

## DIAGNOSTIC EVALUATION OF RHABDOMYOLYSIS

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Accepted 9 February 2015

**ABSTRACT:** Rhabdomyolysis is characterized by severe acute muscle injury resulting in muscle pain, weakness, and/or swelling with release of myofiber contents into the bloodstream. Symptoms develop over hours to days after an inciting factor and may be associated with dark pigmentation of the urine. Serum creatine kinase and urine myoglobin levels are markedly elevated. Clinical examination, history, laboratory studies, muscle biopsy, and genetic testing are useful tools for diagnosis of rhabdomyolysis, and they can help differentiate acquired from inherited causes of rhabdomyolysis. Acquired causes include substance abuse, medication or toxic exposures, electrolyte abnormalities, endocrine disturbances, and autoimmune myopathies. Inherited predisposition to rhabdomyolysis can occur with disorders of glycogen metabolism, fatty acid  $\beta$ -oxidation, and mitochondrial oxidative phosphorylation. Less common inherited causes of rhabdomyolysis include structural myopathies, chondrocytomas, and sickle-cell disease. This review focuses on the differentiation of acquired and inherited causes of rhabdomyolysis and proposes a practical diagnostic algorithm.

*Muscle Nerve* 51: 793–810, 2015

Rhabdomyolysis is a condition characterized by severe acute muscle injury resulting in muscle pain, weakness, and/or swelling with release of myofiber contents into the bloodstream. This review focuses on acquired and inherited causes of rhabdomyolysis, with an emphasis on the diagnostic evaluation. Rhabdomyolysis caused by crush injury and hypoxic/ischemic injury has been reviewed elsewhere.<sup>1–3</sup>

### CLINICAL FEATURES OF RHABDOMYOLYSIS

The characteristic clinical features of rhabdomyolysis include myalgia, muscle weakness, and muscle swelling, which develop over hours to days.<sup>4,5</sup> In a case series of 37 pediatric patients with elevated creatine kinase (CK)  $\geq 1,000$  U/L, the most common presenting symptoms were muscle pain (84%), weakness (73%), and muscle swelling (8.1%).<sup>6</sup> In a

case series of 77 adult patients hospitalized with rhabdomyolysis, 50% reported muscle pain, and 15% had muscle swelling.<sup>7</sup> In another series of adult patients, 52% presented with muscle swelling.<sup>8</sup> Historically, observation of dark-colored urine (pigmenturia), caused by myoglobin excretion, has been considered a major clinical feature for diagnosis of rhabdomyolysis. In 1 case series, as many as 80% of adults in had dark urine.<sup>9</sup> However, in the pediatric population, pigmenturia has been seen or reported in 5.3%–68% of cases.<sup>6,10</sup>

Muscle weakness may or may not be present between episodes of rhabdomyolysis. In some metabolic myopathies, fixed weakness is absent in childhood but develops in adulthood. In some muscular dystrophies associated with rhabdomyolysis, muscle atrophy or hypertrophy may be noted.

Many diseases associated with rhabdomyolysis include extramuscular manifestations, but these are not covered in detail in this review. Acquired causes, especially, may present in the setting of multisystem organ failure. However, it should be noted that glycogen storage diseases may present with extramuscular manifestations, such as liver dysfunction or hepatomegaly, especially when the disease manifests in neonates or infants. In contrast, those that present in adulthood more frequently have predominant muscle disease. In the mitochondrial disorders, there is a very wide spectrum of potential extramuscular manifestations. These can include cardiomyopathies, endocrinopathies, and encephalopathies. In patients with rhabdomyolysis who have other organ system involvement, the constellation of these disorders may help guide the diagnostic evaluation.

### TESTING IN PATIENTS WITH RHABDOMYOLYSIS

**Biochemical Diagnosis.** Establishing a diagnosis of rhabdomyolysis is based primarily on the appearance of myoglobin in the urine (myoglobinuria) or by a marked elevation in serum CK levels. After muscle injury, plasma myoglobin increases rapidly and is cleared quickly through renal excretion, and a normal level is re-established within 24 hours.<sup>11</sup> In contrast, serum CK levels rise 2–12 hours after onset of muscle injury, peak at 3–5 days after injury, and decline over the subsequent

**Abbreviations:** ATP, adenosine triphosphate; CK, creatine kinase; COX, cytochrome c oxidase; CPTII, carnitine palmitoyltransferase type 2; EMG, electromyography; FET, forearm exercise test; GT, Gomori trichrome; LDH, lactate dehydrogenase; LGMD, limb-girdle muscular dystrophy; PAS, periodic acid-Schiff; PFK, phosphofructokinase; PGK, phosphoglycerate kinase; RER, respiratory exchange ratio; RRF, ragged red fibers; SDH, succinyl dehydrogenase

**Key words:** etiology; inherited myopathy; metabolic myopathy; rhabdomyolysis; symptoms

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© 2015 Wiley Periodicals, Inc.  
Published online 11 February 2015 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/mus.24606

6–10 days.<sup>12,13</sup> Given that not all patients present within 24 hours of muscle damage, measurement of CK levels may provide the most reliable biochemical marker of rhabdomyolysis and its severity. Investigators from several large case series of rhabdomyolysis have agreed that CK elevation 5 times the upper limit of normal is the defining biochemical abnormality for this condition.<sup>4–7,14,15</sup> However, some studies have suggested using a higher value.<sup>16–18</sup> It should be noted that chronic muscle diseases, such as inflammatory myopathies and muscular dystrophies, may present with CK levels well above 5 times the normal limit. The presence of acute symptoms of muscle pain, weakness, and swelling differentiate rhabdomyolysis from these conditions.

**Serum Lactate.** After the onset of intense activity or isometric exercise, anaerobic metabolism predominates. In this circumstance, muscle glycogen is broken down into glucose, which is then metabolized to pyruvate.<sup>19,20</sup> Normally, pyruvate is converted into lactate. However, in cases where defects of the respiratory chain preclude using lactate or pyruvate as an energy source, an abnormal lactate:pyruvate ratio may be measured. In addition, elevated serum lactate in the resting period indicates an underlying mitochondrial myopathy.

**Forearm Exercise Test.** First described by McArdle in the initial report of what is now known as myophosphorylase deficiency,<sup>21</sup> a revised protocol, described in 1970, addressed changes in the levels of lactate, pyruvate, and ammonia after isometric exercise.<sup>22</sup> To perform the forearm exercise test (FET), a catheter is inserted into an antecubital vein, and baseline measurements are obtained. Thereafter, a blood pressure cuff is inflated above the elbow to produce stasis. The subject is then asked to repeatedly squeeze an ergometer against resistance for 1 minute. Then, the subject stops squeezing, and the blood pressure cuff around the arm is deflated. Samples obtained at 1, 3, 5, 6, 10, and 15 minutes later are measured for lactate, pyruvate, and ammonia levels. In individuals without metabolic disease, lactate increases 3–5-fold within the first 3 minutes of exercise, followed by a gradual decrease over the next 12 minutes to baseline levels.<sup>23</sup> Failure of lactate and ammonia levels to increase indicates submaximal effort. A decreased or inadequate rise in lactate with an adequate rise in ammonia indicates disruption in the conversion of glycogen to pyruvate, which is the typical defect in glycogen storage disease. An elevation in pyruvate with an inadequate rise in lactate level can help distinguish lactate dehydrogenase deficiency.<sup>24</sup>

In individuals with glycogen storage disorders, the ischemic isometric exercise may induce painful cramping and may cause muscle damage. If forearm muscle cramping is severe, the test should be aborted. In fact, Kazemi-Esfarjani *et al.* showed that a modified protocol without induction of ischemia is more comfortable, less damaging, and as reliable as the original protocol.<sup>25</sup> For this reason, we recommend use of the non-ischemic FET for evaluation of suspected disorders of glycogen metabolism.

**Acylcarnitine Profile.** Analysis of the acylcarnitine profile by mass spectrometry may be useful for diagnosis of fatty acid oxidation disorders. In a study of 31 asymptomatic patients with recurrent rhabdomyolysis, a diagnosis of fatty acid oxidation disorder was achieved in 7 who had abnormal serum acylcarnitine profiles.<sup>26</sup> It is unclear whether this test has higher yield at the time of muscle symptoms or rhabdomyolysis compared with the resting state. In what follows, we comment on typical acylcarnitine abnormalities associated with specific metabolic myopathies. We typically check interictal acylcarnitine profiles in patients with suspected fatty acid oxidation disorders and may also seek to obtain the same studies at the time of acute muscle symptoms or rhabdomyolysis, if they recur.

**Graded Exercise Testing.** Graded increases in exercise intensity alter inspired oxygen and expired carbon dioxide concentrations. Specifically, in metabolically normal individuals during low-intensity exercise, oxygen consumption is balanced with carbon dioxide production. With higher intensity exercise, oxygen consumption cannot keep pace with demand, and the production of carbon dioxide is greater, thus triggering an increased ventilatory rate. This ventilatory threshold signifies the transition of metabolism from the aerobic to anaerobic state and coincides with increased production of lactate. The respiratory exchange ratio (RER) represents the rate of carbon dioxide production relative to oxygen consumption. Interestingly, at different levels of exercise, the time to reach the ventilatory threshold and the RER at the point of exhaustion can help differentiate between defects in glycogen metabolism, fatty acid metabolism, and respiratory chain dysfunction.<sup>27</sup> It should be noted, however, that abnormalities on graded exercise testing may be seen in deconditioned individuals who may not have an underlying metabolic myopathy.

**Muscle Biopsy.** Muscle biopsy is an important test in patients with suspected metabolic myopathies. In the case of rhabdomyolysis, timing of the

muscle biopsy is important. With the overwhelming necrosis associated with rhabdomyolysis, there is concern that underlying features of inherited myopathies could be obscured. Thus, we suggest that, if indicated, a muscle biopsy should be deferred until the patient has recovered from rhabdomyolysis. In patients with myalgia, muscle biopsy as a tool for diagnosis is thought to have the highest yield when patients present with 1 or more of the following characteristics: myoglobinuria; presence of a second wind phenomenon; muscle hypertrophy/atrophy; CK levels greater than 2 or 3 times normal levels; or the presence of a myopathy on electromyography (EMG).<sup>28</sup> Specific stains can help to identify histopathological features suggestive of certain causes of rhabdomyolysis. For example, in patients with mitochondrial myopathies, Gomori trichrome (GT) staining may show ragged red fibers, and oxidative stains succinyl dehydrogenase (SDH) and cytochrome oxidase (COX) may show SDH-dark and/or COX-negative fibers. Periodic acid-Schiff (PAS) and hematoxylin-eosin (H&E) staining may demonstrate the presence of increased glycogen or glycogen-containing vacuoles, which can guide the diagnosis of glycogen storage disease. Increased lipid content in myofibers may suggest a disorder of fatty acid oxidation or mitochondrial cytopathy. If specific conditions are suspected, muscle immunohistochemistry can identify enzyme deficiencies, such as myophosphorylase or phosphofructokinase deficiency. In glycogen storage diseases, activities of specific enzymes can be studied in the muscle. Specific respiratory chain enzymes may be assessed and may be helpful to evaluate respiratory chain functions in suspected mitochondrial disease.

**Genetic Testing.** Numerous options are now available for genetic testing in suspected cases of inherited muscle disease. These include single gene testing, genetic panel tests, targeted exome sequencing, whole exome sequencing, and mitochondrial genome testing. The technologies used for these evaluations are quickly evolving and beyond the scope of this review. However, in what follows, we discuss recommendations for genetic testing in association with specific suspected conditions.

#### ACQUIRED CAUSES OF RHABDOMYOLYSIS

**Alcohol and Illicit Substances.** Several reports have shown that acute and/or chronic exposure to alcohol and illicit drugs may be a common trigger of rhabdomyolysis. In 1 study, 28 of 93 (30%) hospitalized patients with a CK >5,000 U/L had a significant history of substance abuse.<sup>16</sup> In another series of 77 hospitalized patients with CK >500 U/L, 82% had a history of chronic alcoholism, acute

alcohol intoxication, positive serum screen for drugs of abuse, and/or admitted drug use.<sup>7</sup> A large series of 475 patients with rhabdomyolysis included 163 (35%) cases caused by illicit drugs and/or alcohol.<sup>4</sup> In addition to acute and chronic alcohol intoxication,<sup>29-31</sup> there have been reports of rhabdomyolysis induced by heroin,<sup>32</sup> cocaine,<sup>33-35</sup> and methamphetamine.<sup>36,37</sup> Ecstasy (3,4-methylenedioxymethamphetamine)<sup>38</sup> and LSD (lysergic acid diethylamide)<sup>39-41</sup> have been associated with acute-onset rhabdomyolysis in the setting of hyperthermia and muscle rigidity. Delayed-onset rhabdomyolysis has also been attributed to ecstasy abuse.<sup>42</sup> The increased risk of rhabdomyolysis with each of these substances has been attributed to the direct toxic effect of the drug or contaminants, increased sympathomimetic stimulation, and/or nutritional deficiency in the setting of addiction. Given its prevalence, obtaining a history of substance use is a critical part of a rhabdomyolysis evaluation. Furthermore, because patients with rhabdomyolysis can present in an obtunded and comatose state as a result of toxic and metabolic exposures,<sup>8,29,30,43</sup> clinicians should have a low clinical threshold to suspect rhabdomyolysis in this setting and screen for the condition by checking serum CK.

**Prescription Medications.** Prescription medications associated with rhabdomyolysis are numerous (see Table 1). Antipsychotic medications that trigger the neuroleptic malignant syndrome were a notable cause of rhabdomyolysis in series of adults and children<sup>4,44,45</sup> and in multiple case reports recently reviewed by Packard *et al.*<sup>46</sup> Among the psychiatric medications, antidepressants have also been associated with rhabdomyolysis.<sup>47,48</sup> Although HMG-CoA reductase inhibitors (statin medications) are frequently associated with mild muscle complaints, rhabdomyolysis is extremely infrequent,<sup>49,50</sup> probably occurring only at a rate of 0.4 per 10,000 person-years.<sup>51</sup> Risk factors for muscle side effects of statins, as reviewed by Mammen *et al.*, are numerous and include advanced age, systemic or infectious illness, underlying hepatic disease, alcohol abuse, and major surgery.<sup>52</sup> Administration of statins in the setting of hypothyroidism also increases the risk of rhabdomyolysis.<sup>53</sup> Statin-related rhabdomyolysis risk may be increased markedly with co-administration of fibrates. A review of the U.S. Food and Drug Administration's post-marketing database of rhabdomyolysis (CK ≥10,000) showed that, of 866 cases reported between 1987 and 2001, 44% were related to combination therapy, as compared with statins alone.<sup>18</sup> Of note, some data suggest fewer instances of rhabdomyolysis with a fenofibrate-statin combination compared with a

<b>Table 1.</b> Selected medications associated with rhabdomyolysis.	
Amino-caproic acid	
Antidepressants	
Tricyclic antidepressants	
Venlafaxine	
Sertraline	
Escitalopram	
Antihistamines	
Antipsychotics	
Aripiprazole	
Clozapine	
Haloperidol	
Olanzapine	
Risperidone	
Quetiapine	
Anti-retrovirals	
Tenofovir/abacavir	
Raltegravir	
Colchicine	
Colchicine + clarithromycin	
Colchicine + cyclosporine/tacrolimus	
Daptomycin	
Depakote	
Interferon- $\alpha$	
Lithium	
Ofloxacin/levofloxacin	
Statins (increased risk with hypothyroidism, certain genetic polymorphisms, liver disease, and diabetes)	
Statin + fibrates	
Statin + CYP450 inhibitors	
Statin + CYP3A4 inhibitors	
Diltiazem/amirodarone/verapamil	
Macrolide antibiotics (erythromycin/clarithromycin)	
Protease inhibitors	
Stiglaglipin	
Colchicine	
Statin + daptomycin	
Statin + fluconazole	
Statin + tacrolimus/cyclosporine	

gemfibrozil–statin combination.<sup>54</sup> In addition, the risk of statin-induced rhabdomyolysis in patients taking CYP3A4-metabolized forms of this medication (e.g., simvastatin, atorvastatin, and pravastatin) increases with co-administration of other CYP450-metabolized medications, including calcium channel blockers,<sup>55</sup> amiodarone,<sup>56</sup> macrolide antibiotics,<sup>57</sup> and human immunodeficiency virus–protease inhibitors.<sup>58</sup> Of note, the risk of statin-triggered myopathy is particularly increased in patients with a single-nucleotide polymorphism located within the *SLCO1B1* gene, which encodes a transport protein involved in regulation of hepatic statin uptake.<sup>59</sup>

**Metabolic/Electrolyte/Endocrine Disturbance.** Rhabdomyolysis can occur as a result of electrolyte abnormalities (hypokalemia, hypophosphatemia, hyponatremia, and hypernatremia) in the setting of endocrine diseases, such as diabetes,<sup>60–63</sup> thyroid dysfunction,<sup>64,65</sup> primary hyperaldosteronism,<sup>66</sup> pri-

mary adrenal insufficiency,<sup>67</sup> central diabetes insipidus,<sup>68</sup> postpartum hypernatremia,<sup>69</sup> and pituitary dysfunction.<sup>70</sup> Cases of rhabdomyolysis have also been attributed to electrolyte disturbances (primarily hypokalemia and hyponatremia) in the setting of laxative and diuretic misuse/abuse.<sup>71–73</sup> Rhabdomyolysis can be the presenting event in cases of inherited or acquired renal tubular dysfunction with profound hypokalemia, or it can be triggered by illness or discontinuation of medical treatment.<sup>74,75</sup> These causes can be screened for with serum and urine electrolyte panels and studies of endocrine function.

**Poisons/Toxins.** Venoms, toxins, pesticides, and poisons are relatively rare causes of rhabdomyolysis. Venom from several snakes can cause rhabdomyolysis by direct myotoxicity and/or from muscle ischemia related to coagulopathy.<sup>76,77</sup> Wasp stings<sup>78</sup> and spider bites<sup>79</sup> have also been associated with rhabdomyolysis. Ingestion of European quail that feed on hemlock seeds may cause rhabdomyolysis.<sup>80</sup> Haff disease, a rare sporadic syndrome of rhabdomyolysis, develops after eating buffalo fish that are thought to contain an unidentified toxin.<sup>81</sup> Ingestion of certain mushroom species is also associated with rhabdomyolysis.<sup>82,83</sup> Furthermore, pesticides and chemical poisonings can cause rhabdomyoysis.<sup>15</sup> Of note, patients with these toxic exposures often present with rhabdomyolysis as just 1 feature of widespread systemic illness. This highlights the importance of screening for rhabdomyolysis in suspected toxic exposure.

**Autoimmune Myopathies.** The autoimmune myopathies are a heterogeneous family of diseases, including dermatomyositis and polymyositis, characterized by muscle weakness, elevated CK levels, and lymphocytic infiltrates on muscle biopsy. Affected patients require immunosuppressive agents to control their disease. Although the onset of myositis is typically subacute, it may present acutely with typical features of rhabdomyolysis, including muscle pain and marked CK elevation. Indeed, autoimmune myositis has been described in a significant proportion of adult and pediatric rhabdomyolysis cases.<sup>4,84</sup> As patients with myositis often have other systemic manifestations of autoimmunity, these features may help guide clinicians to the correct diagnosis. For example, the presence of heliotrope rash and/or Gottron papules is pathognomonic for dermatomyositis.<sup>85</sup> Additional features of systemic autoimmunity in patients with dermatomyositis and polymyositis include arthritis, interstitial lung disease, and fever.

As previously noted, we do not usually recommend muscle biopsy at the time of acute rhabdomyolysis presentation, because delaying biopsy

**Table 2.** Muscle biopsy investigations for diagnosis of rhabdomyolysis.

Glycogen storage disorders
Routine histochemistry to evaluate for PAS-positive vacuoles
Enzyme immunohistochemistry (muscle phosphorylase or PFK)
Direct testing of enzymatic activity on frozen muscle
Glycogen content and structure
Muscle phosphorylase activity
Phosphofructokinase activity
Lactate dehydrogenase activity
Phosphorylase b activity
Phosphoglyceraldehyde kinase activity
Phosphoglycerate mutase activity
Phosphoglucomutase activity
Fatty acid oxidation disorders
Routine histochemistry to evaluate for abnormal lipid content
Muscle carnitine and acylcarnitine levels
Testing of enzymatic activity for $\beta$ -oxidation and carnitine transport
Mitochondrial myopathies
Ragged-red fibers on Gomori trichrome staining
Immunohistochemistry to evaluate COX and SDH activity
Electron microscopy to evaluate mitochondrial structure and distribution
Mitochondrial content and coenzyme 10 levels
Photometric evaluation of electron transport chain activity (fresh muscle is preferable)
Oxidative phosphorylation activity of complexes I–V (fresh muscle only)
Genetic testing for mutations in mitochondrial DNA in muscle tissue
Autoimmune myopathies
Dermatomyositis
Routine histochemistry: perifascicular atrophy (pathognomonic) and perivascular inflammation
Polymyositis/inclusion-body myositis
Routine histochemistry: non-necrotic myofibers surrounded and invaded by inflammatory cells and/or rimmed vacuoles
Muscular dystrophies
Features of necrotizing myopathy
Fibrosis
Increased internalized nuclei
Degeneration and regeneration
Abnormal immunohistochemistry for dystrophin, sarcoglycans, dysferlin, fukutin, or anoctamin-5
RYR1-related myopathy
Immunohistochemistry demonstrating central cores or multimimic cores on NADH, COX, and SDH stains

allows muscle cells to regenerate and ensures that overwhelming necrosis does not obscure the underlying pathology indicative of certain inherited conditions. However, because rapid initiation of immunosuppressive therapy may be indicated in suspected myositis, biopsy may be required to confirm the presence of lymphocytic cellular infiltrates and/or perifascicular atrophy. Of note, patients with immune-mediated necrotizing myopathy may have prominent necrosis on muscle biopsy without inflammation, making a histologic diagnosis of an autoimmune process challenging. In these cases, testing for antibodies associated with autoimmune necrotizing myopathies (i.e., anti-signal recogni-

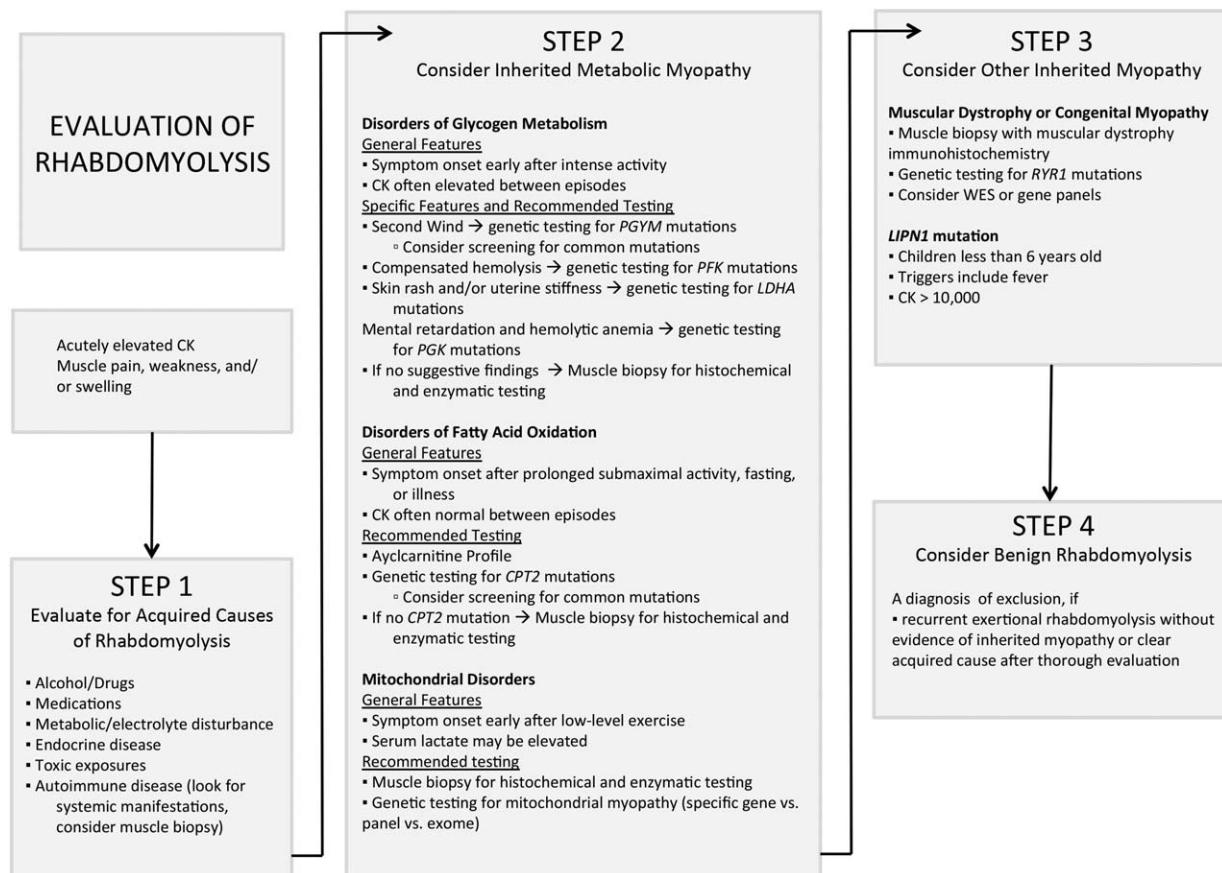
tion particle or anti-HMG-CoA reductase autoantibodies) may facilitate making the correct diagnosis.

### GENETIC CAUSES OF RHABDOMYOLYSIS

If the history, physical exam, and initial laboratory evaluation do not reveal an acquired cause for rhabdomyolysis, then the possibility of an inherited susceptibility should be considered. Genetic conditions that predispose to rhabdomyolysis include metabolic myopathies, muscular dystrophies, and channelopathies. Many of these conditions are associated with exercise intolerance and exertional rhabdomyolysis. Although numerous distinct inherited muscle diseases are associated with rhabdomyolysis, the differential diagnosis may be restricted based on the precise clinical features. Thus, it is important to determine whether there is baseline muscle weakness, a history of exercise intolerance, or, if present, the pattern of exercise that precipitates rhabdomyolysis. Also, because muscle pain, weakness, and dark urine may not always be sufficiently severe to prompt consultation with a physician, it is important to ask the patient about a history of these symptoms. Although these are inherited conditions, a family history of exercise intolerance or rhabdomyolysis may not be elicited, because the majority of these conditions are autosomal recessive.

As discussed below, abnormalities in laboratory tests, muscle biopsy findings, and functional testing can be used further guide decision-making in the diagnostic evaluation of rhabdomyolysis. In cases where an inherited predisposition to rhabdomyolysis is suspected, specific clinical features should prompt the clinician to proceed to targeted genetic testing. For patients in whom there are non-specific clinical features, or in cases where initial genetic testing is inconclusive, we recommend muscle biopsy with enzyme immunohistochemistry and testing of glycolytic enzyme activity. Muscle biopsy investigations for diagnosis of rhabdomyolysis are listed in Table 2. Alternatively, if available, the clinician may pursue testing via an appropriate next-generation gene sequencing panel or whole exome sequencing. A suggested approach to diagnosis is summarized in Figure 1.

**Metabolic Myopathies Associated with Rhabdomyolysis.** *Muscle Energetics and Metabolic Myopathies.* Metabolic myopathies associated with rhabdomyolysis can be differentiated by several features, which are summarized in Table 3. Various types of exercise, fasting, fever, and illness are major triggers of rhabdomyolysis, and these patterns can be helpful in narrowing the differential diagnosis for metabolic myopathies.



**FIGURE 1.** A diagnostic algorithm for patients with rhabdomyolysis.

During physical activity, muscle contraction and relaxation rely on a constant source of adenosine triphosphate (ATP). When exercise continues in the absence of adequate ATP production, muscle damage and rhabdomyolysis may result. A framework for understanding metabolic myopathies (and formulating a differential diagnosis) requires a brief explanation of energy sources available to and required by the muscle during different modes of activity.<sup>19,20</sup>

In the fed state, at rest, and with low-intensity or prolonged activity, the primary source of energy for muscle is fatty acid metabolism. Therefore, disorders of fatty acid metabolism present after prolonged submaximal activity and during periods of fasting or illness, when the main source of energy is through fatty acid  $\beta$ -oxidation. After initiation of moderate-intensity exercise, muscle first utilizes free glucose from the blood and glucose derived primarily from liver glycogen stores before switching to fatty acid metabolism. During maximum-intensity bursts of activity or during isometric contraction, muscle relies on anaerobic metabolism with breakdown of muscle glycogen to glucose and, ultimately, to pyruvate. Thus, disorders affecting muscle glycogen metabolism cause muscle

symptoms and injury early in association with intense or isometric activity. ATP production via oxidative phosphorylation requires a supply of oxygen. Thus, disorders of mitochondrial oxidative phosphorylation present when aerobic metabolic pathways predominate.

**Disorders of Glycogen Metabolism.** Enzymes involved in the metabolism of glycogen to glucose and glucose to pyruvate are relatively frequent targets of mutations in patients with an inherited predisposition to rhabdomyolysis. In patients with dysfunctional glycogen metabolism, rhabdomyolysis most characteristically occurs early after onset of moderate to intense activity, short bursts of intense activity, and isometric activity. Many patients also have elevated CK levels between rhabdomyolysis episodes. Characteristic diagnostic features of disorders of glycogen metabolism are listed in Table 4. In what follows, we discuss in detail the characteristics of several individual disorders of glycogen metabolism.

**Muscle Phosphorylase Deficiency.** Muscle phosphorylase deficiency is caused by a mutation in the muscle phosphorylase gene *PYGM*. *PYGM* encodes a muscle-specific enzyme that converts glycogen to

**Table 3.** General characteristics of metabolic diseases associated with rhabdomyolysis.\*

Metabolic category	Typical triggers	Interictal CK level	Interictal weakness	Muscle biopsy features
Glycogen storage disorders	Onset early after intense exercise or isometric activity	Elevated	More likely in adults	Increased glycogen, subsarcolemmal PAS-positive vacuoles
Fatty acid oxidation disorders	Onset later after prolonged submaximal activity, or in setting of fever, fasting or illness.	Normal	Rare	Increased lipid content
Mitochondrial disorders	Onset early or later after submaximal activity or leisurely activity, or in the setting of fasting fever or illness	Normal or elevated	Possible	Mitochondrial proliferation and/or abnormal lipid >content

\*Symptoms of muscle injury include muscle pain, cramping, weakness, and fatigue.

glucose during periods of anaerobic exercise. The prevalence of pathologic mutations in this gene is approximately 1 in 100,000.<sup>86</sup> Symptom onset typically occurs in childhood to adolescence with muscle pain, cramping, and stiffness,<sup>87</sup> often within minutes after onset of intense activity. If the activity level is maintained after symptoms begin, severe muscle contractures occur, and about half of patients develop rhabdomyolysis.<sup>88–90</sup>

The characteristic clinical feature of muscle phosphorylase deficiency, which differentiates it from the other glycogen storage diseases, is the “second wind phenomenon.”<sup>91</sup> This phenomenon is characterized by resolution of fatigue and pain with rest for a few minutes after onset of symptoms, and is caused by recruitment of free circulating glucose brought on by glycogenolysis in organs other than muscle.<sup>91</sup> After this rest period, patients are able to resume activity. The second wind phenomenon is experienced by the majority of patients, as many as 86% in a Spanish series of 239 cases.<sup>90</sup>

In a case series of 32 patients reported by Aquaron *et al.*, the majority (30 of 32) had elevated CK at rest, and a minority (7 of 32) had weakness.<sup>89</sup> In the Martin *et al.* series of 54 patients with phosphorylase deficiency, the findings were similar, with fixed weakness in 14 of 54 patients, all of whom were >40 years of age.<sup>88</sup> On the FET, most patients have an absent lactate response, and a small percentage have an inadequate lactate response, reflecting partial enzyme activity. Typical muscle biopsy findings include myopathic features, increased glycogen accumulation on PAS staining, and absence of immunohistochemical muscle phosphorylase staining.<sup>87</sup>

Muscle phosphorylase deficiency is the most commonly reported of the glycogen metabolic disorders. Therefore, when rhabdomyolysis is triggered by short-duration, high-intensity exercise, the patient gives a history of the second wind phenomenon, the CK is elevated at baseline, and interictal strength is normal (at least in younger

patients), we recommend proceeding directly to genetic testing to confirm the diagnosis. Of note, different mutations are common among individuals of different ethnic backgrounds. In individuals of European, American, and Spanish descent, the nonsense mutation pArg50\* is seen in >50% of patients.<sup>88–90</sup> In a smaller series of patients in Japan, the pArg50\* mutation was not observed.<sup>92</sup>

**Phosphofructokinase Deficiency.** Mutations in the PFKM gene, which encodes a glycolytic enzyme that catalyzes phosphorylation of fructose 6-phosphate to fructose 1,6-bisphosphate, cause phosphofructokinase (PFK) deficiency. This rare autosomal recessive condition was first described in 3 Japanese siblings with easy fatigability and onset of weakness and stiffness provoked by vigorous or prolonged exertion; 1 sibling developed myoglobinuria.<sup>93</sup>

Muscle symptoms, especially exercise intolerance, often occur first in childhood. Many patients, however, do not present until adulthood because of the mild nature of the condition.<sup>94</sup> Rhabdomyolysis is rare.<sup>93,95</sup> Interestingly, these patients tend to feel more fatigued before or during exercise after a high-carbohydrate meal, because use of free glucose from the blood is blocked.<sup>96</sup> In fact, they may have better exercise performance in the fasting state or with increased circulating free fatty acids, as they are able to use this fuel during oxidative exercise.<sup>96</sup> Affected patients typically have elevated CK levels at baseline, but weakness is rare, particularly in patients <50 years of age.<sup>97–100</sup> There is typically an absent or subnormal increase in lactate on the FET.<sup>101</sup> The muscle biopsy can show mild myopathic features, and PAS-positive vacuoles may be present. PFK enzyme immunohistochemistry shows decreased or absent PFK activity. Although the muscle PFK isoform is expressed in cardiac myocytes, mild hypertrophic cardiomyopathy has been described in only 1 patient.<sup>101</sup>

Muscle PFK is composed of 4 muscle subunits, and red blood cell PFK contains 2 of 4 muscle subunits. Thus, a unique feature of PFK deficiency is

**Table 4.** Characteristic diagnostic features of disorders of glycogen metabolism.

Disorder of glycogen metabolism	Inheritance	Non-ischemic forearm exercise test response	Multisystem involvement and other characteristic features
Muscle phosphorylase deficiency	Recessive	Inadequate lactate	Second wind phenomenon
Phosphofructokinase deficiency	Recessive	Inadequate lactate	Hemolysis
Phosphoglycerate kinase deficiency	X-linked	Inadequate lactate	Hemolysis encephalopathy
Lactate dehydrogenase deficiency	Recessive	Inadequate lactate, excessive pyruvate	Uterine stiffness in pregnancy, seasonal rash
Phosphoglucomutase deficiency	Recessive	Normal lactate, excessive ammonia	Hepatopathy, bifid uvula
Phosphorylase b deficiency	X-linked	Normal lactate	
Phosphoglycerate mutase deficiency	Recessive	Normal lactate	Muscle biopsy with tubular aggregates

compensated hemolysis, which can be exacerbated in situations that worsen muscle symptoms.<sup>102</sup> This is associated with a baseline reticulocytosis and hyperuricemia in most patients.

Thus, for the patient with exercise-induced rhabdomyolysis who gives a history of exercise intolerance, no second wind phenomenon, elevation of resting CK, and laboratory evidence of compensated hemolysis, we recommend proceeding directly to genetic testing for mutations in the *PFKM* gene.

**Muscle Lactate Dehydrogenase Deficiency.** Muscle lactate dehydrogenase (LDH) deficiency is a recessive condition caused by mutations in the *LDHA* gene (OMIM 612933) that disrupt the ability of the enzyme to interconvert pyruvate and lactate. The first cases were described in Japanese patients,<sup>24,103</sup> but the condition has also been described in Caucasians.<sup>104,105</sup> The condition is characterized by onset of muscle pain, stiffness, and cramping in the setting of strenuous activity; 1 child had initial onset of symptoms during a 100-meter dash at age 9 years.<sup>106</sup> Exertional pigmenturia is a frequently reported symptom, and there are several reports of rhabdomyolysis with renal failure.<sup>104,106,107</sup>

Resting CK levels are usually elevated.<sup>24,104,106,107</sup> After exercise, there is a large increase in CK, but a smaller than expected increase in serum LDH<sup>106,107</sup>; this biochemical discrepancy is a unique feature of muscle LDH deficiency. The FET shows an absent or inadequate lactate response along with an exaggerated increase in pyruvate levels.<sup>24</sup> Muscle biopsy pathology is described infrequently in this condition, but nonspecific myopathic changes have been observed.<sup>104</sup>

There are 2 unique clinical features of patients with muscle LDH deficiency. First, some women have only mild exercise intolerance but develop prominent uterine stiffness during pregnancy that requires delivery by Cesarean section.<sup>106,108</sup> Second, muscle LDH deficiency has been associated with an erythematous rash on the extensor surfaces

of the extremities, which worsens during the summer.<sup>105,109,110</sup>

Thus, in a patient with rhabdomyolysis in the context of strenuous activity, no second wind phenomenon, presence of a seasonal erythematous rash on extensor surfaces, or uterine stiffness during pregnancy genetic testing for LDH deficiency is suggested.

**Muscle Phosphorylase b Kinase Deficiency.** Muscle phosphorylase b kinase deficiency is associated with mutations in the *PHKA1* gene, located on the X chromosome; this enzyme encodes the muscle-specific isoform of the regulatory  $\alpha$ -subunit of phosphorylase b kinase. This is a cAMP-dependent protein kinase composed of 4 subunits that catalyzes phosphorylation and activation of myophosphorylase. Despite its role in activation of myophosphorylase, this condition presents slightly differently from myophosphorylase deficiency.<sup>111-122</sup> Patients present in childhood or as young adults with exercise-induced muscle pain and cramping. Some have intermittent exercise-induced pigmenturia. Unlike those with myophosphorylase deficiency, contracture in response to strenuous or prolonged exercise is not commonly reported, and there is no second wind phenomenon. Furthermore, there have been no reports of severe rhabdomyolysis with acute renal failure. The majority of patients are male, but early childhood hypotonia without hepatic features has been described in 2 girls with phosphorylase b kinase deficiency.<sup>111,112</sup>

There are a few biochemical features to help to distinguish phosphorylase b kinase deficiency from other muscle glycogen storage diseases. The baseline CK level may or may not be elevated.<sup>123</sup> In the FET, there is typically a normal rise in lactate and ammonia.<sup>121,123</sup> During submaximal cycling exercise testing in 1 patient with known *PHKA1* mutation, lactate failed to increase to the same degree as controls,<sup>121</sup> suggesting that abnormality of phosphorylase b kinase activity is more disruptive to glycogen metabolism and energy production during

submaximal dynamic exercise than on strenuous isometric exercise.<sup>120</sup>

There have been several reports of patients with muscle phosphorylase b kinase deficiency due to mutations in the *PHKA1* gene.<sup>115,116,118,119,121,122</sup> Two features, however, suggest that the protein dysfunction causing muscle phosphorylase b kinase deficiency extends beyond mutations in *PHKA1* and other genes encoding subunits of muscle phosphorylase b kinase protein. *PHKA1* is found on the X-chromosome, and, although a majority of patients described with deficient phosphorylase b kinase activity in the muscle biopsy are male, there have been several reports of affected females,<sup>111,112,124</sup> suggesting autosomal inheritance in some patients. In addition, when Burwinkel *et al.* screened 6 patients with reduced muscle phosphorylase b kinase activity for mutations in 8 genes encoding components of the enzyme, only 1 mutation in 1 gene, *PHKA1*, was found in a single patient.<sup>118</sup>

Because the genetic causes of decreased muscle phosphorylase b kinase activity are not fully defined, we recommend muscle biopsy with enzyme testing in suspected cases.

**Phosphoglycerate Kinase Deficiency.** Phosphoglycerate kinase (PGK) deficiency is an X-linked disorder caused by a mutation in the *PGK1* gene (OMIM 311800), which encodes the enzyme catalyzing the final step in the glycolytic pathway with formation of 3-phosphoglycerate and ATP. There is a brain isozyme and a muscle isozyme. An intermediate isozyme composed of both subunit types is expressed variably in other tissues, but deficiency of this isozyme manifests most frequently in red blood cells as hemolytic anemia. Reports of isolated myopathies with decreased PGK activity are rare.<sup>125–129</sup> Most cases of PGK deficiency manifest with 1 or more combinations of myopathy, encephalopathy, and/or hemolytic anemia. The combination of epileptic encephalopathy and myopathy can manifest as rhabdomyolysis presenting after seizures.<sup>130</sup> Patients with rhabdomyolysis have similar characteristics of childhood exercise intolerance with painful muscle cramps. Pigmenturia is seen in almost all patients. Rhabdomyolysis with acute renal failure has been described.<sup>125,126,130</sup>

Biochemically, affected patients share common features with other muscle glycogen storage disorders.<sup>125–129</sup> Resting CK may be normal or elevated. The FET induces early fatigue with cramping, and there is an absent or an inappropriately low rise in lactate. The muscle biopsy can be normal or show vacuoles containing PAS-positive material. As in PFK deficiency, blood testing may reveal a hemolytic anemia. Although the presence of encephalopathy or an X-linked inheritance pattern would suggest the former, distinguishing between PGK

and phosphofructokinase deficiency may be difficult. If clinically suspected, we recommend either genetic testing for both diseases or performance of a muscle biopsy with PFK immunohistochemistry and muscle enzyme testing.

**Phosphoglycerate Mutase Deficiency.** Phosphoglycerate mutase deficiency is caused by a mutation in the *PGAM2* gene, which encodes an enzyme that catalyzes conversion of 3-phosphoglycerate to 2-phosphoglycerate. The first case, described in 1981, was a 52-year-old man with adolescent-onset muscle pain, stiffness, weakness, and pigmenturia after strenuous activity.<sup>131</sup> In subsequent reports, most patients present with muscle pain, contracture, and myoglobinuria after strenuous exercise.<sup>132–140</sup> The majority of patients described so far have been of African American descent.

Baseline CK levels are often elevated. The FET shows slightly reduced or normal lactate elevation. Muscle biopsy can show increased glycogen content with PAS-positive subsarcolemmal vacuoles, or it can be normal. Tubular aggregates are sometimes seen on muscle biopsy.<sup>139,141</sup>

As with other patients who do not have unique distinguishing features of a particular metabolic myopathy, these patients may be diagnosed by muscle biopsy, including enzymatic testing. Alternatively, an appropriate gene-sequencing panel or whole exome sequencing may be undertaken to facilitate diagnosis.

**Phosphoglucomutase Deficiency.** Phosphoglucomutase deficiency is an autosomal recessive condition caused by a mutation in the *PGM1* gene, which encodes an enzyme that catalyzes the transfer of phosphate between the 1 and 6 positions of the glucose molecule. The first case report of phosphoglucomutase was of a 35-year-old man with recurrent activity-induced muscle cramping and pigmenturia associated with strenuous exercise.<sup>142</sup> He had an elevated resting CK level, a myopathic EMG, and an FET showing a normal lactate response with excessive ammonia elevation. Muscle biopsy showed subsarcolemmal vacuoles containing normally structured glycogen and decreased phosphoglucomutase activity. Thereafter, a mutation was confirmed in the *PGM1* gene.

More recently, Tegtmeyer *et al.* identified 19 individuals from 16 families with mutations in the *PGM1* gene.<sup>143</sup> At birth, a bifid uvula was present in just over 80% of the patients. Later, all patients developed hepatopathy. Exercise intolerance with recurrent rhabdomyolysis was reported in about half of the patients. Malignant hyperthermia with severe rhabdomyolysis occurred in 2 patients. The investigators concluded that mutations in *PGM1* cause both a glycogen storage disorder and a mixed-type disorder of congenital glycosylation.

Resting CK levels and FET results were not described.

Thus, phosphoglucomutase deficiency is a rare condition with rhabdomyolysis that can occur as an isolated feature or together with hepatopathy. The presence of a bifid uvula, which was not reported in the patient described by Stojkovic *et al.*, may prompt genetic testing for mutations in *PGM1*.<sup>142</sup> Otherwise, unless a gene panel or whole exome sequencing is readily available, muscle biopsy with enzymatic testing may be the most efficient way of diagnosing this disease.

#### **Disorders of Fatty Acid Oxidation Associated with Rhabdomyolysis.**

Mutations in enzymes involved in the metabolism of fatty acids and transport of acyl-CoA-conjugated fatty acids across the mitochondrial membrane are a cause of rhabdomyolysis, often triggered by prolonged submaximal activity, fasting, stress, and/or illness. Other characteristic features of these diseases include a normal baseline CK level, acylcarnitine abnormalities, and muscle biopsies showing evidence of a lipid storage myopathy. It should be noted that patients who are not in a catabolic state may not show the specific abnormalities that indicate the underlying fatty acid oxidation disorder.

**Carnitine Palmitoyltransferase II Deficiency.** Carnitine palmitoyltransferase (CPTII) is a protein located in the mitochondrial inner membrane that functions (along with CPTI located in the outer mitochondrial membrane) to transfer acyl-CoA-conjugated long-chain fatty acids from the cytosol into the mitochondrial matrix for  $\beta$ -oxidation. Mutations in the *CPT2* gene are the most common cause of rhabdomyolysis due to fatty acid oxidation disorders.<sup>144</sup> The condition manifests in late childhood to early adolescence and, for unknown reasons, occurs more commonly in males.<sup>145,146</sup> Typically, prolonged muscle exercise causes weakness, pain, cramping, and pigmenturia; these symptoms may also be precipitated by cold, fasting, illness, or emotional stress.<sup>145–148</sup> In younger children, rhabdomyolysis is more likely to be due to illness or fasting and may be accompanied by encephalopathy and non-ketotic hypoglycemia.<sup>147</sup> Valproic acid<sup>149</sup> and anesthesia<sup>150</sup> have also been identified as triggers. In contrast to the glycogen storage diseases, which may affect the exercised muscle in isolation, CPTII-deficient patients may have diffuse weakness. Consequently, monitoring for respiratory failure is necessary in severe rhabdomyolysis in CPTII deficiency.<sup>148,151</sup> Furthermore, up to 30% of patients may develop acute renal failure due to rhabdomyolysis.<sup>146,148</sup>

Despite potentially severe weakness when in crisis,<sup>145,146</sup> the majority of patients with recurrent

rhabdomyolysis have normal CK levels and neurological examinations between episodes<sup>151</sup>; elevated baseline CK levels were reported in just 10% of patients in 1 series.<sup>152</sup> Anichini *et al.* reviewed muscle biopsies from 23 patients and found that typical histopathological findings included internalized nuclei (91%), type 2 fiber prevalence (65%), and lipid droplets (40%).<sup>145</sup> On FET, lactate and ammonia responses are normal.<sup>151</sup> Elevation of plasma long-chain acylcarnitine species, particularly C16:0 and C18:1, on mass spectrometry strongly suggests CPTII deficiency.<sup>153</sup> In CPTII deficiency, no significant differences have been noted in acylcarnitine profile testing between symptomatic and asymptomatic patients, and interictal acylcarnitine profile abnormalities may not be apparent if the patient is metabolically stable and well-rested.<sup>145</sup>

In patients with suggestive clinical features of CPTII deficiency, we recommend genetic screening for common *CPT2* mutations (p.S113L and p.P50H in addition to several others).<sup>145,146,148</sup> Normal C16:0 and C18:1 acylcarnitine levels should not necessarily preclude genetic testing if the clinical suspicion for a *CPT2* mutation is high. If common mutation screening does not confirm the cause, full sequencing of the gene should be considered. If gene testing is inconclusive, muscle biopsy may be performed to check for CPTII activity by radioisotope assay.<sup>154,155</sup> Finally, it should be noted that heterozygous carriers of *CPT2* mutations can manifest with subtle symptoms due to partial inability to metabolize long-chain fatty acids.<sup>156</sup>

**Other Fatty Acid Oxidation Disorders.** Intramitochondrial fatty acid oxidation can be impaired by mutations in the acyl-coenzyme A dehydrogenases. The most commonly described is very-long-chain acyl-coenzyme A dehydrogenase deficiency (VLCAD). In a case series of 13 patients with VLCAD, the onset of muscle symptoms was typically in middle to late childhood, with symptoms of exercise intolerance and recurrent pigmenturia triggered by activity, cold exposure, or fasting.<sup>157</sup> Younger patients may manifest with hepatopathy or cardiomyopathy and recurrent hypoglycemia. Rhabdomyolysis with acute renal failure has been reported. These patients have normal interictal CK levels and muscle strength. Muscle biopsy can show mitochondrial proliferation and/or increased lipid content, especially in type I myofibers.<sup>157</sup>

Mutations with similar clinical presentations have been described with mitochondrial trifunctional protein deficiency, in which mutation causes decreased long-chain 3-hydroxyacyl-coenzyme A dehydrogenase activity.<sup>158–160</sup> The adult-onset form of this disease is rare, but those with

the condition present with exercise intolerance and recurrent pigmenturia, and often with a length-dependent axonal sensorimotor neuropathy. Long-chain and 3-hydroxy long-chain acylcarnitine species may be elevated. Medium-chain acylcoenzyme A dehydrogenase deficiency is a rare cause of recurrent rhabdomyolysis and usually occurs with encephalopathy.<sup>161</sup>

#### **Mitochondrial Myopathies Associated with Rhabdomyolysis.**

Mutations in components of the mitochondrial respiratory chain that impair oxidative phosphorylation and ATP production may cause multisystem disease, sometimes including skeletal muscle. However, we highlight only those mitochondrial disorders that have been associated with rhabdomyolysis.

Intact mitochondrial function and respiratory chain activity is necessary for aerobic and anaerobic exercise. Consequently, muscle symptoms may occur early with strenuous exercise or later after relatively low levels of activity. Patients often report excessive fatigue out of proportion to weakness. CK and lactate levels can be elevated or normal.

In rhabdomyolysis patients with suspected mitochondrial myopathy based on clinical features (e.g., other organ system involvement, external ophthalmoplegia, etc.) or maternal inheritance pattern, muscle biopsy is often performed to confirm mitochondrial dysfunction. Ragged red fibers (RRF), which represent muscle cells with increased subsarcolemmal accumulations of mitochondria, are among the most common histological abnormalities associated with mitochondrial diseases, and muscle fibers with absent cytochrome oxidase activity, known as COX-negative fibers, are also suggestive of mitochondrial disease.<sup>162,163</sup> In healthy individuals, COX-negative fibers and RRF numbers increase with age.<sup>164</sup> Based on the modified Walker criteria for mitochondrial disease,<sup>165</sup> >2% RRF is considered abnormal at any age. For COX-negative fibers, >2% is considered abnormal in patients <50 years of age. At age ≥50, the presence of >5% COX-negative fibers is considered abnormal. Importantly, RRF and/or COX-negative fibers may be increased in patients with other conditions, including autoimmune myopathy,<sup>166</sup> oculopharyngeal muscular dystrophy,<sup>167</sup> or myasthenia gravis.<sup>168</sup> Thus, the clinical history and additional features seen on muscle biopsy are important in determining the significance of RRF and COX-negative fibers.

After muscle biopsy, testing of respiratory chain enzyme activity can be performed. As with interpretation of histopathological features, it is important to recognize that reduced activity may be due to primary or secondary mitochondrial

abnormalities.<sup>169</sup> If muscle biopsy reveals evidence of mitochondrial disease, but respiratory enzyme activity analysis does not reveal the specific deficiency, genetic testing may be considered. It is important to recognize that disorders of mitochondrial function can arise from mutations in either the mitochondrial or nuclear genomes. When caused by mutations in nuclear DNA, mitochondrial disease may be inherited in either an autosomal dominant or recessive pattern. Mitochondrial genome mutations are transmitted maternally and can result in heteroplasmy, whereby some cells or organs contain a higher burden of mutant mitochondrial genomes than others. Because of this phenomenon, muscle tissue as the source of mitochondrial DNA will have the highest yield in patients with muscle symptoms such as rhabdomyolysis.<sup>169</sup>

*Coenzyme Q10 Deficiency.* Coenzyme Q10 deficiency was first described in 2 sisters with onset of early exertional fatigue beginning in childhood and episodic rhabdomyolysis.<sup>170</sup> These sisters, and some other patients, also had encephalopathy, ataxia, and/or progressive proximal weakness. Some patients with coenzyme Q deficiency have seizure disorders with recurrent rhabdomyolysis after convulsions.<sup>170–172</sup> Illness may also be also a provoking factor.<sup>170</sup> The patients have elevations in venous lactate and lactate/pyruvate ratio.

*Cytochrome c Mutations.* Cytochrome c mutations have been reported in patients with adult-onset rhabdomyolysis. This type of mutation was triggered in 1 patient by walking and, in another patient, symptoms began 3 hours after heavy lifting.<sup>173,174</sup> Another patient developed muscle pain and pigmenturia, first with a viral illness and a second time after exercise.<sup>175</sup>

*Cytochrome b Mutation.* Cytochrome b mutation was associated with rhabdomyolysis in a patient with late-childhood-onset fatigue and pain with exercise.<sup>176</sup> He had rhabdomyolysis after shoveling snow and subsequently developed progressive muscle weakness. His lactate level was chronically elevated. Baseline CK level was normal.

*COX I Mutation.* COX I mutation was reported in a patient with childhood-onset exercise intolerance, especially with endurance activities.<sup>177</sup> He developed recurrent rhabdomyolysis at age 22 years. The resting lactate and CK levels were normal.

*Mitochondrial DNA tRNA Mutations.* Mitochondrial DNA tRNA mutations have also been described in association with rhabdomyolysis. For example, a 36-year-old woman with recurrent rhabdomyolysis triggered by intense exercise was found to have a mutation in the tRNA-isoleucine gene.<sup>178</sup> Another mutation in the tRNA-leucine gene

(identical to a mutation described in mitochondrial encephalopathy, lactic acidosis, and strokelike episodes, or MELAS) was reported in a 65-year-old woman with recurrent rhabdomyolysis triggered by dehydration or minor trauma.<sup>179</sup>

**Mutation in the MT-CO2 Gene.** Mutation in the *MT-CO2* gene was described recently in an adult man with onset of exercise intolerance and recurrent rhabdomyolysis in childhood.<sup>180</sup> He had mild weakness on exam at age 43 years. Resting CK was normal, and resting lactate was normal or elevated.

**Structural Myopathies.** Although patients with structural myopathies typically present with progressive muscle weakness as the most prominent muscle feature, some patients with these disorders may also have rhabdomyolysis.

**Dystrophinopathy.** Several case reports and small series described patients with dystrophin gene mutations and exercise-induced rhabdomyolysis. Not all cases specifically addressed the activities provoking the episodes. In 3 cases described by Figarella-Branger *et al*, the baseline CK level was elevated, and EMG was normal. One of the patients had both calf hypertrophy and dilated cardiomyopathy at age 21 years.<sup>181</sup> The muscle biopsies of all 3 patients revealed absent immunohistochemical staining to the Dys 1 antibody, which labels the rod domain. Two additional patients with recurrent rhabdomyolysis after prolonged exercise were found to have an identical mutation in exon 15 of the dystrophin gene.<sup>182</sup> These patients may have been more likely to have had baseline weakness on physical examination.

**LGMD2I.** Five patients with limb-girdle muscular dystrophy 2I (LGMD2I) and exercise-induced rhabdomyolysis were found to have identical mutations in the *FKRP* gene encoding fukutin-related protein.<sup>183</sup> Onset of muscle pain and cramping after activity was reported during late childhood, adolescence, and early adulthood. Baseline CK was markedly elevated, and patients with rhabdomyolysis developed baseline weakness.

**Dysferlinopathy.** A patient without previous history of exercise intolerance was found to have a mutation in the dysferlin gene, after presentation with rhabdomyolysis at age 15 years.<sup>184</sup> He had no weakness, but his baseline CK remained elevated, prompting muscle biopsy. Biopsy showed a necrotizing myopathy with severe type 2 fiber predominance. Immunohistochemical staining revealed absent dysferlin.

**Anoctamin-5 Myopathy.** Exercise intolerance with muscle pain and myoglobinuria has been described in association with mutation in the anoctamin-5 gene.<sup>185,186</sup> Baseline CK levels were

elevated. In a patient with exercise intolerance and muscle pain, muscle biopsy was described as a mild necrotizing myopathy with congophilic deposits of amyloid in some myofibers.<sup>186</sup>

**Sarcoglycanopathy.** A 5-year-old boy developed rhabdomyolysis associated with infection and was later diagnosed with  $\alpha$ -sarcoglycan deficiency.<sup>187</sup> Another boy had onset of easy fatigability and was found to have elevated CK levels at age 8 years, prompting muscle biopsy with normal metabolic evaluation and normal genetic testing for dystrophinopathy.<sup>188</sup> Subsequent episodes of recurrent rhabdomyolysis led to repeat muscle biopsy, which showed reduced  $\alpha$ -sarcoglycan staining on immunohistochemistry. Exercise-induced recurrent rhabdomyolysis was also described in a 12-year-old boy with  $\beta$ -sarcoglycanopathy.<sup>189</sup> All patients had elevated baseline CK levels.

**FHSD.** In a series of 122 cases of fascioscapulo-humeral muscular dystrophy (FSHD), 1 patient was described as having myoglobinuria.<sup>190</sup>

**Channelopathies.** *RYR1* gene mutations have historically been associated with central core disease, multimimicore disease, and malignant hyperthermia.<sup>191,192</sup> More recently, Dlamini *et al* described 24 patients from 14 families with exercise intolerance and/or rhabdomyolysis who were found to have mutations in *RYR1*.<sup>193</sup> Fifteen of 24 patients presented with rhabdomyolysis, and 10 had recurrent episodes. The most common trigger was exercise, but events were also triggered by heat exposure, illness, and alcohol consumption. Mild proximal weakness was detected in 5 of 24 patients, and ptosis was present in 2 families. Interval CK levels were normal in most patients. Muscle stiffness in response to cold was described by 3 patients. In the available muscle biopsies from 15 patients, most showed fiber size variability, increased internalized nuclei, type 1 fiber predominance, and corelike areas on oxidative stains. The link between exertional heat stroke, rhabdomyolysis, and susceptibility to malignant hyperthermia has not been fully characterized.<sup>194,195</sup>

**SCN4A Gene Mutation.** SCN4A gene mutation was recently discovered in an 8-year-old girl with recurrent rhabdomyolysis triggered by emotional stress, exercise, and infection.<sup>196</sup> Baseline CK levels between the attacks were normal or mildly elevated. Her examination showed proximal weakness and mild thenar percussion myotonia. EMG showed myotonic discharges. On muscle biopsy, she had a non-vacuolar necrotizing myopathy.

**Lipin-1.** Mutations in the lipin-1 gene (*LIPN1*) have been described recently in pediatric patients with recurrent rhabdomyolysis. *LIPN1* encodes lipin-1, a phosphatidate phosphatase that is

important for triacylglycerol and phospholipid biosynthesis and acts as a transcriptional co-activator. It was first described in 3 related healthy children with recurrent rhabdomyolysis triggered by febrile illness.<sup>197</sup> The children had normal CK and strength between episodes. In this original description, 22 other children with recurrent rhabdomyolysis were screened, and 4 additional cases with similar characteristics were identified. Muscle biopsies showed increased lipid content in 2 muscle biopsies, and the others were normal.

Michot *et al.* screened a group of 29 patients <5 years of age, who had recurrent rhabdomyolysis and CK levels >10,000 U/L, and found homozygous or compound heterozygous *LPIN1* mutations in 59%.<sup>198</sup> The average age was 21 months. Fever and/or fasting were the triggering factors for all patients in whom a trigger was reported. In 3 patients, fever, fasting, and local anesthesia were reported to be triggers. One patient developed rhabdomyolysis after exposure to general anesthesia.

In another series, which included a subset of patients with recurrent severe rhabdomyolysis (CK >10,000 U/L), where the first episode occurred at <6 years of age, there was a *LPIN1* mutation in 37% and in 19% of patients with severe rhabdomyolysis in adult and pediatric age groups.<sup>198</sup> *LPIN1* mutations were not found in other patients in the series with mild rhabdomyolysis (CK <10,000) or patients with myalgias. Episodes of rhabdomyolysis in the lipin-1 patients were triggered most frequently by febrile illness and less frequently by intense exercise, anesthesia, or fasting. Six patients had mild proximal weakness. Six other patients died of cardiac arrhythmia, which was attributed to possible hyperkalemia. Forty percent of heterozygotes reported exercise-induced myalgia or cramping. Three adults with heterozygous mutations in *LPIN1* have been described with statin-induced myopathy.<sup>197</sup>

**Sickle-Cell Disease.** In patients with homozygous sickle-cell disease, rhabdomyolysis can occur in the setting of intravascular coagulation in sickle-cell crisis; this may be triggered by stress, illness, metabolic acidosis, and/or dehydration.<sup>199</sup> Rhabdomyolysis with acute renal failure, and sometimes sudden death, has been reported in athletes (often football players) and military recruits with the heterozygous sickle-cell trait after intense exertion or heat illness.<sup>200–203</sup>

**“Benign Exertional Rhabdomyolysis.”** A condition known as “benign exertional rhabdomyolysis” has been described in otherwise healthy people who develop muscle pain, elevated CK levels, and/or pigmenturia after intense exercise. This has been

documented particularly well in military recruits during basic training. Similar elevations in CK and/or myoglobin have also been described in asymptomatic ice skaters and marathon runners.<sup>204,205</sup> Of note, individuals in better physical condition and with lower body mass index show a smaller degree of post-exercise increase in CK levels compared with unconditioned athletes.<sup>206–208</sup> Also, serum CK levels rose higher after high-intensity exercise than after moderate-intensity exercise on a treadmill.<sup>206</sup> There may be some influence of race and gender, as baseline and post-exercise CK levels have been shown to be elevated in men compared with women<sup>209</sup> and in blacks compared with whites.<sup>209,210</sup> In 1 study of exertional rhabdomyolysis, men were 4.1 times more likely than women to have had exertional rhabdomyolysis.<sup>211</sup> Interestingly, when CK levels were followed in all basic training participants, some recruits remained asymptomatic despite CK elevations that are associated with muscle symptoms in other individuals.<sup>208,210,212</sup>

Emerging evidence suggests that certain genetic factors influence the likelihood of developing benign exertional rhabdomyolysis. For example, single nucleotide polymorphisms in *CKMM* (CK muscle isoform), *ACTN3* ( $\alpha$ -actinin-3), and *MYLK2* (myosin light chain kinase) have been associated with this condition.<sup>211,213</sup> However, in some cases of exertional rhabdomyolysis, no acquired or genetic cause can be identified despite extensive evaluation. In our opinion, many of these individuals likely have another, unidentified genetic susceptibility for exertional rhabdomyolysis.

## CONCLUSION

When patients present with symptoms of muscle pain, cramping, and/or pigmenturia (especially in the context of exertion, fasting, or illness), an elevated CK level during or immediately after an acute episode indicates that the symptoms are most likely due to rhabdomyolysis.

Once the diagnosis of rhabdomyolysis is established, the physician should inquire about previous episodes, other affected family members, medication exposure, illicit drug use, and alcohol history. Important initial laboratory assessments include electrolyte analysis, toxicology screening, and thyroid function tests to look for evidence of acquired, and treatable, causes of rhabdomyolysis. In the acute phase, we do not recommend a muscle biopsy unless autoimmune myopathy is considered in the differential diagnosis and immunotherapy would be indicated. Rather, we prefer to defer diagnostic muscle biopsies for at least 1 month (and preferably longer) after an episode of acute rhabdomyolysis.

Figure 1 summarizes a diagnostic approach to the evaluation of rhabdomyolysis. If no acquired cause of rhabdomyolysis is identified, we suggest attempting to categorize the patient into 1 of the following 4 groups to help guide subsequent testing for inherited muscle disease:

- Glycogen storage disease:** In these patients, rhabdomyolysis is often triggered by short periods of intense exercise, often accompanied by pain and cramping; contractures may occur with prolonged strenuous activity or isometric exercise; baseline CK level may be elevated.
- Disorders of fatty acid metabolism:** Symptoms of pain and cramping are triggered by prolonged low-to-moderate intensity activity; contractures are not a prominent feature; CK is often normal between episodes.
- Mitochondrial myopathy:** Muscle symptoms are triggered soon after exercise and/or after prolonged activity; excessive and early fatigue is a major complaint. The interictal CK level can be normal or abnormal; an elevated lactate level or lactate/pyruvate ratio may be found.
- Structural muscle disease:** Symptoms of pain and cramping are triggered by prolonged low-to-moderate intensity activity; contractures are not a prominent feature; CK is typically elevated between episodes.

If patients easily fit into either of the first 2 groups, and especially if they have some very characteristic feature of a specific disease (e.g., the second wind phenomenon in myophosphorylase deficiency), then genetic testing may be considered without performing a muscle biopsy. If genetic testing is unsuccessful, a muscle biopsy should be performed, followed by appropriate histologic, immunohistochemical, and enzymatic analyses.

If mitochondrial myopathy is suspected, a muscle biopsy is usually suggested to confirm the presence of mitochondrial dysfunction and to obtain the best tissue for subsequent genetic analysis. A muscle biopsy may also be considered in patients with suspected structural myopathies in whom the differential diagnosis remains broad even after an otherwise extensive evaluation; appropriate testing of the tissue may provide important clues to facilitate diagnosis (e.g., absence of sarcoglycan staining).

In patients in whom an acquired or intrinsic cause of rhabdomyolysis cannot be easily identified, the physician is faced with the question of the utility and cost of further evaluation (e.g., whole exome sequencing). In general, after a single episode of rhabdomyolysis in which no acquired cause can be identified, we do not necessarily pursue

additional testing or muscle biopsy unless there is additional evidence suggesting an inherited muscle disease. However, in the case of recurrent rhabdomyolysis, we pursue genetic testing and/or muscle biopsy. In patients with recurrent rhabdomyolysis with no clear acquired cause or specific clinical features and with normal muscle biopsy and enzymatic testing, we consider gene panels and/or whole exome sequencing. Currently, we consider benign exertional rhabdomyolysis to be a diagnosis of exclusion. As clinical genetic testing and whole exome sequencing become more widely available, we expect that additional genetic factors predisposing individuals to recurrent rhabdomyolysis will be identified.

This work was supported in part by the Intramural Research Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health.

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