Diagnosing Metabolic Myopathies

Metabolic myopathies can be accurately and efficiently diagnosed by keeping key clinical features in mind.

By Salman Bhai, MD

Metabolic myopathies are a set of rare disorders that disrupt energy metabolism. Skeletal muscle is involved primarily because of its high energy demand, but multisystem dysfunction can occur. In this review, disorders affecting glycogen and lipid metabolism as well as mitochondrial disorders will be discussed. Although symptoms of these disorders may appear during childhood, many affected individuals present to neurologists later in life with mild, protean symptoms. A practical diagnostic approach is offered to aid in the diagnosis of these disorders.

Biochemistry

Understanding metabolic myopathies requires understanding the biochemical pathways involved in energy production during rest, exercise, and physiologic stress. Although a complete review is beyond the scope of this article, a brief overview is provided to contextualize the metabolic myopathies.

Pulmonary, cardiovascular, musculoskeletal, and metabolic systems are all involved in the physiologic changes that occur in response to exercise. Adenosine triphosphate (ATP) is the primary source of the energy required for muscle contraction and relaxation. The main sources of ATP are glycogen, glucose, and free fatty acids. At rest, fatty acids (FAs) are the primary source of fuel for skeletal muscle.[1] The transition from rest-to-exercise requires immediate utilization of ATP, sourced from the phosphocreatine shuttle, which is independent of oxygen supply. This provides energy for 8 to 10 seconds, after which other metabolic pathways are activated, depending on the intensity of activity, type of exercise, duration of exertion, and physical conditioning and diet of the individual. High-intensity exercise requiring short bursts of power relies on anaerobic glycolysis—the metabolism of glucose to produce ATP. With submaximal exercise, oxidative phosphorylation is a more efficient mechanism for producing ATP. Oxidative phosphorylation metabolizes glycogen, glucose, and FAs to produce nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), which donate electrons in the mitochondrial electron transport chain to produce ATP. The maximal level of oxygen transport and use (VO_2max) defines the aerobic capacity of an individual. Submaximal low-intensity aerobic exercise favors metabolism of FA and glycogen, whereas high-intensity exercise favors glycogen as a primary source of energy with aerobic glycolysis contributing in both instances.[1,2] As the duration of submaximal exercise increases, FAs become the primary source of energy. Practically speaking, a marathon runner 'hits the wall' because the intensity of running is too high for the athlete's fitness level, favoring glycogen over FAs for fuel. Favoring glycogen use results in the depletion of glucose and glycogen stores, which causes profound fatigue. A person can typically store approximately 2,000 calories worth of glycogen and each mile run 'costs' approximately 100 calories. This explains why runners typically 'hit the wall' around mile 20, making the last 6.2 miles far too memorable for many marathon participants.

Metabolic myopathies can result from a defect in any of the above-described pathways and are categorized by the pathway with the defect. Glycogenoses are disorders of glycogen or glucose degradation (glycogenolysis or glycolysis, respectively) or glycogen synthesis (glycogenesis) and lead to an abnormal accumulation of glycogen; these are thus termed glycogen storage disorders (GSDs). Disorders of lipid metabolism primarily include FA oxidation disorders (FAODs), which are defects of beta-oxidation or carnitine cycle disorders, but also include other pathways. Mitochondrial diseases can result from many defects including those that affect respiratory chain proteins.

The challenge in diagnosing patients begins with the wide phenotypic range of these conditions with protean manifestations. Broadly, this range is partially explained by residual enzymatic activity, in which reduced activity correlates with more severe clinical manifestations and greater activity with milder clinical manifestations. Depending on the enzyme activity level,

symptoms can present in infancy with devastating multisystem involvement to late in life with more subtle symptoms.

Clinical Presentation

The primary symptoms are exercise intolerance, fatigue, myalgias, and/or weakness (Table). At clinical presentation, individuals may be asymptomatic without fixed weakness. Some metabolic myopathies, particularly glycogen storage diseases, cause muscle cramps and/or contractures along with rhabdomyolysis. Those with mitochondrial myopathies typically have systemic complications, but symptoms can be isolated to muscle.

It is important for the clinician to understand why exercise intolerance is occurring, whether it is due to fatigue, myalgias, weakness, cramps, or shortness of breath, and in what context it is occurring.[2-4] Although these diverse symptoms may occur in other conditions, when associated with metabolic myopathies, they typically manifest during activity or present in the context of physiologic stressors, such as fever or fasting. Rhabdomyolysis and myoglobinuria can signal the presence of a metabolic myopathy but can also occur with high-intensity exercise in untrained, otherwise healthy individuals. The latter scenario is typically benign. The type of activity that leads to the symptoms provides another clue to the diagnosis. High-intensity exercise (eg, lifting weights or sprinting) that brings on symptoms within minutes should lead to consideration of the glycogenoses. Complaints of fatigue and weakness after prolonged low-intensity exercise (ie, endurance sports) may suggest a lipid or mitochondrial disorder. Dyspnea on exertion with endurance sports may suggest a mitochondrial myopathy. Lastly, inquiring about a patient's athletic ability in childhood may bring to light a history of difficulty 'keeping up with classmates.'

Outside of systemic symptoms (eg, hearing or vision loss, ptosis, or ophthalmoplegia) related to mitochondrial myopathies, the physical exam is often normal. Careful examination may reveal fixed weakness in proximal muscles, which are more common in GSDs than in disorders of lipid metabolism. Fixed contractures occur more frequently with muscular dystrophies, whereas transient "contractures" are more common in GSDs, especially certain subtypes (eg, McArdle disease).[4]

Laboratory findings, such as an elevated creatine kinase (CK) or lactic acid values, are nonspecific, with suspicion for a metabolic myopathy likely to arise from the appropriate clinical history. Mimics occur and are discussed below. 'Growing pains' and 'laziness' are unfortunately common misdiagnoses.[5] Symptoms are often endured by patients and misinterpreted by themselves, their parents, and even their physicians.

Glycogen Storage Disorders

Patients with less severe GSDs typically present in the second or third decade of life but often have attributable symptoms in childhood. There is a marked diagnostic delay, more often in women than in men, as seen in McArdle disease (GSD5).[5] Within seconds to minutes of exercise, affected persons complain of muscle cramps and exercise intolerance, explained by the skeletal muscle's reliance on glucose and glycogen early in the activity. Intermittent rhabdomyolysis is a common feature, particularly in McArdle and Tarui (GSD7) disease, whereas Pompe (GSD2) disease is characterized by myopathy without rhabdomyolysis.

McArdle Disease. The most common disorder of carbohydrate metabolism is McArdle disease, which is caused by an autosomal recessive mutation in the *glycogen phosphorylase* (*PYGM*) gene leading to a myophosphorylase deficiency. People with McArdle disease have exercise intolerance early in exercise because of premature fatigue, myalgias, muscle contractures, and rhabdomyolysis. The 'second wind' phenomenon, which is characterized by an improvement in exercise tolerance after approximately 10 minutes of low-intensity exercise (a 'warm-up' period), is pathognomonic.[6] This is evident in physiology studies where an initial inappropriate exertional tachycardia improves with a reduction in heart rate within 10 minutes of activity. Muscle symptoms (eg, myalgias) improve as well. This clinical phenomenon is not present in other disorders.[3] Some people with McArdle disease can also develop fixed proximal muscle weakness.[7] Sucrose intake before exercise mitigates symptoms.[8]

Tarui Disease. In contrast to McArdle disease, Tarui disease has an 'out-of-wind' phenomenon when sugar is taken before exercise, worsening symptoms.[9] Tarui disease is

TABLE. SUGGESTIVE CLINICAL FEATURES OF METABOLIC MYOPATHIES

	Glycogen storage disorders	Fatty acid oxidation defects	Mitochondrial myopathies
Exercise intolerance	To high-intensity activities	To low-intensity activities	To low-intensity activities Shortness of breath with exercise
Muscle symptoms	Rhabdomyolysis, cramps, and transient contractures	Myalgias, rhabdomyolysis	Myalgias
Strength	Possible fixed proximal weakness	Possible fixed proximal weakness	Possible fixed proximal weakness
Other	'Second wind" or "out-of-wind"	Fasting or illness trigger muscle symptoms	Multisystem disease

caused by an autosomal recessive mutation in the *phosphofructokinase* (*PFKM*) gene. Adult-onset forms of Tarui disease present with exercise intolerance, intermittent rhabdomyolysis, and weakness. Hemolytic anemia may occur because phosphofructokinase is expressed in erythrocytes.

Pompe Disease. Autosomal recessive mutations in the *alpha-glucosidase* (*GAA*) gene cause an enzymatic deficiency in acid maltase that results in Pompe disease. In addition to limb-girdle weakness, ventilatory failure and cardiomyopathy are possible.[10] Late-onset acid maltase deficiency can result in early respiratory insufficiency with proximal muscle weakness and scapular winging with exercise intolerance caused primarily by dyspnea. In Pompe disease, myotonic discharges may be seen in the paraspinal muscles. Enzyme replacement is an available treatment option for Pompe disease.

Laboratory Findings. The baseline CK value in GSDs is often normal but is more often elevated in McArdle and Pompe disease. Liver and cardiac involvement are possible. Specific diagnostics are discussed below.

Disorders of Lipid Metabolism

Like GSDs, there is commonly a delay in the diagnosis of late-onset FAODs. Symptoms typically consist of exercise-induced weakness, fatigue, and myalgias in response to prolonged low-intensity exercise. Cramping can occur, although not as prominently as in GSDs. Rhabdomyolysis can occur and be triggered by the 3 F's: fasting, fever (infection), or freezing (prolonged exposure to cold temperatures). Common late-onset forms include *carnitine palmitoyltransferase II* (*CPTII*) deficiency and *very long-chain acyl-coenzyme A dehydrogenase* (*VLCAD*) deficiency, which can both be difficult to distinguish on clinical grounds; laboratory studies are typically needed. Lipin-1 deficiency is caused by a *lipin 1* (*LPIN1*) mutation that leads to deficiency in phosphatidic acid phosphatase, and manifests as severe, recurrent rhabdomyolysis triggered by fevers in children.[11] Multiple acyl-CoA dehydrogenase deficiency (MADD) is caused by mutations in *electron transfer flavoprotein dehydrogenase* (*ETFDH*) or *electron transfer flavoprotein subunit A* or *B* (*ETFA/B*). MADD can present with slowly progressive proximal weakness and fatigue resulting in exercise intolerance that may be responsive to riboflavin supplementation (riboflavin responsive–MADD, most frequently with *ETFDH* mutations).[12] Coenzyme Q10 (CoQ10) deficiency can coexist with MADD so CoQ10 supplementation is also given. Many other disorders of beta-oxidation present in infancy with severe multisystem disease; these are outside the scope of this review.

Laboratory Findings. The baseline CK is typically normal. Patients may present with recurrent hypoketotic hypoglycemia. Liver and cardiac involvement are possible. Specific diagnostics are discussed below.

Mitochondrial Myopathies

Mitochondria possess two genomes, nuclear DNA and mitochondrial DNA (mtDNA), the latter of which is maternally inherited. The nuclear genome follows Mendelian inheritance. Thus, mitochondrial myopathies can occur via maternal mtDNA inheritance, autosomal dominant or recessive patterns, or X-linked inheritance.[13,14] Complicating matters, there is a poor genotype-phenotype correlation for several mitochondrial diseases.[14] Premature fatigue leading to exercise intolerance with myalgias (at times described as leg heaviness or burning) is a common symptom. Cramping is typically not a prominent feature. Weakness is mild when present.[15] There are well-known, named syndromes that may be more rapidly diagnosed (eg, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes [MELAS]). Other times, people with mitochondrial myopathies may be misdiagnosed with chronic fatigue syndrome or fibromyalgia.

Pseudometabolic Myopathies

Considering the common clinical occurrence of myalgias, cramps, and exercise intolerance, several conditions may mimic metabolic myopathies. Limb-girdle muscular dystrophies, such as dysferlinopathies (LGMD 2B) or sarcoglycanopathies (LGMD 2C and 2E), Becker muscular dystrophy (ie, mild adult-onset form or manifesting genetically female carriers), late-onset congenital myopathies (ie, core or nemaline myopathy), myositis, or myotonic dystrophy type 2 are possible mimics.[3,4] These may have similar patterns of weakness along with myalgias and/or cramping. Because ptosis and ophthalmoplegia are features of mitochondrial myopathies, there may be phenotypic overlap with oculopharyngeal muscular dystrophy or myasthenia gravis. Although a careful history, physical examination, and targeted work-up can distinguish these mimics from metabolic myopathies, overlapping features, especially early in clinical presentation, may pose diagnostic dilemmas.

Diagnostic Testing

When clinical features suggest a metabolic myopathy, targeted work-up can be initiated to confirm or exclude specific diagnoses. There is no definitive approach and each work-up should be tailored to the individual's clinical and biochemical features (Figure).

Laboratory Studies

Blood serum and urine studies should be obtained. Although CK levels are not specific, abnormal values may help identify potential mimics or suggest a specific diagnosis (eg, McArdle or Pompe disease in the proper clinical context). False positive CK elevations can be caused by exercise, statin use, or normal variations. Serum lactic acid elevations at baseline may suggest a mitochondrial myopathy; however, false positives can occur due to exercise, prolonged

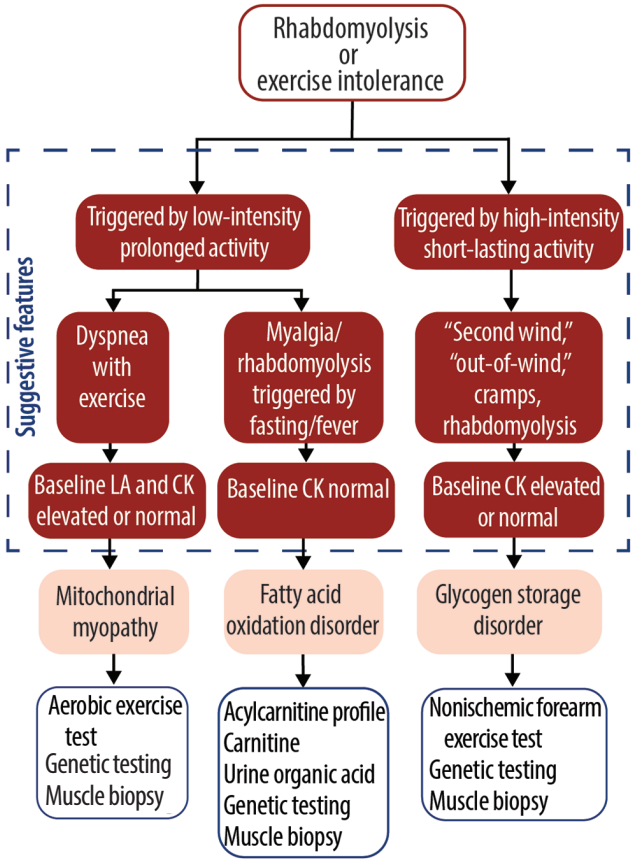

Figure. Diagnostic Algorithm for Metabolic Myopathies. Abbreviations: CK, creatinine kinase, LA, lactic acid.

tourniquet time, and other factors. False negatives can occur if physiologic stressors are required to provoke an elevation. For suspected FAODs, plasma acylcarnitine profile, plasma total and free carnitine levels, and urine organic acid levels should be measured. Specific patterns within these biochemical studies can suggest a diagnosis (eg, acylcarnitine profile with elevation of short-, medium-, and long-chain FAs and urine organic acid profile with elevated glutaric acid and other dicarboxylic acids suggest MADD). False negative results are common, and the diagnostic yield is higher with fasting or post-exercise sampling.

If biochemical studies suggest a particular class of disorders, then next-generation sequencing (NGS) of DNA can be an efficient and economical pathway forward. Although NGS is useful when pathogenic variants are found, variants of unknown significance (VUS) are common, as are potentially false-negative results. This is particularly true of mitochondrial myopathies. Blood or saliva mtDNA testing is helpful for identifying point mutations; however, given the wide range of genetic abnormalities causing mitochondrial myopathies, muscle is the ideal tissue for analysis, especially for mtDNA deletions and heteroplasmy—given accessibility and yield if blood or saliva testing is negative. As whole exome sequencing (WES) becomes more commonly used, further testing may be necessary to resolve ambiguous results.

Electrophysiology and Exercise Testing

EMG is a nonspecific test but can help identify mimics. In metabolic myopathies, EMGs may be normal or show myopathic units. Spontaneous activity is typically absent.

Exercise testing provides a unique lens to measure physiologic and biochemical responses to exercise and is especially useful when genetic testing and/or biopsy results are nondiagnostic. Nonischemic forearm exercise testing, as opposed to ischemic testing, is recommended to evaluate for GSDs because it provides similar sensitivity and specificity without the added risk of rhabdomyolysis or acute compartment syndrome.[16] A normal lactate elevation rules out GSDs, and no further evaluation is then necessary if the test was optimally performed. Aerobic cycling exercise testing is typically performed using a standard Bruce protocol with a gradual increase in workload on a cycle ergometer. A hallmark of mitochondrial dysfunction is reduced VO_2max, reduced peripheral oxygen extraction (arteriovenous oxygen difference), and a hyperkinetic circulation (elevated baseline cardiac output).[17] Falsely reduced VO_2max can be seen in people who are physically inactive, which leads to loss of mitochondrial enzyme activity.

Muscle Biopsy

A muscle biopsy can be of use in identifying mimics, performing enzyme analysis, or running tissue-specific sequencing. Biopsy with electron microscopy is particularly helpful for mitochondrial myopathies. Ragged red or ragged blue fibers can be seen on histochemical studies along with subsarcolemmal or intermyofibrillar mitochondrial accumulation, mitochondrial morphologic abnormalities, or inclusions on electron microscopy.[3,15] Reliance on solely ragged red fibers as a diagnostic feature should be done with caution because the number of such fibers normally increases with age. In FAODs, muscle biopsy may show abnormal lipid accumulation. The degree of FA accumulation can narrow the differential diagnosis. More FA accumulation suggests MADD, primary carnitine deficiencey, or neutral lipid storage disease, whereas the other FAODs have less FA accumulation. Biopsy can appear normal despite a clinically symptomatic FAOD.

Mitochondrial disease may require more extensive systemic work-up, especially for children, which is beyond the scope of this article.

Conclusion

Metabolic myopathies are a heterogenous set of rare disorders that may present with exercise intolerance, myalgias, weakness, cramps, or rhabdomyolysis. A careful

history may narrow the differential from among the multiple biochemical pathways involved. GSDs present within minutes of high-intensity exercise, whereas FAODs and mitochondrial myopathies present after prolonged low-intensity exercise. The physical exam is typically normal during initial presentation. Work-up should focus on the suspected biochemical pathway involved, eventually leading to genetic testing. Accurate diagnosis can prevent unnecessary testing and allow for lifestyle and nutritional interventions as well as pharmacologic interventions in select cases. Though rare, these disorders can be accurately and efficiently diagnosed if the key clinical features are kept in mind. ■

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Disclosures

SB reports no disclosures

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