no drop or even a slight increase in oxygenation (arterialization) of the venous blood occurs after exercise in patients with a mitochondrial myopathy. Phosphorus (^{31}P) MRS has also been used to show rapid phosphocreatine hydrolysis, an increase in lactate during exercise, or a delayed ATP recovery following exercise[33,72]; however, exercise MRS is best used by specialized centers.

EMG is often normal in the mitochondrial myopathies but may show a nonspecific myopathic pattern with small, brief, early recruiting action potentials. EMG is perhaps best used as a tool to rule out myotonic disorders and muscular dystrophies if the diagnosis is not clear. Similarly, nerve conduction studies are often normal in mitochondrial myopathies but may show an axonal sensory (eg, POLG1 mutations) or sensorimotor neuropathy (eg, myoclonic epilepsy with ragged red fibers [MERRF]; mitochondrial neurogastrointestinal encephalomyopathy [MNGIE]; and neuropathy, ataxia, retinitis pigmentosa [NARP] syndrome).

The muscle biopsy is more helpful in the analysis of mitochondrial myopathies as compared to fatty acid oxidation defects and glycogen-storage diseases for several reasons. First, the histologic changes may give a clue to the genetic defect. For example, the presence of ragged red fibers (subsarcolemmal accumulation of mitochondria on modified Gomori trichrome staining) or cytochrome *c* oxidase–negative fibers can suggest an mtDNA mutation. The

KEY POINT

- The muscle biopsy is more helpful in the analysis of mitochondrial myopathies as compared to fatty acid oxidation defects and glycogen-storage diseases.

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presence of ragged blue fibers (succinate dehydrogenase plus cytochrome *c* oxidase staining combined) is also suggestive of an mtDNA mutation. The finding of strongly positive succinate dehydrogenase–stained blood vessels is suggestive of MELAS syndrome. Second, skeletal muscle is the ideal choice for DNA extraction for mtDNA analysis in a suspected mitochondrial myopathy as mtDNA deletions are notoriously absent in blood and mtDNA heteroplasmy is often very low to nondetectable in blood. Finally, the muscle biopsy is a good source for electron transport chain enzyme analysis given that some mitochondrial myopathies do not manifest enzymatic defects in fibroblasts or white blood cells. The author of this article recommends electron microscopy in every case of suspected mitochondrial disease for it can reveal mitochondrial alterations (eg, pleomorphic mitochondria, paracrystalline inclusions, abnormal cristae) before the light microscopic changes are evident.[73]

Many ways exist to evaluate electron transport chain enzyme activity/protein content; however, most centers use spectrophotometric methods in skeletal muscle homogenates or isolated mitochondria.[58,74] Single enzyme defects are often seen in complex assembly genes (eg, *SCO2*) or with mutations in specific electron transport chain subunits, while multiple defects can be seen in transfer RNA mutations or mutations in genes involved in mtDNA maintenance (eg, *POLG1*) or any of the many recently discovered genes under the umbrella of combined oxidative phosphorylation defects.

A large number of genetic testing methods are available for diagnosis of mitochondrial myopathy; however, most are being replaced by next-generation sequencing because of cost and throughput reasons.[58,75] mtDNA sequencing (next-generation sequencing or Sanger sequencing) of the entire mtDNA is a fast and easy way to screen for mtDNA mutations if the testing is suggestive of such a defect. Muscle is the ideal tissue to use for mtDNA testing; a moderate to high level of mutant heteroplasmy in a known gene can establish the diagnosis. Blood is not ideal for mtDNA analysis because of lower or nondetectable mutational heteroplasmy or mtDNA deletions. Variants of uncertain significance do require more sophisticated evaluation in a research-based laboratory. Long-range PCR has been used to screen muscle for mtDNA deletions given that a negative test rules out disease (high sensitivity) and a positive test can be followed up with more definitive testing such as next-generation sequencing or ND1/ND4 ratios (specific regions within the mtDNA) with PCR. Next-generation sequencing panels are rather popular, and are currently able to screen dozens to hundreds of nuclear encoded genes at once; however, with the lower cost of next-generation sequencing and the discovery of many new genes associated with mitochondrial cytopathies (eg, combined oxidative phosphorylation defects are now up to 26 recently discovered genes), many experts are using whole-exome sequencing with next-generation sequencing methodology (**Table 4-3**).

Treatment. Mitochondrial myopathies lead to a reduction in aerobic energy transduction, increased free radical production, and a greater reliance on alternative energy stores (eg, phosphocreatine). Therefore, interventions have usually focused on ameliorating one or several of these consequences. Attempts to bypass specific electron transport chain complex impairments have included succinate and riboflavin to bypass complex I and coenzyme Q_{10} to bypass complex I and II. Antioxidants have been heavily studied, including vitamin E, vitamin C, α-lipoic acid, idebenone, and coenzyme Q_{10}.[76] Creatine monohydrate has been used to provide an alternative energy source with variable success.[64,77] The most common approach is the use of a combination of

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compounds that target multiple final common pathways of mitochondria.[59,78,79]

There have been very few randomized, double-blind, controlled clinical trials in mitochondrial myopathies but we have shown some objective benefits to exercise capacity with creatine monohydrate,[64] coenzyme Q_{10},[76] and combined coenzyme Q_{10} plus vitamin E, α-lipoic acid, and creatine monohydrate.[78] Some visual improvement was noted in patients with Leber hereditary optic neuropathy using idebenone[80,81]; however, no exercise outcomes were reported, and most patients with Leber hereditary optic neuropathy do not have myopathic symptoms. Some evidence exists that a coenzyme Q_{10} analogue called EPI-743 may have therapeutic potential[82]; however, randomized double-blind studies are needed.[83] Studies have found lower lactate and some exercise improvements in patients with mitochondrial myopathy using a drug called dichloroacetate that activates pyruvate dehydrogenase[84]; however, safety concerns have raised serious questions about long-term clinical utility.[83,85]

As expected, significant improvements in exercise capacity and quality of life have occurred with endurance exercise training in patients with mitochondrial myopathy.[86–89] One study found significant improvements in strength following a resistance exercise program in patients with predominantly chronic progressive external ophthalmoplegia.[90] Studies in both endurance and resistance exercise appear to be safe[86,87,90] and also appear to improve both mitochondrial enzyme capacity[86,88] as well as reduce the mutational burden in sporadic mitochondrial myopathies.[91] A summary of some of the possible treatments is present in **Table 4-4**.

CONCLUSION

A detailed history of the triggering symptoms often points to a specific type of metabolic myopathy. For example, the glycogen-storage diseases present early on during high-intensity exercise whereas the fatty acid oxidation defects and mitochondrial myopathies usually present during longer-duration/endurance type activities or during fasting or other acute illness. Clinical examination is usually normal in the glycogen-storage diseases or fatty acid oxidation defects but can show other neurologic features in patients with mitochondrial myopathies (ptosis, external ophthalmoplegia, hypoacusis, visual loss, ataxia, neuropathy). The clinical examination can be supplemented by blood (CK, lactate, uric acid, amino acids, acylcarnitine) and urine tests (organic acids).

A relatively simple nonischemic forearm exercise test can be readily done in most clinics and is helpful to rule in or rule out several of the metabolic myopathies. The author of this article uses a 22 Ga plastic catheter in the antecubital vein and a three-way stop cock and takes resting samples (on ice) for CK, lactate, ammonia, acylcarnitines, and blood gas (the latter only if mitochondrial disease is suspected). Following this, the author instructs the subjects to perform 30 contractions in 60 seconds (1 second on:1 second off or 9 seconds on:1 sec off repeated six times) and takes a postexercise sample after 1 minute for lactate, ammonia, acylcarnitines, and blood gas (optional). A normal test rules out essentially all glycogen-storage diseases, and a normal resting lactate and normal deoxygenation lowers the posttest probability of mitochondrial disease. A normal acylcarnitine level before and after exercise in the fasted state lowers the posttest probability of a fatty acid oxidation defect. If these tests do not provide a high likelihood of a specific disorder for genetic testing, clinicians can then consider a graded exercise stress test with VO_{2max} and respiratory exchange ratio measurements as well as the blood tests mentioned previously (except blood gases). A muscle biopsy should be considered in

KEY POINT

- Exercise and resistance exercises are effective therapies for some patients with metabolic myopathies but must be individualized and titrated to tolerance.

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cases without a definitive diagnosis in whom weakness and a high CK are found or if there is a high index of suspicion for a mitochondria myopathy.

Prompt and accurate identification of the specific metabolic myopathy can lead to effective therapies such as lifestyle modification, nutritional intervention, cofactor treatment, and proper exercise prescription in order to prevent or delay rhabdomyolysis and eventual muscle weakness. An accurate diagnosis is also important from a genetic counseling perspective.

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