REVIEW ARTICLE

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Metabolic Myopathies

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ABSTRACT

PURPOSE OF REVIEW: Metabolic myopathies are disorders that affect skeletal muscle substrate oxidation. Although some drugs and hormones can affect metabolism in skeletal muscle, this review will focus on the genetic metabolic myopathies.

RECENT FINDINGS: Impairments in glycogenolysis/glycolysis (glycogen storage disease), fatty acid transport/oxidation (fatty acid oxidation defects), and mitochondrial metabolism (mitochondrial myopathies) represent most metabolic myopathies; however, they often overlap clinically with structural genetic myopathies, referred to as pseudometabolic myopathies. Although metabolic myopathies can present in the neonatal period with hypotonia, hypoglycemia, and encephalopathy, most cases present clinically in children or young adults with exercise intolerance, rhabdomyolysis, and weakness. In general, the glycogen storage diseases manifest during brief bouts of high-intensity exercise; in contrast, fatty acid oxidation defects and mitochondrial myopathies usually manifest during longer-duration endurance-type activities, often with fasting or other metabolic stressors (eg, surgery, fever). The neurologic examination is often normal between events (except in the pseudometabolic myopathies) and evaluation requires one or more of the following tests: exercise stress testing, blood (eg, creatine kinase, acylcarnitine profile, lactate, amino acids), urine (eg, organic acids, myoglobin), muscle biopsy (eg, histology, ultrastructure, enzyme testing), and targeted (specific gene) or untargeted (myopathy panels) genetic tests.

SUMMARY: Definitive identification of a specific metabolic myopathy often leads to specific interventions, including lifestyle, exercise, and nutritional modifications; cofactor treatments; accurate genetic counseling; avoidance of specific triggers; and rapid treatment of rhabdomyolysis.

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INTRODUCTION

The metabolic myopathies are genetic disorders that impact the enzymes and other proteins (eg, transporters, translocases) involved in the intermediary metabolism of glucose and free fatty acids in skeletal muscle. Typically, patients with metabolic myopathies present with muscle pains and cramps during exercise, with some progressing to rhabdomyolysis (the breakdown of skeletal muscle leading to a creatine kinase [CK] rise of greater than 10 times the upper limit of normal). This article focuses on the metabolic myopathies associated with glycogen storage diseases, fatty acid oxidation defects, and mitochondrial myopathies

(TABLE 10-1);[9] however, several other metabolic myopathy mimics (ie, pseudometabolic myopathies) and some acquired causes of exercise-induced rhabdomyolysis (ie, statins, vitamin D deficiency, hypothyroidism) will be discussed.

PSEUDOMETABOLIC MYOPATHIES

Pseudometabolic myopathies are structural myopathies that mimic metabolic myopathies by initially presenting as exercise-induced rhabdomyolysis. Although energy depletion during exercise is a trigger, these disorders are structural or calcium dysregulation myopathies and are not directly involved in substrate metabolism per se.[1-3] The most common disorders with a pseudometabolic presentation are the limb-girdle muscular dystrophies (*TTN, SGCA, SGCB, SGCD, ANO5,* and *DYS* gene mutations) and Becker muscular dystrophy (*DMD* gene mutation).[4,5] Rhabdomyolysis in these disorders is likely due to exercise-induced sarcolemmal damage, excessive calcium influx, or both. Even before fixed proximal weakness occurs, a clue to their existence is a CK elevation persisting for more than 10 days following a bout of rhabdomyolysis (CASE 10-1).

In contrast, hyperCKemia is not seen with the excitation-contraction coupling associated mutations (*RYR1* and *CACNA1S*) seen in malignant hyperthermia susceptibility myopathies. Exercise-induced rhabdomyolysis with autosomal dominant mutations in the *RYR1* or *CACNA1S* gene has been reported.[4,6] These proteins link depolarization of the transverse tubule (dihydropyridine receptor, *CACNA1S* gene) to calcium release from the sarcoplasmic reticulum (ryanodine receptor, *RYR1* gene) with mutations leading to isolated malignant hyperthermia, core myopathy, or exercise-induced rhabdomyolysis.[7] A correlation between *RYR1* mutation phenotype and rhabdomyolysis does not seem to exist, although biallelic *RYR1* variants are usually associated with a more severe fixed weakness phenotype/core myopathy.[7] Practically, patients with malignant hyperthermia should avoid exercise in the heat or when dehydrated and should wear a medical alert bracelet.

In addition, it is important to recognize that several acquired disorders can lead to exercise-induced rhabdomyolysis. Statins are one of the most commonly prescribed medications in the world and are a well-known trigger of

Metabolic Myopathies in Skeletal Muscle

TABLE 10-1

Category	Examples
Glycogen storage disease	McArdle (GSD5, myophosphorylase deficiency); Tarui (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 palmitoyl transferase 2 deficiency, trifunctional protein deficiency, very-long-chain acyl-CoA dehydrogenase deficiency
Mitochondrial myopathy	mtDNA mutations (MELAS, cytochrome b, cytochrome c oxidase), nuclear DNA mutations (*POLG*, *TK2*)

CoA = coenzyme A; mtDNA = mitochondrial DNA; MELAS = mitochondrial encephalomyopathy lactic acidosis and strokelike episodes; *POLG* = polymerase gamma; *TK2* = thymidine kinase.

rhabdomyolysis; they can even trigger an autoimmune process mediated by anti–3-hydroxy-3-methylglutaryl coenzyme A reductase antibodies.[8-10] Statins result in a higher CK response to standardized exercise,[11,12] can lead to myalgia in approximately 10% of individuals, and may unmask an underlying genetic metabolic myopathy.[13]

Vitamin D deficiency (<30 nmol/L) can lead to exercise intolerance, rhabdomyolysis, and persistent hyperCKemia, with a good clinical and laboratory response to vitamin D supplementation. A reduction in or resolution of statin-associated myalgia was reported in vitamin D–deficient patients following supplementation.[14-18] Consequently, it is reasonable to measure vitamin D levels in all cases of exertional rhabdomyolysis or statin-associated myalgia/myopathy and replace them to achieve sufficient levels (typically >75 nmol/L).

Hypothyroidism can lead to a fixed myopathy with hyperCKemia[19,20] and weakness,[21] but predisposes to exertional rhabdomyolysis.[22-25] Hypothyroidism can lead to mitochondrial dysfunction and carnitine depletion,[26] which likely explains the relationship to exercise-induced rhabdomyolysis. Although less common, hyperthyroidism can also lead to rhabdomyolysis.[27-29] It is therefore reasonable to check plasma thyroid-stimulating hormone (TSH) and thyroxine levels in cases of exertional rhabdomyolysis.

BRIEF OVERVIEW OF SKELETAL MUSCLE METABOLISM

At the onset of exercise, an immediate drop in adenosine triphosphate (ATP) occurs; this leads to an increased flux through the adenylate kinase (AK) enzyme

CASE 10-1

A 23-year-old woman presented to the emergency department with rhabdomyolysis following a 30-minute spin class. Her creatine kinase (CK) peaked at 56,000 U/L (normal <220 U/L) during 2 days of in-hospital IV fluids, and she was discharged home with a requisition to measure CK 2 weeks later. The CK 2 weeks later was still at 1200 U/L and remained at 1100 U/L 4 weeks after the initial event.

She was referred to the neuromuscular clinic as her CK did not normalize. Her neurologic examination was normal except for hypertrophic calf muscles. A dystrophin genetic test for deletions and duplications was normal, her *DMD* gene was sequenced, and a known pathogenic stop codon at c.6118-3C>A in IVS 42 was found.

COMMENT

This is a typical case of a pseudometabolic myopathy and provided the patient with an accurate diagnosis of manifesting carrier state for Duchenne muscular dystrophy and allowed for appropriate genetic counseling given that she was engaged and planning a family. Echocardiogram was normal, but echocardiography was recommended every 5 years or if she developed any cardiac symptoms. The patient was able to slowly work up to cardiovascular exercise four times a week for 30 to 45 minutes, with no further rise of CK and no further bouts of rhabdomyolysis.

(ADP + ADP > AK > ATP + AMP), which is maintained by the adenosine monophosphate deaminase 1 (AMPD1) pathway. The AMPD1 enzyme catalyzes the deamination of adenosine monophosphate (AMP) to inosine monophosphate which, after several enzymatic steps, leads to the conversion of xanthine to uric acid. This pathway is active in muscle contraction in healthy people but is enhanced in those with glycogen storage diseases and can lead to gout through increased uric acid production (myogenic hyperuricemia).[30]

Traditionally, myoadenylate deaminase deficiency was considered to be a metabolic myopathy[31,32]; however, the AMPD1 enzyme is not directly involved in substrate metabolism and its role in metabolic myopathies has been called into question for several reasons: (1) the prevalence of the most commonly reported "pathogenic" stop gain variant in *AMPD1* (c.34C>T;p.Gln12Ter) was present in 8.7% of a random sample of 282,334 healthy people (gnomad.broadinstitute.org/gene/ENSG00000116748?dataset=gnomad_r2_1) with approximately 2% being homozygous; (2) muscle blood flow is increased with no significant power reduction in skeletal muscle[33]; (3) homozygous patients who are *AMPD1* deficient do not have exercise impairment or any of the predicted deleterious metabolic consequences in skeletal muscle.[34] Thus, AMPD1 deficiency is not a metabolic myopathy and humans appear to compensate well for complete AMPD1 deficiency.

The creatine-phosphocreatine system is also activated at the onset of exercise, and adenosine diphosphate (ADP) is rephosphorylated by phosphocreatine to produce ATP and free creatine (Cr) via the cytosolic CK enzyme. A proton (H^+) is also part of the reaction (ADP + PCr + H^+ > CK > ATP + Cr) and this reaction is driven by the H^+ produced by anaerobic glycolysis and glycogenolysis. Skeletal muscle phosphocreatine stores are depleted after approximately 10 seconds of muscle contraction and are restored about 2 minutes after stopping exercise by mitochondrially derived ATP. The activation of the creatine-phosphocreatine system is also important in stimulating mitochondrial respiration. Genetic defects occur in the creatine-phosphocreatine system, including creatine synthesis defects (eg, arginine:glycine aminotransferase deficiency)[35] and creatine transporter defects[36]; however, the impact on exercise is unclear as these disorders lead to severe infantile and childhood encephalopathic symptoms.

At the onset of exercise, glycogenolysis and glycolysis are activated and [lactate$^-$ + H^+] are formed by lactate dehydrogenase. After the first few minutes of muscle contraction, an increase in aerobic respiration occurs through the tricarboxylic acid (TCA) cycle and the mitochondria. The generation of pyruvate increases the flux of acetyl coenzyme A (CoA) into the TCA cycle via the pyruvate dehydrogenase pathway to form citrate and increase TCA cycle flux/content via anaplerosis. Reducing equivalents (NADH + H^+ and $FADH_2$) from the TCA cycle and fatty acid β-oxidation enter the mitochondria at complex I and II, respectively, and drive protons to the intermembrane space and build up the proton motive force. The electrons from the oxidation of NADH + H^+ and $FADH_2$ are used to reduce molecular oxygen to water at complex IV. The proton motive force is used to drive ATP synthesis at complex V.

Exercise-mediated substrate fuel selection is determined by a number of factors, including exercise intensity and duration, training status, habitual dietary intake, and biological sex. Aerobic exercise intensity is usually measured as a percentage of the maximal oxygen consumption (VO_{2max}). Most people will oxidize free fatty acids at exercise intensities less than 50% VO_{2max}, with the

KEY POINTS

- Metabolic and pseudometabolic disorders present during or following some form of exercise/physical activity and with generalized "tiredness" or daily fatigue.
- Metabolic myopathies present with muscle pains and/or cramps during exercise with some patients progressing to rhabdomyolysis (the breakdown of skeletal muscle leading to a creatine kinase rise of greater than 10 times the upper limit of normal).
- Severe vitamin D deficiency can lead to hyperCKemia and/or rhabdomyolysis.
- Common drugs such as statins and common disorders such as vitamin D deficiency and hypothyroidism can lower the threshold for rhabdomyolysis in patients with inborn errors of metabolism and can even rarely lead to rhabdomyolysis in otherwise healthy individuals.

carbohydrate contribution increasing at higher exercise intensities and free fatty acids being predominant with longer-duration endurance exercise.[37] Women oxidize proportionately more lipid at any relative exercise intensity as compared to men.[38-40]

The main source of carbohydrates during exercise is intramuscular glycogen and muscle glycogen stores, and mitochondrial and free fatty acid metabolic enzymes are higher following endurance exercise training.[38,41,42] In addition, the depletion of glycogen during the same absolute exercise intensity is less than after endurance exercise training.[39] Muscle glycogen can also be manipulated by diet, with the short-term (3-day) consumption of a high-carbohydrate diet resulting in a significant increase in muscle glycogen,[43,44] especially in men.[45]

GENERAL CLINICAL APPROACH TO THE PATIENT WITH EXERTIONAL RHABDOMYOLYSIS

The history is the most important aspect of the assessment of the patient presenting with exercise-induced rhabdomyolysis. Most patients with a metabolic myopathy will have symptoms that were apparent in childhood with comments such as, "the worst athlete in the class" being common. Obtaining a family history is important and a history of consanguinity increases the likelihood of metabolic myopathy. A childhood history of myalgia or pigmenturia or encephalopathy with superimposed illness or fever raises suspicion for a fatty acid oxidation defect or mitochondrial myopathy. Glycogen storage diseases usually present with higher-intensity exercise or at the onset of exercise initiation, while fatty acid oxidation defects present with

TABLE 10-2 Features From the History Suggesting Specific Metabolic Myopathies

History	Disorders
Rhabdomyolysis/pigmenturia	Glycogen storage diseases, fatty acid oxidation defects, mitochondrial
Myalgia with endurance sports	Fatty acid oxidation defects, mitochondrial
Shortness of breath with endurance sports	Mitochondrial mainly but others can report this symptom
Myalgia/cramps with power/sprint sports	Glycogen storage disease
Rhabdomyolysis triggered by fasting or superimposed illness	Fatty acid oxidation defect, mitochondrial
Gout/myogenic hyperuricemia	Glycogen storage disease (mainly GSD5 and GSD7)
Nausea/vomiting with exercise	Mitochondrial and GSD7
Multiple system involvement	Mitochondrial
Family history: X-linked	Phosphorylase b kinase deficiency, phosphoglycerate kinase 1 deficiency
Family history: maternal	Mitochondrial (mtDNA only)
Family history: autosomal recessive/ consanguinity	Fatty acid oxidation defects, most glycogen storage diseases, non-mtDNA mitochondrial disease

mtDNA = mitochondrial DNA.

longer-duration exercise often after fasting or other superimposed metabolic stressors. Mitochondrial myopathies often manifest symptoms during longer-duration activity or during physical activity performed under additional metabolic stress. Another key to a mitochondrial defect is a history of other associated features by history or examination (eg, hypoacusis, ptosis, optic atrophy, epilepsy, ataxia, cardiomyopathy, type 2 diabetes).

Patients with a history of recurrent rhabdomyolysis are more likely to have an underlying metabolic myopathy or pseudometabolic myopathy and require further investigation. The most common reason for exertion rhabdomyolysis is unaccustomed exercise including forced exercise situations, such as military or police academy recruitment or starting a new exercise program. A common scenario is an individual who was an athlete and takes years to decades away from formal exercise and then goes back to an exercise program. A huge interindividual variability exists in the susceptibility to rhabdomyolysis even among those without a genetic metabolic or pseudometabolic myopathy. It is important to note that all individuals, including those with metabolic myopathy, can adapt to exercise training if done carefully and progressively.

Several other scenarios can occur where the threshold for rhabdomyolysis is reduced, including dehydration, superimposed flulike illness (especially with fever), high heat and humidity, prolonged fasting, hypothyroidism or hyperthyroidism, and severe vitamin D deficiency. It is important to follow the serum CK activity until it shows a normalization trend. Renal function monitoring is important, as acute tubular necrosis is the most ominous outcome of rhabdomyolysis. Follow-up blood work is recommended to ensure that CK normalizes, and an acylcarnitine determination is usually recommended upon initial presentation to screen for fatty acid oxidation defects (see Fatty Acid Oxidation Defects section). Every patient should have a complete neurologic examination, and for those who do not show normalization of serum CK activity an EMG and nerve conduction study is recommended. Patients who remain very active can have a low-grade CK elevation, and clinicians should consider a monitoring period of up to 7 days to see if the CK normalizes. Some patients can have nonpathologic chronic CK elevations of up to 1000 U/L; if the neurologic examination is normal and the patient is otherwise healthy, no additional evaluation is needed.

DISORDERS OF GLYCOLYSIS/GLYCOGENOLYSIS (GLYCOGEN STORAGE DISEASES)

The first metabolic myopathy to be described was named McArdle disease, after the senior author of the paper, which described a man with exercise-induced cramps.[46] This glycogen storage disease, also called GSD5, is caused by a mutation in the myophosphorylase gene (*PYGM*). Several other glycogen storage diseases were described before McArdle disease, but they mainly affect hepatic metabolism (ie, GSD1, GSD3, and GSD4) or are now considered to be lysosomal storage diseases (GSD2, Pompe disease) and do not impact energy delivery during exercise.[47] Many enzymes in the glycolytic and glycogenolytic pathways are associated with metabolic myopathies (**TABLE 10-2**).

All glycogen storage diseases show autosomal recessive inheritance, except for phosphorylase b kinase deficiency (GSD9) and phosphoglycerate kinase 1 deficiency (X-linked recessive inheritance). These are all rare to ultrarare disorders, with McArdle disease being the most common metabolic myopathy

KEY POINTS

- **Most of the metabolic myopathies will have some symptoms present in childhood but often the compensatory strategies can mask the earlier presentation.**
- **The history is a critical part of the workup in a patient presenting with rhabdomyolysis, with a lifelong history of exercise intolerance and recurrent rhabdomyolysis (even if induced by fever or other metabolic insult) being the two most common predictors of an underlying genetic metabolic myopathy/inborn error of metabolism.**
- **All patients with rhabdomyolysis require a complete neurologic examination.**

(approximately 1 per 100,000). GSD9 is a glycogenolytic glycogen storage disease presenting similarly to McArdle disease; however, the phenotype may be mild and show variable penetrance.[48,49] Tarui disease (GSD7) is the most common glycolytic glycogen storage disease and is due to impaired phosphofructokinase activity. Patients with Tarui disease (and other glycolytic disorders) present with symptoms similar to patients with McArdle disease but do not have a second-wind phenomenon.[50,51] Other glycolytic disorders include phosphoglycerate kinase 1 deficiency, phosphoglucomutase 1 deficiency (also known as congenital disorder of glycosylation type It), phosphoglycerate mutase deficiency (GSD10), lactate dehydrogenase deficiency (GSD11), aldolase A deficiency (GSD12), and β-enolase deficiency (GSD13).

Clinical Presentation

Patients with myopathic glycogen storage diseases usually exhibit symptoms within the first few seconds to minutes of activity or if the intensity of activity increases beyond the anaerobic threshold. Most myopathic glycogen storage disease patients present with exercise intolerance, and most will experience rhabdomyolysis at some point in their lives. Cramping symptoms during exercise

CASE 10-2

A 45-year-old man presented to the emergency department with severe muscle pains in the legs and arms 24 hours after helping a friend move out of his house. His creatine kinase (CK) was 8000 U/L, but he was anuric and his creatinine was twice the upper limit of normal. He was hydrated and carefully followed for a week and his CK returned to 700 U/L and fluctuated around 1000 U/L for 2 months, but his creatinine normalized. His past medical history was notable only for type 2 diabetes.

The patient was referred to a neuromuscular clinic for assessment. On further history, the patient noted that he had always avoided exercise as a child, and recalled going to Europe with his family as a teenager and not being able to keep up with his grandmother on a city tour, especially when climbing stairs; however, if he slowed down and rested a bit he could keep going all day, albeit at a low intensity.

His neurologic examination was normal aside from a reduction in vibration sensation in the toes and he had a deformed first metatarsophalangeal joint from recurrent episodes of gout.

Given the typical history of McArdle disease, his *PYGM* gene was sequenced and he was found to be homozygous for the common p.Arg50* mutation.

COMMENT

This is a typical history for a patient with McArdle disease, with lifelong myalgia/cramps with high-intensity activity and a second-wind phenomenon. The gout was due to myogenic hyperuricemia, and failure of his CK to normalize is typical of McArdle disease but not of most other glycogen storage diseases. With preexercise sucrose and knowledge of his disease and its triggers, he was able to exercise 3 times a week for 30 minutes with no further bouts of rhabdomyolysis.

may be alleviated by reducing exercise intensity or resting and then carefully resuming activity (second-wind phenomenon). Often there is delayed-onset muscle soreness that may be associated with dark urine/pigmenturia that patients often describe as "cola," "tea," "red," "brown," or "black." The pigment comes from myoglobin which can lead to acute tubular necrosis. Rhabdomyolysis is defined as an acute rise in CK to over 10 times the upper limit of normal (usually >2000 U/L).

The diagnosis of myopathic glycogen storage diseases is often delayed until the second or third decade as many patients assume that they are just "not good athletes" and often adapt activities to minimize the symptoms. Targeted questioning usually reveals a childhood history of pigmenturia, excessive shortness of breath upon exertion, or not "keeping up" or being the "worst athlete in the class." Patients with McArdle disease often report fewer symptoms following a high-carbohydrate meal; in contrast, patients with glycolytic defects often feel improvement in their symptoms after a prolonged fast (CASE 10-2).

The neurologic examination in most of the metabolic myopathies is usually normal between bouts of rhabdomyolysis; however, some patients (mainly those with GSD5[52] and GSD12) eventually develop fixed proximal weakness. Ptosis (14.2%) and pattern retinal dystrophy (36.6%) have also been reported in patients with McArdle disease.[52] CK between rhabdomyolysis events is usually normal with most glycogen storage diseases; however, CK is chronically elevated in nearly all McArdle disease patients. Hemolysis and even hemolytic anemia can be seen in GSD7, GSD12, and phosphoglycerate kinase 1 deficiency. Because of the compensatory increased flux through AMPD1 and the xanthine oxidase pathways, both glycogenolytic and glycolytic defects can have myogenic hyperuricemia, precipitating gout in approximately 25% of patients.[52] A higher-than-expected incidence of hypothyroidism (15.2%) was reported in McArdle disease,[52] further supporting the suggestion that treatable secondary disorders (eg, hypothyroidism, vitamin D or B_{12} deficiency, hypogonadism[53]) should be screened for in all metabolic and structural myopathy patients. A summary of some key features revealed by the history in specific glycogen storage diseases can be found in TABLE 10-3.

Diagnostic Testing

The classic diagnostic test to rule in or rule out a glycogen storage disease is the forearm ischemic test, which shows a blunted lactate and exaggerated ammonia response postexercise.[30] Typically, a sphygmomanometer cuff is inflated above arterial pressure and 1 minute of rhythmic maximal handgrip exercise is performed, followed by the collection of preexercise and postexercise samples for plasma lactate and ammonia measurements. A normal response is an increase in both lactate and ammonia greater than 3 times baseline. Most glycolytic and glycogenolytic defects (except GSD9[48] and, rarely, GSD10) will show a markedly attenuated lactate rise and an accentuated ammonia rise. A suboptimal effort is reflected as a failure of both lactate and ammonia to rise following exercise. The sphygmomanometer cuff is not strictly necessary and rhythmic contraction per se is sufficient to yield good test sensitivity and specificity.[54,55] Consequently, a 1-minute nonischemic forearm exercise test is routinely used to lower the risk of rhabdomyolysis and acute compartment syndrome.

The current nonischemic forearm exercise test protocol involves placing a plastic catheter into an antecubital vein and taking a blood sample for plasma

KEY POINTS

- The creatine kinase will normalize in most of the glycogen storage diseases, except in McArdle disease where it is persistently elevated.
- Patients with myopathic glycogen storage diseases typically have recurrent bouts of cramps with or without rhabdomyolysis with shorter-duration/repetitive and/or higher-intensity physical activities.
- There is no added diagnostic value from an ischemic versus nonischemic forearm exercise test, yet it adds to the risk of local rhabdomyolysis and compartment syndrome; consequently, the nonischemic version is recommended.

TABLE 10-3 **Specific Testing for Metabolic Myopathies**

Disorders	Testing
Glycogen storage diseases	CK (chronic elevation in McArdle), approximately 50% of patients will have elevated uric acid
	Nonischemic forearm exercise test or graded exercise stress test with minimal to no lactate rise, and exaggerated ammonia rise
	Graded exercise stress test with a second-wind phenomenon is more common in McArdle disease
	Graded exercise stress test without a second-wind phenomenon is more consistent with glycolytic defects and GSD9
	EMG/NCV is usually normal
	Muscle biopsy with or without high glycogen: no phosphorylase activity is consistent with McArdle disease; no phosphofructokinase activity is consistent with GSD7
	Next-generation sequencing panels for glycogen storage diseases, rhabdomyolysis or myopathy panels with glycogen storage disease genes or whole-exome sequencing (research)
Fatty acid oxidation defects	CK normal between bouts of rhabdomyolysis
	Total carnitine usually normal
	Acylcarnitine profile often abnormal (fasted or following a graded exercise stress test)
	Urine organic acids (dicarboxylic acids) may be elevated in beta-oxidation defects
	Hypoketotic hypoglycemia during an event
	EMG/NCV is often normal
	Muscle biopsy may show increased neutral lipids but can be normal (ie, carnitine palmitoyl transferase 2 deficiency)
	Enzyme analysis and acylcarnitine in fibroblasts
	Next-generation sequencing panels for fatty acid oxidation defect, rhabdomyolysis or myopathy panels or whole-exome sequencing (research)
Mitochondrial myopathy	CK may be chronically elevated
	Lactate elevated in approximately 65% of patients with primary mitochondrial myopathy
	Alanine elevated in approximately 20% of patients with primary mitochondrial myopathy
	Urine organic acids (tricarboxylic acids or 3-methyl glutaconic acid) may be elevated
	Nonischemic forearm exercise test shows no deoxygenation with blood gas
	Graded exercise stress test shows a low VO_{2max}, high respiratory exchange ratio, hyperkinetic heart rate, and ventilation response
	EMG is often normal (TK2, often myopathic)
	Muscle biopsy may show ragged red fibers, cytochrome c oxidase deficiency, and paracrystalline inclusions (ultrastructure)
	Enzyme analysis on muscle can show mixed or single electron transport chain defects but cannot be used as sole diagnostic source
	mtDNA sequencing if mtDNA is suspected (ie, MELAS), ideally from muscle and not blood
	Next-generation sequencing mitochondrial panels or whole-exome sequencing for suspected nuclear defects

CK = creatine kinase; EMG = electromyography; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes; mtDNA = mitochondrial DNA; NCV = nerve conduction velocity; TK2 = thymidine kinase; VO_{2max} = maximal oxygen consumption.

lactate and ammonia into wet ice-chilled tubes, followed by 1 minute of maximal handgrip dynamometry with a 9 second on, 1 second off ratio, and then taking blood samples after 1 minute.[30] A normal test with proper effort rules out every glycolytic and glycogenolytic defect except for GSD9[48] and GSD10.[56]

Nerve conduction studies and EMG are normal in myopathic glycogen storage diseases except during a muscle contracture when there will be electrical silence. Magnetic resonance spectroscopy shows enhanced phosphocreatine hydrolysis, a lack of acidosis, and an increase in phosphomonoesters in distal glycolytic defects. The author's clinic generally does not use magnetic resonance spectroscopy as we have not found that it adds any diagnostic value beyond the history, examination, blood work, exercise testing, and genetic testing.

If the history is highly suspicious for a glycolytic or glycogenolytic defect, the author often proceeds directly to genetic testing, and only uses the nonischemic forearm exercise test for more atypical cases and in low pretest probability cases of ill-defined "exercise intolerance." Alternatively, a graded exercise stress test with VO_{2max} and prelactate and postlactate can be used to evaluate mitochondrial disease and glycogen storage diseases, including GSD9.[48]

The author has been sending most patients with moderate to high pretest probability of myopathy or rhabdomyolysis for next-generation sequencing panels for the past 10 years. Several CLIA (Clinical Laboratory Improvement Amendments) certified laboratories offer full sequencing of the coding and intron/exon boundary regions for all known glycolytic and glycogenolytic defects and all the possible pseudometabolic disorders mentioned previously. For a searchable database to find laboratories that offer rhabdomyolysis or myopathy panels, it is best to use the National Institutes of Health (NIH) Genetic Test Registry website (ncbi.nlm.nih.gov/gtr/). The author is doing fewer muscle biopsies in the past 10 years and generally only in patients with a negative myopathy panel result or when only a single pathogenic variant is discovered in an autosomal recessive disorder that fits the phenotype. In the latter case, the muscle can be used for specific enzyme analysis and, if that is positive, RNA sequencing and whole-genome sequencing or targeted intronic sequencing can be performed to discover a second variant that is not discoverable with exome slice–based or Sanger-based panels. Another advantage of performing a muscle biopsy in atypical cases is that it is possible that histologic features of a pseudometabolic myopathy can lead to an accurate diagnosis. Some examples that the author has encountered include cores in *RYR1* and *CACNA1S* mutations, abnormal dystrophin staining (Becker muscular dystrophy), ragged red fibers (mitochondrial myopathy), or membrane-bound glycogen (Pompe disease). A summary of some of the helpful tests in glycogen storage diseases is presented in **TABLE 10-3**.

KEY POINT

- **Next-generation sequencing panels are replacing many of the previously used diagnostic tests but must be interpreted in the clinical context and may need additional metabolomic, histological, or biochemical support.**

Treatment

Many patients alter their lifestyle activities to mitigate symptoms even decades before a definitive diagnosis is made. Most patients avoid high-intensity activities and start any exercise at a low intensity and titrate intensity to minimize symptoms. Patients who experience a second wind usually know the duration, intensity, and type of activity that leads to symptoms and ease off before the symptoms are too severe and resume activity when the second wind "kicks in." It is important for patients with glycogen storage diseases to start exercising at a lower intensity and gradually increase the intensity and duration while

monitoring for symptoms and reducing the intensity as needed. Although once thought to be a contraindication, regular exercise actually lessens symptoms of McArdle disease.[57-59] The author tells patients to not exercise on days when they have a superimposed cold, flu, virus, or fever; to listen to their bodies; and to monitor for greater than typical mild exercise-induced myalgia and reduce exercise intensity or duration. The consumption of carbohydrates containing glucose (including sucrose, which is comprised of fructose and glucose) shortly before exercise can "bypass" glycogenolytic metabolic defects and improve exercise tolerance, allowing patients with McArdle disease to proceed to their second wind more rapidly.[60,61] One study found that 37 grams of oral sucrose consumed 5 to 10 minutes before exercise improved exercise capacity and reduced symptoms.[60] Another study found that patients with GSD3 (debranching enzyme deficiency) also showed improvements in exercise capacity with preexercise fructose ingestion[62]; however, neither oral sucrose nor IV glucose improved exercise capacity in patients with GSD9.[63] In contrast, patients with glycolytic defects (ie, GSD7) tolerate exercise better in the fasted state and do worse with carbohydrate feeding given that carbohydrates attenuate the liberation of free fatty acids via lipolysis as an alternative fuel source.[64]

TABLE 10-4 **Specific Metabolic Myopathy Treatments**

Disease	Treatment
Glycogen storage diseases	Careful and progressive exercise training
	Preexercise sucrose/glucose in McArdle disease
	Overnight fasting for glycolytic defects (eg, phosphofructokinase deficiency)
	Creatine monohydrate (no greater than 0.1 g/kg/d)
	Pyridoxine 50 mg/d for null phosphorylase mutations
	Check for and treat hyperuricemia/gout
	High-protein diet (approximately 15% total calories)
	Possibly ketogenic diet, but further studies required
Fatty acid oxidation defects	Careful and progressive exercise training in fed state
	Avoid fasting and exercise during illness/fever
	L-carnitine supplementation (only if low total levels, eg, *OCTN2*-associated carnitine transporter defect)
	High-carbohydrate diet
	Carbohydrates before and during exercise
	Triheptanoin may be used in severe or treatment-resistant cases, subject to local regulatory availability and approval
Primary mitochondrial myopathies	Careful and progressive exercise training
	Avoid fasting and exercise during illness/fever
	Cocktail treatment (coenzyme Q10 or idebenone, α-lipoic acid, vitamin E, creatine monohydrate)
	L-carnitine only if levels are low

Patients with McArdle disease carry *PYGM* mutations that lead to nonsense-mediated mRNA transcript decay (ie, p.R49X), have no PYGM protein, and thus can have a secondary pyridoxine (vitamin B_6) deficiency. Consequently, pyridoxine supplementation (approximately 50 mg/d) has been suggested for GSD5 patients with null mutations.[65,66] The clinical efficacy of pyridoxine supplementation has not been confirmed in a randomized clinical trial; however, it seems to be a low-risk suggestion, especially because pyridoxine is a known cofactor for enzymes involved in the liberation of amino acids that can be used as an energy source in glycogen storage diseases during longer-duration exercise. High-protein diets may increase alternative fuel (amino acid) availability; however, branched-chain amino acid (ie, leucine, isoleucine, and valine) supplements did not show a benefit in a very small cohort.[67] Creatine monohydrate in low dose (approximately 0.1 g/kg/d) showed bioenergetic improvements in McArdle disease patients during exercise[68]; however, the same group showed that higher creatine doses (approximately 0.3 g/kg/d) led to exercise impairment and myalgia.[69] Studies have also shown that ribose, verapamil, and dantrolene sodium were not effective in McArdle disease[70] and show side effects, including diarrhea and hypoglycemia symptoms (ribose) and fatigue, vertigo, and muscle weakness (dantrolene sodium). A randomized clinical trial also evaluated the effect of an odd-chain free fatty acid called triheptanoin in patients with McArdle disease but found no clinical benefit.[71] Finally, one study found mild improvements in exercise capacity and improved symptoms with 2.5 mg of ramipril in patients with an angiotensin-converting enzyme deletion/deletion haplotype (approximately 30% of the general population).[72] General suggestions for patients are given in TABLE 10-4.

KEY POINTS

- Although acute exercise can be a trigger for rhabdomyolysis in patients with inborn errors of metabolism, all patients can adapt to carefully designed exercise training programs and raise the exercise threshold for induction of rhabdomyolysis and confer long-term protection.
- Given that sucrose is a disaccharide made from glucose and fructose, one can get approximately 25 g of preexercise sucrose equivalent carbohydrate from 250 mL of fruit juice (fructose and glucose) or soda, or 400 mL of sport drink. (Although the latter two examples have no other nutritional value, they do contain high-fructose corn syrup [fructose and glucose].)
- Creatine monohydrate (approximately 100 mg/kg/d) and a high-protein diet may confer some benefit in patients with glycogen storage diseases, but it is important to not use higher creatine doses.
- Carnitine palmitoyltransferase 2 deficiency is the most common fatty acid oxidation defect, but trifunctional protein and very-long-chain acyl-CoA dehydrogenase deficiencies can present in an identical manner.

FATTY ACID OXIDATION DEFECTS

Fatty acids are categorized according to the number of carbons as short (2 to 4), medium (6 to 12), long (14 to 18), and very-long (20 and above) chain fatty acids. The long- and very-long-chain free fatty acids require the carnitine palmitoyltransferase system for mitochondrial transport, whereas short- and medium-chain free fatty acids can directly enter the mitochondrial matrix for β oxidation. All the metabolic myopathy–associated fatty acid oxidation defects are autosomal recessive disorders, with carnitine palmitoyltransferase 2 (CPT2) deficiency being approximately 2.5 times less common (approximately 1/250,000) than McArdle disease. Trifunctional protein (TFP) and very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD) deficiencies are clinically indistinguishable from CPT2 deficiency but are less common.

Clinical Presentation

Most of the fatty acid oxidation defects present with exercise-induced myalgia in contrast to the actual cramping symptoms seen in glycogen storage diseases. Patients with fatty acid oxidation defects usually experience pigmenturia later the same day or within 24 hours of exercise-induced rhabdomyolysis, often with significant delayed-onset muscle soreness. Symptoms of fatty acid oxidation defects are usually precipitated by fasting, prolonged exercise, or superimposed illness. In retrospect, many patients with fatty acid oxidation defects recall having myalgia and occasionally pigmenturia with superimposed illness and

many are not diagnosed until their teenage years when they experience rhabdomyolysis with longer-duration exercise (TABLE 10-2).

Diagnostic Testing

Blood testing is usually completely normal for resting CK, lactate, and glucose between episodes of rhabdomyolysis. During an acute bout of rhabdomyolysis the CK will rise within 2 hours and patients can also show hyperkalemia and hypoketotic hypoglycemia. Patients with rhabdomyolysis can experience acute renal failure with increased potassium, creatinine, and urea.

A serum acylcarnitine profile is the most sensitive and specific test for a fatty acid oxidation defect. This test is usually abnormal between acute events; however, testing in the overnight fasted state, following an aerobic exercise test, or during an acute bout of rhabdomyolysis will further elevate the levels and improve sensitivity and specificity. A specific acylcarnitine profile can suggest the specific defect and support genetic testing. Even though the author and others use myopathy genetic panels earlier in the diagnostic pathway, other tests such as for acylcarnitines are very helpful in evaluating the common scenario where multiple variants of uncertain significance (VUSs) are found in a panel and a congruent metabolite pattern to the specific VUS in the appropriate pathway provides confidence in the diagnosis and stops the diagnostic odyssey. In contrast to the acylcarnitine profiling, the total free carnitine levels are usually only abnormal (low) with severe nutritional deficiency, renal failure, valproic acid use, or systemic carnitine deficiency due to mutations in *SLC22A5*. Urine organic acid analysis may show an elevation of characteristic dicarboxylic acids in β-oxidation defects, but often only during an acute bout of rhabdomyolysis.

As mentioned previously, the next-generation-sequencing–based gene panels cover the more common fatty acid oxidation defects leading to rhabdomyolysis (eg, CPT2, TFP, VLCAD) and some of the more rare fatty acid oxidation defects associated with exercise-induced rhabdomyolysis (eg, medium-chain acyl-CoA dehydrogenase deficiency, carnitine-acylcarnitine translocase deficiency). Most rhabdomyolysis panels will also include the *LIPIN1* gene which encodes a magnesium-dependent phosphatidic acid phosphohydrolase involved in the sarcolemma that is usually triggered by fever or other superimposed illness; however, *LIPIN1* mutations have not yet been associated with exercise-induced rhabdomyolysis.

In rare cases where the fasting acylcarnitine profile is normal and the genetic panel is nonrevealing, the author usually does a graded exercise stress test (cycle or treadmill) in the fasted state with preexercise and postexercise lactate and postexercise acylcarnitine profiling.[73] In addition to screening for a glycolytic/glycogenolytic defect, a high resting lactate in combination with a low Vo_{2max} and a high respiratory exchange ratio can indicate a mitochondrial myopathy. The author rarely does a muscle biopsy given that the diagnosis is obtainable with genetic testing and acylcarnitine profiling; however, a significant increase in neutral lipids (ie, oil-red-O or Sudan black staining) seen in a biopsy from a patient with a myopathy should raise suspicion for a fatty acid oxidation defect or mitochondrial disease. A massive increase in neutral lipids on the biopsy with a high CK should also raise the possibility of autosomal recessive neutral lipid storage disease with myopathy (NLSDM) due to mutations in the *PNPLA2* gene that encodes the ATGL protein that is required to breakdown intramyocellular lipids. Although this disorder leads to slowly progressive myopathic weakness

and cardiomyopathy in the second and third decades, many patients do note exercise intolerance when young.[74,75] EMG and nerve conduction studies are usually normal in fatty acid oxidation defects; however, a mixed axonal neuropathy can be seen in cases of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency leading to progressive distal weakness (TABLE 10-3).

Treatment

The general strategy for most patients with fatty acid oxidation defects is to avoid disease triggers including physical activity in the fasted state or with a superimposed illness and/or long-duration endurance exercise. Most patients tolerate resistance exercise or shorter burst-type activity and many patients consume higher-carbohydrate foods immediately before exercise; however, one study did not find benefit from oral glucose administration.[76] The author recommends a habitual diet with relatively low fat (less than 30%) and higher carbohydrates.[77] Despite the biochemical plausibility for the use of riboflavin, medium-chain triglycerides, and L-carnitine,[78,79] they have not been proven to be effective in clinical trials with small subject numbers. The author recommends that total carnitine levels be checked and replaced with oral L-carnitine if patients are deficient.

Initial in vitro studies suggested the use of the fibric acid derivative, bezafibrate[80]; however, class I evidence suggests no clinical benefit in CPT2 deficiency.[81] Much interest in the use of triheptanoin exists given that it was shown to improve clinical metrics in patients with fatty acid oxidation defects,[82,83] including cardiomyopathy.[84] Triheptanoin was shown to reduce hospitalizations in patients with fatty acid oxidation defects in a retrospective study,[85] improved exercise capacity in patients with CPT2[83] and other fatty acid oxidation defects,[86] and reduced major clinical events in patients with fatty acid oxidation defects in a prospective study.[87] Some of the potential treatment options for fatty acid oxidation defects,[88] including triheptanoin,[89] have been recently reviewed, and are also summarized in TABLE 10-4.

KEY POINTS

- A serum acylcarnitine profile, especially when fasted or during a bout of rhabdomyolysis, is the most sensitive and specific test for fatty acid oxidation defects.
- A high-carbohydrate diet is the main recommendation to reduce symptoms in patients with fatty acid oxidation defects.
- The mitochondria are the final common pathway for the oxidation of fat, carbohydrates, and proteins.

MITOCHONDRIAL MYOPATHIES

Primary mitochondrial myopathies are genetic disorders that impair electron transport chain function and/or another biochemical function of the mitochondria. A reduction in electron transport chain function leads to a decreased ability to oxidatively metabolize fat, carbohydrates, and amino acids, lowering ATP production. Dysfunction of the electron transport chain can also lead to an increase in reactive oxygen species that can damage lipids, proteins, and DNA. Most patients with primary mitochondrial myopathies manifest symptoms during periods of high ATP demand such as fasting, superimposed illness, and/or long-duration exercise. Many patients also experience fixed multisystemic manifestations in other tissues with a high metabolic demand such as the brain (especially cranial nerves II and VIII) and even the gastrointestinal tract. Patients with primary mitochondrial myopathies may have extra-muscle manifestations with unaccustomed exercise including exercise-induced deafness or amblyopia or abdominal pain and/or vomiting. Patients with primary mitochondrial myopathies can present with fixed weakness and exercise intolerance with or without rhabdomyolysis. Given the complexity of the mitochondrial cytopathies and primary mitochondrial myopathies in terms

of workup and management, readers are referred to other resources[90-92]; this article will focus on the metabolic myopathy aspects of primary mitochondrial myopathies.

The mitochondria are cellular organelles present in all cells except mature red blood cells. The mitochondria are dynamic and interact with other organelles such as the endoplasmic reticulum. The evolutionary origin of mitochondria as a vestige from bacteria is reflected in the fact that they retain a tiny fragment of circular, maternally inherited, double-stranded DNA called mitochondrial DNA (mtDNA). The 16,569–base pair mtDNA in humans encodes 38 genes including 2 ribosomal RNAs, 22 transfer RNAs, 13 protein-encoding mRNAs (complex I, III, IV, and V), and a protein called MOTS-c. Mitochondrial replication requires many nuclear-encoded proteins including polymerase gamma (POLG) and a helicase called twinkle (*TWNK* gene), among others. Because the replication of the mtDNA is not dependent on the cell cycle, mitochondrial biogenesis can occur in skeletal muscle in response to cellular stressors such as exercise.

The first mtDNA mutations linked to human disease were point mutations at positions 3243 (m.3243A>G) and 11,778 (m.11778G>A) of the mtDNA, associated with mitochondrial encephalomyopathy, lactic acidosis, and strokelike episodes (MELAS) and Leber hereditary optic neuropathy (LHON), respectively, and a large-scale mtDNA deletion was reported in Kearns-Sayre syndrome.[93-95] The mtDNA contains many benign polymorphisms that may have contributed to evolutionary biological fitness and some define specific mitochondrial haplotypes. The increasing recognition of rare mtDNA variants is a challenge from a diagnostic perspective as a rare or previously unreported VUS discovered in a patient with possible primary mitochondrial myopathy is not necessarily disease causing. With an increasing number of mtDNA sequences being stored in public databases, one can interrogate a VUS using the allele search and MITOMASTER tools at mitomap.org/MITOMAP. A search for the nuclear-encoded DNA variants linked to mitochondrial disorders can also be done in MITOMAP.

Copies of the pathogenic mtDNA mutations are usually present in varying proportions of mutant versus wild type within a cell/tissue (heteroplasmy). In some disorders, such as LHON, all copies of mtDNA are mutant (homoplasmy). In general, a higher mutant heteroplasmy will have a more deleterious effect on cellular energetics and more severe clinical manifestation(s). Cells that rapidly turn over (eg, blood cells) may partially or totally selectively eliminate the mutant mtDNA genomes; consequently, a normal blood mtDNA analysis may not rule out a mtDNA-associated primary mitochondrial myopathy and is another reason to consider a muscle biopsy if a primary mitochondrial myopathy is suspected.

Clinical Presentation

Mitochondrial cytopathies show a broad range of phenotypic and genotypic heterogeneity. MELAS shows phenotypic heterogeneity in that patients with the same genetic mutation (ie, m.3243A>G) may be asymptomatic, show only maternally inherited diabetes and deafness (MIDD), or display the most severe manifestation with childhood onset of strokes, seizures, cardiomyopathy, short stature, and intellectual disability/dementia. In contrast, chronic progressive external ophthalmoplegia (CPEO) shows genotypic heterogeneity where

patients with the same phenotype may have a sporadic mtDNA deletion (most patients) or an mtDNA deletion secondary to a nuclear-encoded mtDNA maintenance gene mutation, or a specific mtDNA point mutation.[96]

Most patients with primary mitochondrial myopathy will have exercise intolerance due to low VO_{2max}.[97] A clinical challenge is that many disorders present with exercise intolerance and can be much more common in the general population, including asthma, chronic obstructive pulmonary disease, cardiac issues, deconditioning, and other medical issues (eg, hypothyroidism, hypogonadism, Addison disease, hypercalcemia, inflammatory disorders, vitamin B_{12} deficiency). In contrast, some patients with primary mitochondrial myopathy will have other manifestations of a mitochondrial cytopathy (eg, seizures, encephalopathy, optic atrophy) that can overshadow the exercise intolerance and even fixed weakness.

Many patients with primary mitochondrial myopathy will report that they "were not into sports" or were "the worst athlete in the class." Patients with primary mitochondrial myopathy often also report shortness of breath on exertion and premature fatigue/myalgia during exertion, and some have fixed weakness that impacts the activities of daily living. Given that the mitochondria are not under metabolic stress in the resting condition, the commonly reported symptoms of being totally exhausted or having nonrestorative sleep are no more common in patients with primary mitochondrial myopathy than in the general population. Unlike fatty acid oxidation defects or glycogen storage diseases where rhabdomyolysis and pigmenturia are very common clinical features, many patients with primary mitochondrial myopathy do not have severe cramps during exercise, but often have exercise-induced myalgia, similar to patients with fatty acid oxidation defects. Exercise-induced rhabdomyolysis has been reported in cases of cytochrome b, cytochrome c oxidase (COX), *TK2*, and MELAS m.3260A>G mutations.[98-101] For an illustrative example of a patient with mitochondrial myopathy, see **CASE 10-3**.

The history and physical examination are often helpful in evaluating a primary mitochondrial myopathy. Findings suggestive for primary mitochondrial myopathy include hypoacusis, optic atrophy, short stature, ptosis, ophthalmoparesis, type 2 diabetes, migraine variant headaches, seizures, strokes and strokelike episodes, head and neck lipomas, peripheral neuropathy, ataxia, spasticity, cardiomyopathy, conduction block, and intestinal pseudoobstruction. Proximal muscle weakness may be seen with or without hyperCKemia in several disorders including mtDNA depletion (*TK2* mutations), MELAS, and CPEO and more rarely in others. A positive maternal family history is helpful to rule in an mtDNA-based primary mitochondrial myopathy; however, a primary mitochondrial myopathy may also appear sporadically or with mendelian inheritance (autosomal recessive, autosomal dominant, or X-linked recessive) (**TABLE 10-2**).

Diagnostic Testing

Testing for a primary mitochondrial myopathy starts with an accurate history and neurologic examination; however, several ancillary tests can help to rule in or rule out a primary mitochondrial myopathy. Serum/plasma lactate is one of the canonical blood tests with elevations seen in approximately 65% of adult patients (sensitivity) with primary mitochondrial myopathy and normal levels seen in over 90% of people without primary mitochondrial myopathy

KEY POINTS

- Many of the mitochondrial myopathies are labeled as acronyms that describe the canonical clinical features.
- A normal mtDNA sequence from blood-derived DNA does not rule out a primary mitochondrial myopathy due to a pathologic mtDNA mutation.
- Most patients with primary mitochondrial myopathies will have exercise intolerance, and chronic daily fatigue is not a distinguishing clinical feature of primary mitochondrial myopathies and can be seen in many other nonmitochondrial disorders.
- Abnormal neurologic examination findings should prompt a further consideration of a primary mitochondrial myopathy in a patient with rhabdomyolysis.

(specificity).[30] Lactate should be taken on ice and analyzed promptly to avoid false-positive results due to red blood cell lactate generation. Other false-positive lactate results can be found in diabetes, with difficult blood draws (eg, struggling, prolonged tourniquet use), and if the patient has recently (within 1 hour) consumed a high-carbohydrate meal. Serum CK activity can be normal or mildly elevated (usually <3 times the upper limit of normal) in patients with primary mitochondrial myopathy with higher levels prompting an assessment for muscular dystrophy. Plasma amino acid testing may show elevated alanine, and urine organic acid testing can show elevations of 3-methyl glutaconic acid and/or tricarboxylic acid intermediates (eg, fumarate, malate, citrate).

EMG may be normal in primary mitochondrial myopathy but may show a nonspecific myopathic pattern with small, brief, early recruiting action potentials. EMG is also helpful to rule out other myopathies as a cause of exercise intolerance or rhabdomyolysis (eg, myotonic potentials, neurogenic changes). Nerve conduction studies are also usually normal in primary mitochondrial myopathies but may show an axonal-sensory (eg, *POLG* mutations) or motor-sensory neuropathy (eg, myoclonic epilepsy with ragged red fibers [MERRF]; mitochondrial neurogastrointestinal encephalopathy [MNGIE]; neuropathy, ataxia, and retinitis pigmentosa [NARP]).

CASE 10-3

A 30-year-old man presented to the emergency department with myalgia following a 45-minute spin class. His initial creatine kinase (CK) was 76,000 U/L, but once he was hydrated it improved to 8000 U/L at the time of discharge and eventually normalized within 3 weeks. Because this was his third documented occurrence of rhabdomyolysis and he recalled similar episodes of fasting or exercise-induced myalgia as a child, he was referred to a neuromuscular clinic for assessment.

His neurologic examination was normal, and tests for fasting acylcarnitines, lactate, amino acids, CK, vitamin D, and thyroid-stimulating hormone (TSH), as well as a 406-gene next-generation sequencing myopathy panel (which included mtDNA sequencing), were also normal. A muscle biopsy of the right vastus lateralis showed ragged red and cytochrome c oxidase–negative fibers with ultrastructural paracrystalline inclusions. Mitochondrial DNA (mtDNA) sequencing from muscle-derived DNA revealed a *MT-CYB* variant (m.15762G>A) at 86% mutant heteroplasmy, and this was confirmed to be nondetectable in blood-derived DNA.

COMMENT

This case highlights that mtDNA mutations may be at low levels in blood due to selective pressure to eliminate pathogenic mutations in rapidly turning over tissues; consequently, a negative mtDNA test from blood-derived DNA cannot rule out a mitochondrial disease. It also highlights the value of a muscle biopsy in a patient with rhabdomyolysis where the diagnosis remains unresolved after next-generation sequencing testing.

Exercise stress testing using a stationary bicycle or treadmill may show a low VO_{2max} and/or a high respiratory exchange ratio (indicative of early lactate production) and/or a disproportionate heart rate response in primary mitochondrial myopathy.[102] Adding a preexercise and postexercise lactate test to a low-intensity exercise test was shown to have only limited sensitivity and specificity,[103] although complex nuances to exercise testing exist beyond the general comments in this article.[104] A normal exercise stress test is helpful in ruling out primary mitochondrial myopathies but an abnormal test can be falsely positive due mainly to hypodynamia-associated disorders (ie, immobilization, arthritis, chronic fatigue syndrome, fibromyalgia). Some authors have also reported the use of a nonischemic forearm exercise test linked with near infrared spectroscopy or venous blood gas measurements to demonstrate an impairment of deoxygenation associated with a mitochondrial defect.[105,106] Practically, most clinics can do a nonischemic forearm exercise test for patients with exercise intolerance/rhabdomyolysis with preexercise/postexercise ammonia, lactate, and venous blood gas tests and evaluate both the glycogen storage diseases and primary mitochondrial myopathies simultaneously. Phosphorus magnetic resonance spectroscopy can show a rapid phosphocreatine hydrolysis and/or an increase in lactate during exercise and/or a delayed phosphocreatine and/or ADP kinetic recovery following exercise.[107,108]

A muscle biopsy is often abnormal in primary mitochondrial myopathies, in contrast to the rare abnormalities seen in fatty acid oxidation defects and glycogen storage diseases. Some of the canonical features of primary mitochondrial myopathies include ragged red fibers (subsarcolemmal accumulation of mitochondria on modified Gomori trichrome staining) and/or COX-negative fibers. Furthermore, skeletal muscle is the preferred tissue for mtDNA analysis given that mtDNA deletions are often only seen in muscle and even some of the primary mitochondrial myopathy–associated mtDNA point mutations are present in muscle and not in blood-derived mtDNA. In addition, the muscle biopsy may provide histological clues to alternative diagnoses such as high neutral lipids with normal mitochondria in a fatty acid oxidation defect, central cores in malignant hyperthermia, dystrophic change in a pseudometabolic myopathy, or an absent myophosphorylase stain in McArdle disease. It is also important to evaluate skeletal muscle ultrastructure with electron microscopy given that the mitochondrial alterations (eg, pleomorphic mitochondria, paracrystalline inclusions, abnormal cristae) may appear before the light microscopic changes.[109]

It is also important to consider mitochondrial enzyme analysis on skeletal muscle in suspected primary mitochondrial myopathy given that enzymatic analysis on fibroblasts or peripheral blood mononuclear cells may be normal. Skeletal muscle electron transport chain enzyme activity and protein content can be evaluated using skeletal muscle homogenates or isolated mitochondria.[91,110] Single enzyme defects can be seen in complex assembly genes (ie, complex IV in *SCO2* mutations) or with mutations in specific electron transport chain subunits (eg, *MT-ND4*, *NDUFV1*, cytochrome c oxidase subunit IV). It is essential to not rely on mitochondrial enzyme analyses for the diagnosis of a primary mitochondrial myopathy in isolation given that even 2 weeks of hypodynamia can lower most of the enzyme activities and protein content by approximately 20%.[111] Multiple electron transport chain complex defects can be seen in tRNA mutations or mutations in genes involved in mtDNA

KEY POINT

- **A normal lactate does not rule out a primary mitochondrial myopathy.**

maintenance (eg, *POLG*) or any of the many recently discovered genes under the umbrella of combined oxidative phosphorylation defects (eg, *NARS2, LARS2, TRMT5*).[112]

Traditionally, mtDNA sequencing was done using the Sanger sequencing method but that has been generally replaced by next-generation sequencing methods.[91,113] A next-generation sequencing–based method has been reported that can sequence the entire mtDNA and 19 nuclear encoded mitochondrial genes simultaneously and reliably detect heteroplasmy down to the 5% level.[114] With sufficient read depth, the next-generation sequencing methods can also measure mtDNA deletions[114] and are replacing methods such as Southern blotting, *MT-ND1*/*MT-ND4* polymerase chain reaction (PCR) ratios, and long-range PCR. A downside of long-range PCR is that it can be too sensitive and tends to overcall deletions and can be falsely positive in people older than age 45 years, but a normal long-range PCR test can rule out an mtDNA deletion–associated primary mitochondrial myopathy (high sensitivity). If a myopathy or rhabdomyolysis panel run on blood-derived DNA (even if it includes mtDNA) is normal and a mitochondrial disorder is still in the differential, it is best to use muscle-derived DNA for mtDNA genetic testing to avoid false-negative mtDNA results. Another advantage of obtaining a muscle sample is that it can resolve a VUS with targeted blue native polyacrylamide gel electrophoresis, laser capture microdissection, Western blotting, and other validation methods, requiring more sophisticated evaluation in a research-based laboratory. Several laboratories also offer next-generation sequencing panels that cover most of the known nuclear-encoded genes associated with primary mitochondrial myopathies and other mitochondrial cytopathies or myopathy or rhabdomyolysis panels that contain many of the nuclear-encoded mitochondrial genes (ncbi.nlm.nih.gov/gtr/). In some unresolved cases, whole-exome sequencing is being used with next-generation sequencing methodologies to discover rare or novel mitochondrial disease-associated genes.[112,115,116] Whole-exome sequencing is also proving helpful in some complex rhabdomyolysis cases by revealing compound heterozygosity (single variants in multiple bioenergetic variants) that would not have been identified with a more targeted panel (**TABLE 10-3**).[117]

Treatment

Primary mitochondrial myopathies result in a reduction of aerobic energy production, increased free radical generation, a greater reliance on alternative energy stores (ie, phosphocreatine), and elevated flux through glycolysis (high lactate). Bypass strategies have included succinate and riboflavin to bypass complex I[118] and coenzyme Q10 to bypass complexes I and II.[119,120] Antioxidants have been heavily studied, including vitamin E, vitamin C, α-lipoic acid, idebenone, and coenzyme Q10.[119,120] The author and others have studied creatine monohydrate as an alternative energy source with variable success[97,121]; however, in the author's opinion, the combination approach using a "mitochondrial cocktail" is the most logical and is the strategy that most clinicians adopt.[92,119,122]

The author's group has shown some improvements in exercise capacity in patients with primary mitochondrial myopathy with creatine monohydrate,[97] and coenzyme Q10,[120] and lower lactate and oxidative stress markers with coenzyme Q10 plus vitamin E, α-lipoic acid, and creatine monohydrate in

combination.[119] Based on the author's research and 25 years of experience with these supplements, the author typically starts with a "mitochondrial cocktail" of coenzyme Q10 (200 mg 2 times a day), α-lipoic acid (200 mg 2 times a day), vitamin E (400 IU 1 time a day or 200 IU 2 times a day) and creatine monohydrate (75 mg/kg/d to 100 mg/kg/d up to a maximum of 5 g/d 1 time a day or divided 2 times a day). The author typically adds to this as needed depending upon measured deficiencies (eg, carnitine, folate, vitamin B_{12}, vitamin D) or specific targets (eg, riboflavin in complex I defects or fatty acid oxidation defects, thiamine in pyruvate dehydrogenase deficiency). Randomized trials show some visual improvement in a subgroup analysis in patients with LHON with the coenzyme Q10 analogue idebenone[123,124]; however, most patients with LHON do not experience exercise intolerance or rhabdomyolysis.

Endurance exercise training has been shown to be safe and effective at improving several clinical metrics of fitness and improving quality of life in patients with primary mitochondrial myopathies.[125-128] Resistance exercise training was found to improve strength[129] and reduce mutational heteroplasmy in sporadic mitochondrial myopathies.[130] A summary of some of the treatment options for primary mitochondrial myopathy is presented in TABLE 10-4.

KEY POINTS

- For nuclear DNA–encoded mitochondrial testing (and for all other myopathies) a blood sample is sufficient for diagnosis with the usual caveats (eg, deep intronic mutations, trinucleotide repeat disorders) that are not identified by standard next-generation sequencing testing.
- A mitochondrial cocktail (multi-ingredient supplement) approach is superior to single agents to target the multiple final common pathways of cellular dysfunction.

CONCLUSION

A detailed history of the events that precipitate the symptoms (eg, rhabdomyolysis, exercise intolerance, exercise-induced cramps, or myalgia) often points to a specific metabolic myopathy. As indicated previously, glycogen storage diseases typically present with high-intensity exercise, whereas fatty acid oxidation defects and primary mitochondrial myopathies usually present during longer-duration/endurance-type activities or are exacerbated by the superimposition of fasting or other acute illness. The neurologic examination is typically normal in patients with glycogen storage diseases and fatty acid oxidation defects; however, patients with primary mitochondrial myopathies may show other canonical features of mitochondrial cytopathies, including ptosis, optic atrophy, external ophthalmoplegia, hypoacusis, ataxia, neuropathy, and fixed muscle weakness. Laboratory tests that can help in the evaluation of a patient with suspected metabolic myopathy include serum CK activity, lactate, uric acid, amino acids, acylcarnitine profile, and urine organic acid profile. Nonischemic forearm exercise testing and/or graded exercise testing can help in ruling in or ruling out metabolic myopathies. A muscle biopsy is necessary less often due to more accurate and available genetic testing, but it still has a significant role in the diagnosis of patients with atypical histories or persistent hyperCKemia (other than McArdle disease), resolving a VUS found on a panel, for mtDNA testing, and when no cause is found for recurrent rhabdomyolysis after extensive testing.

It is important to establish a definitive genetic cause for a patient with metabolic myopathy and this can be achieved in a large number of patients with next-generation-sequencing–based panels. In patients with strong evidence for a metabolic myopathy when no genetic cause is found, referral to centers of excellence that often have access to research studies using whole-exome sequencing, RNA sequencing, or whole-genome sequencing is important to discover rare or unexpected variants or novel genetic causes for metabolic myopathies. An accurate diagnosis for metabolic myopathy is important to

determine appropriate therapies including lifestyle modification, nutritional intervention, cofactor treatment, and proper exercise prescription, and for providing accurate genetic counseling.

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