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REVIEW

Rhabdomyolysis: a review, with emphasis on the pediatric population

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Abstract Rhabdomyolysis is a common clinical syndrome and accounts for 7% of all cases of acute kidney injury (AKI) in the USA. It can result from a wide variety of disorders, such as trauma, exercise, medications and infection, but in the pediatric population, infection and inherited disorders are the most common causes of rhabdomyolysis. Approximately half of patients with rhabdomyolysis present with the triad of myalgias, weakness and dark urine. The clinical suspicion, especially in the setting of trauma or drugs, is supported by elevated creatinine kinase levels and confirmed by the measurement of myoglobin levels in serum or urine. Muscle biopsy and genetic testing should be performed if rhabdomyolysis is recurrent or metabolic myopathy is suspected. Early recognition is important to prevent AKI through the use of aggressive hydration. Prevention is important in patients with inherited forms, but novel therapies may be developed with the better understanding of the pathophysiology and genetics of rhabdomyolysis.

Keywords Acute kidney injury · Genetic disorders · Myoglobin · Pediatric · Rhabdomyolysis

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Introduction

Rhabdomyolysis is a common clinical syndrome, with more than 25,000 cases reported annually in the USA, where it accounts for 7% of all cases of acute kidney injury (AKI) [1, 2]. It is due to injury to muscle tissue, which may be caused by physical (e.g. crush injury), chemical or biological factors. Striated muscle breakdown (rhabdo-myo-lysis) leads to the release of breakdown products from damaged muscle cells into the bloodstream. Some of these, such as myoglobin, are harmful to the kidney and may lead to AKI [3]. Although rhabdomyolysis may result from a wide variety of disorders that injure skeletal muscle, in this review we will focus on those disorders that are prevalent in the pediatric population, especially those that result from inherited disease and metabolic disorders. A variety of published reviews address rhabdomyolysis secondary to trauma, infection and drugs in more detail [4–7].

Rhabdomyolysis in history

The first historical mention of rhabdomyolysis is believed to be in the Old Testament among Jews after eating quail during their exodus from Egypt. The consumption of quail is linked to the development of myolysis caused by hemlock herbs consumed by the birds during their spring migration across the Mediterranean Sea [8]. A surgeon in Napoleon's army in 1812 described limb gangrene from rhabdomyolysis in carbon monoxide victims. In more modern times, German military literature referred to rhabdomyolysis as crush syndrome, and the disease and its mechanisms were well described in World War II during the Blitz of London in 1941. Bywaters identified myoglo-

binuria as the cause of renal failure in five patients from the London Blitz [9].

Clinical picture

Approximately half of all patients with rhabdomyolysis present with the triad of myalgias, weakness and dark (tea-colored) urine with a history of trauma or medication use. Many patients presenting with calf pain or muscle swelling have their diagnosis confounded by other conditions, such as deep venous thrombosis. A history of alcohol or illicit drug use, trauma, loss of consciousness and prolonged immobilization should raise the suspicion of rhabdomyolysis. In a good percentage of patients, rhabdomyolysis can present with one or more of its complications, such as AKI, compartment syndrome and electrolytes abnormalities.

Acute kidney injury is one of the major complications of rhabdomyolysis and occurs in about 24% of patients. The risk of AKI in adults was estimated in one study to be 17–35% [10]; in comparison the risk of AKI in children was estimated to be 42% in a small pediatric series and 5% in a larger series [11]. Rhabdomyolysis has been reported to account for about 5–20% of all cases of AKI. The mortality rate in patients with rhabdomyolysis, complicated by AKI, may be as high as 80%, especially when creatine kinase (CK) levels reach 100,000 U/L. Compartment syndrome may result from underlying etiology, as in the case of fractures of the lower extremities or during the course of treatment with fluid resuscitation, which can cause worsening edema of the extremities [12].

Pathophysiology

Pathophysiology of rhabdomyolysis All disorders causing rhabdomyolysis result in mechanical stress on the cell, which in turn leads to cellular membrane injury, cell hypoxia and the release of degradative enzymes, such as phospholipase A_2, and, subsequently, to mitochondrial breakdown and ATP depletion. The ultimate result is a disruption of intracellular ion concentrations and Na/K ATPase, intracellular calcium influx, hyperactivity of calcium-dependent proteolytic enzymes and the generation of oxidative free radicals. The excessive calcium causes persistent contraction of the myofibers. Further damage occurs from a proinflammatory condition that arises from vasoconstriction, hypoxia and neutrophil aggregation, with the production of proteases and additional free radicals, which ultimately leads to cell death. The loss of cell volume regulation and reperfusion injury contribute to muscle cell swelling along with an increase in blood flow. This may subsequently lead to the development of compartment syndrome from an increase in intracompartmental pressure, as well as to hypovolemia. Injured muscles can sequester up to 12 liters of fluid in a few days [13].

Pathophysiology of kidney injury Damage to the cell membrane and the degradation of myofilaments lead to the leakage of intracellular contents, including CK, myoglobin, phosphate and potassium. The release of excessive myoglobin into the plasma overwhelms the capacity of the binding proteins (mainly haptoglobin). This results in myoglobin then being filtered across the glomerulus, causing tubular damage. The pathophysiology of AKI in rhabdomyolysis is likely to be multifactorial, including vasoconstriction, hypovolemia, direct myoglobin toxicity and intraluminal cast formation [14]. Casts result from the binding of myoglobin to Tamm–Horsfall protein, especially in acidic urine. These pigmented casts are found in distal tubules and collecting ducts. Bywaters et al. reported that in acidic urine, myoglobin dissociates into non-toxic (globin) and toxic (ferrihemate) components. Ferrihemate will increase the level of oxidative free radicals, resulting in further damage to the renal parenchyma [13]. Acidosis caused by etiological factors associated with rhabdomyolysis or as a result of AKI and hypovolemia may further contribute to the formation of myoglobin casts. In addition to low urine pH, hyperuricemia may also be a risk factor for AKI (similar to that seen in urate nephropathy) [15]. Also, vasoactive agents, such as platelet activating factor, endothelins and prostaglandin F2α, which may be increased in patients with rhabdomyolysis, cause the vasoconstriction of renal arterioles.

Etiologies

Most of the literature on rhabdomyolysis came from adult studies with limited data from only a few pediatric case series. Rhabdomyolysis can result from a wide variety of disorders, as shown in Fig. 1 and discussed below. While trauma and drugs are the most common causes of rhabdomyolysis in adults (up to 80% of cases), infection and congenital disorders are the most common causes in the pediatric population [6, 10, 11].

Trauma

Rhabdomyolysis was thought to be caused only by trauma until, less than half a century ago, other causes were described. Trauma is still the most common cause in adults. Rhabdomyolysis and its complications are major problems in people injured in disasters, such as earthquakes. It can result from crush injury, compartment syndrome, electrical

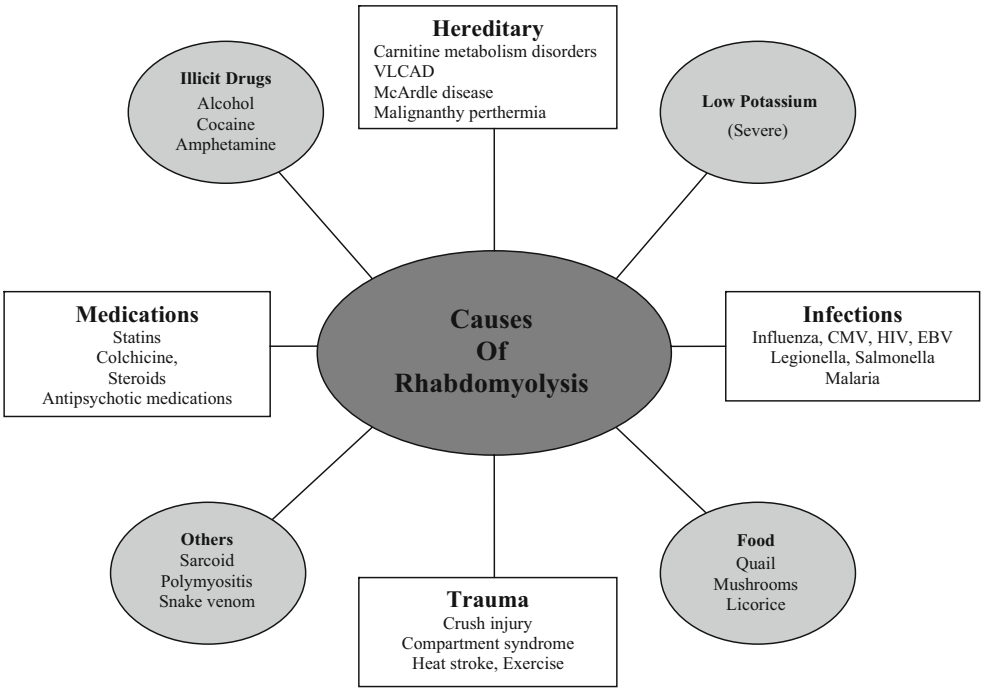

Fig. 1 Causes of rhabdomyolysis. *CMV* Cytomegalovirus, *HIV* human immunodeficiency virus, *EBV* Epstein–Barr virus, *VLCAD* very long chain acyl CoA deficiency

shock or heat stroke. In contrast to high-voltage injuries, rhabdomyolysis is rare in lightning injuries. Rhabdomyolysis, with or without compartment syndrome, can occur after prolonged surgical procedures, such as bariatric surgery [9, 16–23].

Exercise

There are many reported cases of exercise-induced rhabdomyolysis not related to genetic abnormalities, with most being reported among athletes, military recruits and runners [20, 23–27]. Several factors predispose to exercise-induced rhabdomyolysis, such as high humidity, anticholinergic medications, hypokalemia and performance-enhancing drugs. Also, eccentric contractions, which are produced by muscle tension, such as from running downhill, are more likely to cause muscle damage than concentric contractions, which occur with muscle flexion alone. Raver's hematuria has been described in individuals who dance for hours and develop rhabdomyolysis and hematuria, particularly with concomitant ingestion of amphetamines [28]. High altitude is a risk factor for patients with sickle cell anemia. Diseases that cause repetitive or sustained muscle contractions, such as seizures, tetany and delirium tremens, can induce severe muscle damage and lead to rhabdomyolysis [29–31].

Malignant hyperthermia syndrome

This syndrome occurs in individuals with inherited mutations of the sacroplasmic reticulum ryanodine receptor gene (PYR1). In such individuals, a sudden rise in free sacroplasmic calcium, due to the gene mutation, leads to persistent muscle rigidity and rhabdomyolysis. These patients develop skeletal muscle rigidity, hyperventilation and fever when exposed to general anesthesia, especially halothane. Non-anesthetic agents, such as decongestants and gasoline vapors, have also been reported to cause this syndrome [32].

Infection

Many infections are associated with rhabdomyolysis. In adults, infection accounts for about 5% of all cases, but it may be the leading cause of rhabdomyolysis in the pediatric population [11]. Viral infections with influenza A and B, Epstein−Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV; as part of acute retroviral syndrome), bacterial infections with legionella, Group A beta hemolytic streptococci and salmonella and protozoal infections, such as malaria, have been implicated as causes of rhabdomyolysis. Viral infection is one of the most common causes of rhabdomyolysis in children, accounting for more than one third of all cases [11, 33, 34]. Direct viral infection has been implicated in some cases, as in Influenza B, where muscle biopsies show muscle necrosis with interstitial edema and neutrophilic infiltrates [35, 36].

Medications

There are close to 200 medications that have been implicated in the development of rhabdomyolysis [37]. In

adults, drugs account for approximately half of all rhabdomyolysis cases.

Direct muscle damage Direct muscle damage can be caused by statins, [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors]. Statins are more commonly used in adults, but they have also been approved by the Food and Drug Administration for use in children as young as 10 years of age to treat familial hypercholesterolemia. Myalgia is the most common muscle complaint in patients taking statins. There are several case reports of rhabdomyolysis in patients taking HMG-CoA reductase inhibitors, especially with the co-administration of cytochrome P450 (CYP 3A4) inhibitors. Two particularly vulnerable patient populations include transplant patients taking simvastatin in conjunction with cyclosporine and those with liver disease that are prescribed colchicine. Cyclosporine is a potent inhibitor of many membrane transporters, and plasma levels of pravastatin and rosuvastatin are about tenfold higher in transplant patients taking cyclosporine than in control patients. However, cyclosporine does increase fluvastatin concentrations by only two to fourfold, which makes it a relatively safer statin to use in transplant patients [38]. Corticosteroids and HIV medications, such as zidovudine, are also reported to cause rhabdomyolysis [39–43]. Other risk factors associated with statin-induced rhabdomyolysis could be endogenous, such as advanced age, chronic kidney disease, hypothyroidism, McArdle disease, or exogenous factors, including alcohol consumption, excessive exercise and prolonged surgery [5]. Statins can cause a deficiency in coenzyme Q, which is a possible cause of myopathy. Although the risk of serious myopathy from statins is less than 0.1%, the wide use of these drugs makes screening patients for muscle damage, while taking statins, very important.

Indirect muscle damage Illicit drug use is a very important cause of rhabdomyolysis in adults and adolescents. The list includes alcohol (mostly from alcohol withdrawal, including delirium terminus and seizures), cocaine, amphetamine, Ectasy and LSD (lysergic acid diethyl-amide) [44, 45].

Antipsychotic drugs, such as haloperidol, olanzepine, loxapine and risperidone are all associated with rhabdomyolysis. One study found that these medications are the most common cause of rhabdomyolysis in hospitalized patients [46]. Most cases are due to neuroleptic malignant syndromes (NMS), but rhabdomyolysis can occur in the absence of NMS. Muscle breakdown in NMS is likely secondary to excessive heat production by sustained muscle contraction, which can be amplified by sarcolemmal depolarization. Severe cases of serotonergic syndrome, caused by a combination of selective serotonin reuptake inhibitors and monoamine oxidase inhibitors, have been associated with myoglobinuric renal failure. The mechanism mimics that of NMS, but there may also be a component of muscle ischemia [47].

Congenital and genetic conditions

Inherited disorders are important to recognize, especially in children or adults with recurrent rhabdomyolysis.

Exaggerated response to exercise Some individuals are more susceptible to skeletal muscle damage in response to exercise (high responders). The reasons for this are not well understood, but genetic factors have been implicated. There might be an association between this phenomenon and the polymorphisms of two genes. The CK-MM *NcoI* polymorphism is associated with differential CK-MM activity in myocytes, and individuals with the AA genotype may have a sixfold higher risk for an exaggerated CK response to exercise. Some studies suggested that the angiotensin-converting enzyme (ACE) polymorphism may play an important factor as well, as the DD genotype is associated with lower exercise tolerance compared with the ID and II genotypes. Also, the myosin light chain kinase (MLCK) C49T and MLCK C3788A genotypes are thought to be associated with increases in CK in response to exercise (Table 1). The mechanisms by which these genes cause rhabdomyolysis are not known, but researchers are examining several hypotheses. For example, Heled et al. suggested that differential expression of CK-MM may occur, which would then alter the muscle cell. This hypothesis is based on the suggestion that CK-MM gene stability and rate of transcription may be influenced by the localization of the CK-MM polymorphism in the 3-untranslated region, which affects intracellular localization

Table 1 Genes associated with hereditary causes of rhabdomyolysis

Hereditary disorder	Gene
β-Sarcoglycan	*SGCB*
Carnitine palmitoyltransferase II	*CPT2*
Cytochrome (b and c oxidase)	*CYTB, COX*
Familial malignant hyperthermia	*RYR1*
Lactate dehydrogenase	*LDHA*
Myoadenylate deaminase	*AMPDA1*
Myophosphorylase	*PYGM*
Myosin light chain kinase gene mutation	*C49T, C37885A*
Phosphofructokinase	*PFKM*
Phosphoglycerate kinase	*PGK1*
Phosphoglycerate mutase	*PGAMM*
Phosphorylase b kinase	*PHKA1*
Very long chain acyl coenzyme A dehydrogenase	*ACAD9*

of its mRNA. Another theory is that the CK-MM gene location (chromosome 19q13.2–13.3) is in the same region of two other genes associated with muscle diseases and suitability to rhabdomyolysis, namely the myotonic dystrophy disease gene and the RYR1 gene. Detailed studies on the functional linkage between these genes have not yet been reported [48, 49].

Disorders of lipid metabolism (lipodoses) At low exercise intensity, fat is the primary fuel used to sustain exercise. As exercise intensity increases, the rate of fat oxidation increases, reaching a maximum between 48% VO_2 max and 65% VO_2 max. Some studies showed that 48%VO_2 max is the cross-over point of substrate use, where carbohydrates becomes the main source of fuel and its oxidation increases with increasing exercise intensity. Carbohydrates contribute approximately 70% of total substrate oxidation at 85% VO_2 max. In comparison, amino acids contribute only about 2% of total substrate used during intense endurance exercise. For the above reasons, patients with congenital defects of lipid or carbohydrate metabolism are likely to have low exercise tolerance (Fig. 2),

In order for acyl CoA esters to undergo β-oxidation, they need to be *trans*-esterified with carnitine by the action of an outer mitochondrial membrane carnitine palmitoyltransferase I (CPT I) and then transported across the inner mitochondrial membrane, where they are re-esterified to acyl CoA esters by the inner membrane carnitine palmitoyltransferase II (CPT II) and catabolized to acetyl CoA by the acyl-CoA dehydrogenase. Defects in any of these enzymes can lead to lipid myopathies.

1) Disorders of carnitine transport and the carnitine cycle. Carnitine plays an essential role in the transfer of long chain fatty acids across the inner mitochondrial membrane. During fasting, fatty acids are the predominant substrate for energy production.

   a) Primary carnitine deficiency is a rare autosomal recessive disorder due to the lack of carnitine/organic cation transporter (OCTN2), which results in urinary carnitine wasting. Affected patients can have both metabolic and cardiac abnormalities. Some patients are relatively asymptomatic but will have a mild decrease in plasma carnitine levels and elevated

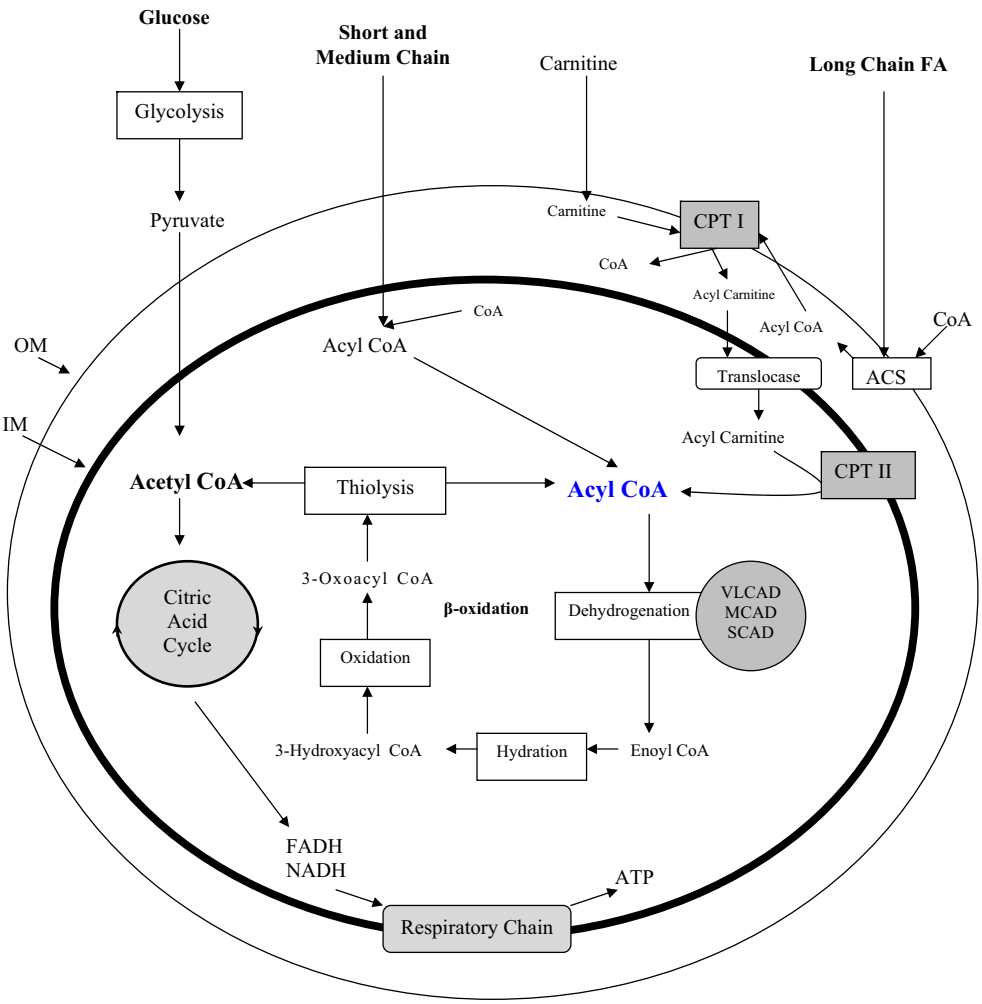

Fig. 2 Energy production by the mitochondria using lipid and carbohydrate substrates. *OM* Outer mitochondrial membrane, *IM* inner mitochondrial membrane, *VLCAD* very long chain acyl-CoA dehydrogenase, *MCAD* medium chain acyl-CoA dehydrogenase, *SCAD* short chain acyl-CoA dehydrogenase, *FADH* flavin adenine dinucleotide, *NADH* reduced nicotinamide adenine dinucleotide, *ACS* acyl CoA synthase, *CPT* carnitine palmitoyltransferase

levels of CK [50]. Acquired carnitine deficiency can result from chronic hemodialysis and sodium valproate and may result in muscle symptoms.

b) Carnitine palmitoyltransferase I (CPT I) deficiency is associated with elevated CK levels in some patients during fasting. Plasma carnitine levels are elevated, and diagnosis is confirmed by CPT I assay in fibroblasts. Children with a severe form of the disease may have developmental delays, but this can be avoided by nighttime feeds and the avoidance of fasting.

c) Carnitine palmitoyltransferase II (CPT II) deficiency is an important metabolic cause of recurrent rhabdomyolysis in children and young adults and is usually triggered by strenuous exercise, prolonged fasting, cold, fever or infection [51]. CPT II is an autosomal recessive disorder that can present in the neonatal period (usually fatal), in childhood or in adults. The infantile form usually presents between 6 and 24 months as episodes of hypoglycemia, cardiomyopathy and arrhythmias. These episodes are usually preceded by fever, infection or fasting. In contrast to patients with phosphorylase and phosphofructokinase deficiency, patients with adult onset CPT II deficiency have a normal rise in lactic acid during muscle exercise. Myoglobinuria occurs in about 80% of cases [52]. Laboratory findings during the episodes include high CK levels and metabolic acidosis; plasma carnitine levels are low, but long chain acylcarnitine levels are elevated. Diagnosis is confirmed by a DNA or enzyme assay. The neonatal form has a very poor response to treatment, while adult onset disease can be controlled with avoiding fasting, limiting exercise and keeping to a high carbohydrate–low fat diet, all of which reduce the abnormal accumulation of long chain acyl CoA and acylcarnitine intermediates. During the acute episodes, the main therapy is glucose infusion in combination with insulin to reduce lipid mobilization [53].

2) Acyl-CoA dehydrogenase deficiency. The acyl-CoA dehydrogenase (ACAD) family of flavoproteins comprised nine known members, five of which are involved in fatty acid oxidation and four in amino acid oxidation. Some of these rare mitochondrial defects that can cause rhabdomyolysis include: long chain 3-hydroxy acyl-coenzyme A dehydrogenase deficiency (LCHAD), very long chain acyl-CoA dehydrogenase (VLCAD) and short-chain acyl-CoA dehydrogenase deficiency (SCAD). There are many clinical similarities between these disorders and disorders of carnitine transport, which suggest that the lack of cellular energy production might be the primary mechanism of disease [54].

a) Long chain 3-hydroxy acyl-coenzyme A dehydrogenase deficiency is caused by a defect in the mitochondrial trifunctional protein (MTP). Acute metabolic crises precipitated by infections usually present with hypoketotic hypoglycemia, cardiomyopathy, hypotonia and hepatomegaly. Some patients present in childhood with myoglobinuria and others as adults with exercise-induced rhabdomyolysis. Diagnosis can be made by assays of fatty acid (palmitic and myristic) oxidation and enzymes (in fibroblasts obtained from skin biopsy).

b) Very long chain acyl-CoA dehydrogenase deficiency is an autosomal recessive disorder with three different phenotypes based on the severity of the disease. Similar to LCHAD deficiency, it impairs the oxidation of dietary and endogenous fatty acids of a long chain length. The accumulation of long chain fatty acid acyl CoA intermediates result in the toxic effects. Infants can present with severe sepsis-like symptoms, hepatomegaly, hypertrophic cardiomyopathy, or coma, and the condition is associated with high mortality. The intermediate phenotype usually presents in infants with hypoglycemia without cardiomyopathy, while the late onset form presents in the second decade of life or later with recurrent rhabdomyolysis with fasting or exertion, i.e. during conditions that require lipolysis. Most of the adult patients have a mild clinical course, especially with lifestyle adjustments. Diagnosis requires high clinical suspicion and can be performed by gas chromatographic analysis of plasma fatty acids, organic acid analysis of the urine and VLCAD enzyme activity and immunohistochemical testing (using VLCAD antibodies) [55, 56].

c) Short chain acyl-coenzyme A dehydrogenase deficiency is an autosomal recessive disorder that prevents short chain fatty acids from being further metabolized in mitochondria. As a result, these short chain fatty acids are not utilized as an energy source during fasting, which can lead to lethargy and hypoglycemia. A SCAD deficiency leads to the accumulation of ethylmalonic acid and butyrylcarnitine in the blood and urine. It can be diagnosed in newborns using tandem mass spectrometry. Infants are usually asymptomatic, which make diagnoses more challenging.

Disorders of glycogen metabolism (glycogenoses) Disorders of glycogenolysis, such as phophorylase kinase deficiency and McArdle disease, are frequently associated with rhabdomyolysis. McArdle disease (glycogen storage disease type 5) is due to mutations in both alleles of the

PYGM gene, which results in the lack of a functional mature protein. It is the most common glycogenosis affecting skeletal muscle, with the resultant accumulation of glycogen in muscle tissue due to myophosphorylase deficiency in type II muscular fibers leading to depletion of ATP and myonecrosis that occurs with exercise. Patients usually have exercise intolerance, myalgias and rhabdomyolysis. It was first described by McArdle in 1951 and can present either in early childhood or later during the second or third decade. Unlike other glycogenoses, it is not fatal. During the first few minutes of strenuous activity, patients develop fatigue, weakness and muscle aches, but a brief rest can improve exercise tolerance (second wind phenomenon). Rhabdomyolysis occurs in up to 50% of patients [57, 58]. Small doses of creatine supplements were shown to improve exercise intolerance in a small randomized trial [59]. Tarui disease (glycogen storage disease type 7) was first described in 1965 and is due to phosphofructokinase-M isoform deficiency; it is characterized by muscle cramps, rhabdomyolysis, myoglobinuria and is often associated with hemolytic anemia and hyperuricemia. The presentation can be very similar to McArdle disease, but carbohydrate intake usually exacerbates exercise intolerance (out of wind phenomenon). Other glycogen metabolism disorders that are associated with rhabdomyolysis are phosphoglycerate mutase and kinase deficiencies, β-enolase deficiency, glycogen synthase deficiency and lactate dehydrogenase deficiency.

Miscellaneous causes Myoadenylate deaminase metabolizes AMP to inosine monophosphate and ammonia during strenuous exercise. Its deficiency is a recessive genetic disorder that affects approximately 1–2% of the populations of European descent. Patients usually develop fatigue and myalgias in response to vigorous exercise [60].

Duchenne's muscular dystrophy is an X-linked recessive disorder due to the absence of dystrophin, a protein that helps keep muscle cells intact. It is a progressive childhood muscle disorder that leads to a marked disability and shortened lifespan. Survival is rare beyond the fourth decade of life. Dystrophin has an important role in the maintenance of the cellular structure and allows signal transduction between the cytoskeleton and extracellular matrix. Its absence leads to calcium accumulation in dystrophic muscle, causing cell damage. It eventually affects all voluntary muscles as well as the heart and diaphragm. The level of CK is markedly elevated with muscle wasting and usually affects the pelvic girdle, with pseudohypertrophy of calf muscles and tongue. Also, it is usually associated with cognitive defects and cardiac involvement (dilated cardiomyopathy and conduction abnormalities) and with restrictive lung disease that usually requires ventilation support. A less severe variant of the disease with a better outcome (Becker dystrophy) starts later in life and is associated with much less cognitive impairment and contracture, although cardiac involvement may be more severe than in patients with Duchenne. Beside the difference in their clinical picture, the two forms can be distinguished using immunoblotting and by differences in dystrophin expression in skeletal muscle [61, 62]. Severe hypokalemia, including inherited diseases that are associated with persistent hypokalemia, such as 11-hydroxylase deficiency, can also predispose to rhabdomyolysis. Potassium mediates vasodilation, which increases the blood flow to muscles during exercise. In addition, hypokalemia depolarizes the muscle cell membrane, affects glycogen synthesis and impairs heat dissipation and responsiveness to catecholamines [27, 63]. Heterozygous mutations in the erythrocyte/muscle isozyme of aldolase are also associated with rhabdomyolysis and hemolytic anemia and are described as distal glycogenoses. Other disorders that can cause rhabdomyolysis in children include status asthmaticus, diabetic ketoacidosis and thyrotoxicosis. Other muscle diseases, such as polymyositis and neurosarcoidosis, can cause rhabdomyolysis, especially in chronically ill patients.

Food and environmental factors

Licorice can cause rhabdomyolysis, likely by inducing hypokalemia from apparent hyperaldosteronism. Ingestions of magic mushrooms and quail are also reported to cause rhabdomyolysis, and toxins, such as the venom of rattlesnakes, hornets and brown recluse spider bites, can cause rhabdomyolysis [64].

Diagnosis

The diagnosis of rhabdomyolysis usually requires a good history intake and a clinical suspicion. Other causes of discolored urine with myalgias need to be considered, especially in the absence of trauma or obvious etiologic causes of rhabdomyolysis. The differential includes—but is not limited to—hemoglobulinuria, porphyria, and patients taking certain drugs, such as vitamin B12, pyridium or rifampin, as well as the ingestion of beet roots.

The diagnosis is highly suspected with an elevated CK level in excess of four to fivefold the upper limit of normal (specifically the CK-MM subtype) and when the urinary dipstick test for blood is positive in the absence of red blood cells. Examining the color of serum can help differentiate between myogloginuria (normal color) and hemoglobinuria (brown or red serum). Other laboratory abnormalities include lactic acidosis, elevated lactate dehydrogenase, hyperkalemia, hyperphosphatemia

and hypocalcemia. The hypocalcemia can be severe in the early phase; however, during recovery, patients may develop rebound hypercalcemia. This can be significant if AKI persists, as these patients often have transient hyperparathyroidism. Hyperuricemia may develop due to the release of purines from damaged muscle cells (Fig. 3).

The diagnosis can be confirmed by quantifying serum or urine myoglobin, but the results may not be known for several days. The rise in serum myoglobin precedes that of CK. The latter usually rises 12 h after the insult and peaks in 2–3 days. The short half life of myoglobin in serum (1–3 h) makes plasma myoglobin levels unreliable, and false negative results may occur based on the timing of measurements [65]. Inflammatory myopathy, such as polymyositis, dermatomyositis and inclusion body myositis, can present with very high CK levels, but not as high as those found in muscle dystrophies, such as Duchenne. Visible myoglobinuria occurs when urinary myoglobin exceeds 250 μg/mL, which corresponds to the destruction of more than 100 g of muscle tissue [66].

If exercise-induced rhabdomyolysis is suspected, further studies may be required, including forearm exercise test (non-ischemic), muscle biopsy and genetic testing. A history of rhabdomyolysis with malignant hyperthermia may be an indication for the genetic testing for the PYR1 mutation and the caffeine contracture test. Inherited abnormalities in lipid metabolism, such as VLCAD, can be diagnosed using a special biochemical analysis of lymphocytes or fibroblasts and molecular analysis of the VLCAD gene. The forearm ischemic test can be helpful in differentiating genetic causes of rhabdomyolysis based on the levels of lactic acid and ammonia before and after exercise (in the setting of ischemia created by inflating the sphygmomanometer cuff to >200 mmHg). In general, patients with suspected metabolic myopathy should undergo muscle biopsy and possible genetic testing (Fig. 4).

Few studies have examined predictors for the development of AKI in patients with rhabdomyolysis. Gabow et al. developed a predictive equation where risk of AKI=0.7 (serum potassium concentration) + 1.1 (serum creatinine concentration) + 0.6 (serum albumin concentration) − 6.6. Other studies showed that potassium, phosphorus, uric acid and calcium levels at the time of initial presentation are independent predictors for the development of AKI. Patients with baseline serum creatinine concentration of <1.7 mg/dL are at very low risk compared to those with a serum creatinine concentration >1.7 mg/dL. Higher CK levels have been shown to be risk factors for AKI [67]. The incidence of AKI is about 19% when peak CK levels are >5000 U/L, but it is only 8% if CK levels are <5000 U/L. However, some studies failed to show a relationship between peak CK levels and the development of AKI [3]. Only 4% of patients with AKI from rhabdomyolysis will require hemodialysis. On the other hand, Sinert et al. reported a complete absence of AKI in their series of 35 rhabdomyolysis patients without metabolic acidosis or hypovolemia.

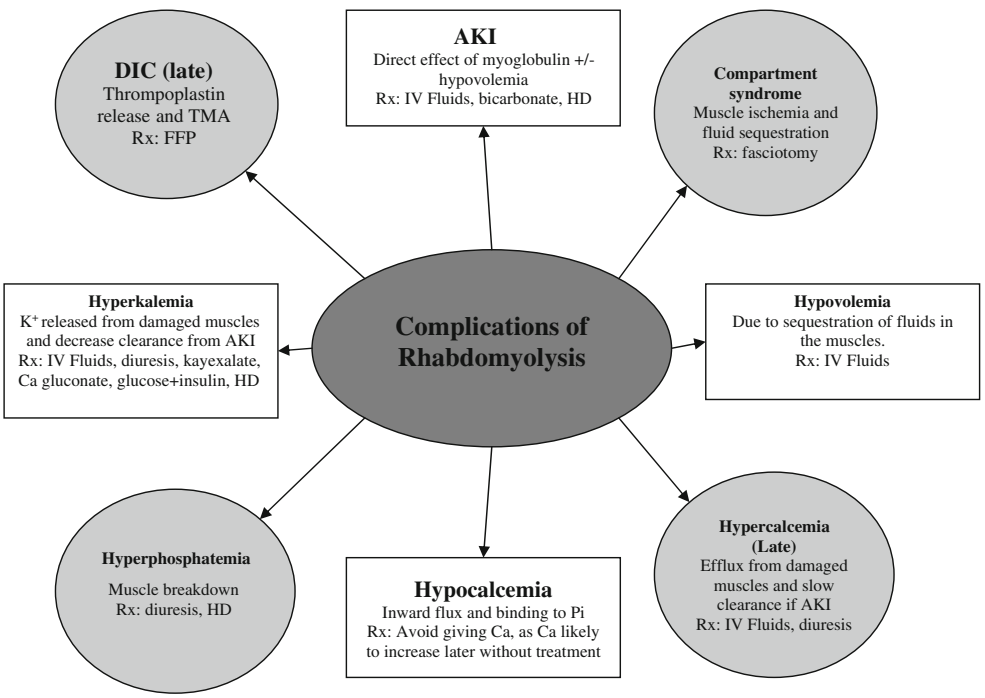

Fig. 3 Complications of rhabdomyolysis. *DIC* Disseminated intravascular coagulation, *TMA* thrombotic microangiopathy, *FFP* fresh frozen plasma, *AKI* acute kidney injury, *HD* hemodialysis, K^+ potassium, *IV* intravenous, *Ca* calcium, *Pi* phosphate, *Rx* treatment

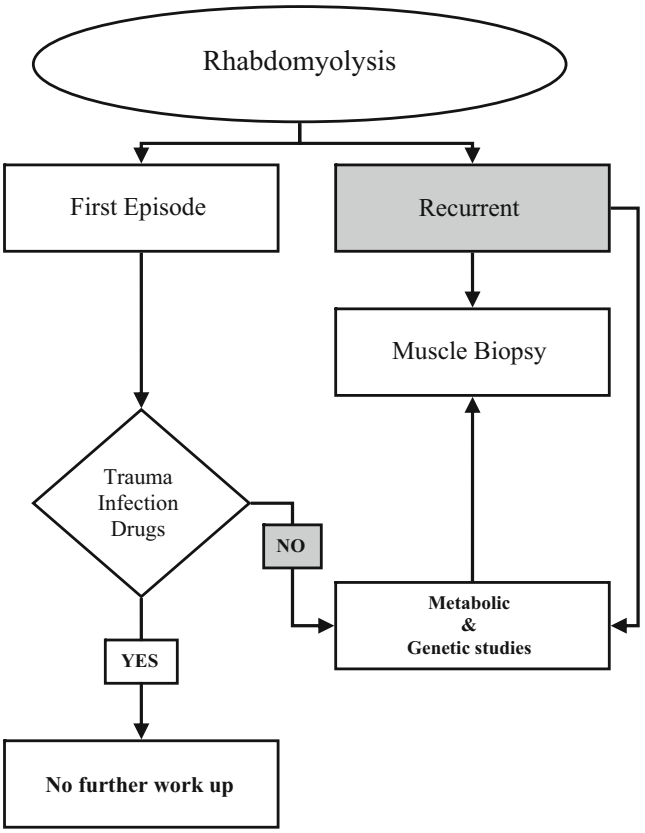

Fig. 4 Evaluation of rhabdomyolysis

Management

Regardless of the underlying etiology, when rhabdomyolysis is suspected from the medical history and preliminary laboratory testing, it is important to initiate early measures to avoid worsening kidney function. This is achieved principally by aggressive hydration. Sequestration of fluids in injured muscles could lead to significant hypovolemia and prerenal azotemia. Therefore, intravenous hydration must start as soon as possible. Better et al. suggest starting saline solution at a rate of 1.5 L/h [68]. Measures to prevent further muscle damage by discontinuing suspected medication should be considered early after ruling out other causes, such as exercise, trauma and drug abuse. The National Lipid Association recommends the discontinuation of statins in patients with intolerable muscle symptoms with or without elevated levels of CK. Once symptoms disappear, the same or a different statin at the same or a lower dose can be restarted to test the reproducibility of symptoms. If symptoms recur with multiple statins and different doses, the initiation of other agents is required [69]. In transplant patients taking statins and cyclosporine, fluvastatin may be the safer drug option compared to pravastatin and rosuvastatin. Early fasciotomy in patients with compartment syndromes is very important in limiting damage to muscles and the kidney. Special attention should be given to electrolyte abnormalities that occur with rhabdomyolysis, and close monitoring is important. Abnormalities may be different in early compared to later stages of rhabdomyolysis, especially if AKI develops. Therefore, initial monitoring in the intensive care unit and invasive hemodynamic monitoring may be initially required in the severely affected patient. Hyperkalemia should be treated with insulin, glucose and sodium bicarbonate. Calcium gluconate should be limited to patients with severe hyperkalemia and hypocalcemia as it may deposit in tissues and result in severe rebound hypercalcemia.

Management and prevention of AKI

Although the pathophysiology of rhabdomyolysis and development of AKI is complicated, current treatment options are limited. The main therapeutic approach remains fluids and hydration, and this treatment usually needs to be aggressive and started early. Intravenous isotonic fluids are used, and most authors recommend a fluid rate that maintains a urine output of at least 200 mL/h until plasma CK levels fall below 1000 U/L. Extracellular fluid volume resuscitation is especially important when hypovolemia and shock exist, which may result from the primary etiology or the sequestration of large amounts of fluid in damaged muscle tissues [68]. Volume expansion enhances the elimination of the heme protein and dilutes out its intaluminal concentration. Studies showed no benefit of diuretics unless signs of volume overload are evident.

Role of bicarbonate and mannitol Most of the evidence supporting the use of mannitol and/or bicarbonate comes from animal studies, and is inconsistent and conflicting. Recommendations for the use of bicarbonate to alkalinize the urine are mostly based on retrospective studies in adults with no supporting data in the literature on pediatric patients [70]. In a study with more than 2000 patients with post-traumatic rhabdomyolysis, Brwon et al. showed that using bicarbonate and mannitol together may be helpful if the CK level is >30,000 U/L. A similar finding was reported in a subgroup analysis carried out by Sharp et al. [71, 72].

Alkalinization of urine may decrease cast formation by inhibiting the formation of ferrihemate, myoglobin casts. Zager et al. showed that at urine pH of 8.0, 78% of exogenous myoglobin load was excreted, while only 32% was excreted when there was an aciduria [2]. Bicarbonate may decrease the risk of hyperkalemia, but it can cause further hypocalcemia by enhancing calcium and phosphate deposition in the tissues.

A mannitol-induced forced osmotic diuresis has both renal and extrarenal effects that may play a role in preventing rhabdomyolysis-associated AKI. In the kidneys,

mannitol-induced forced osmotic diuresis increases both glomerular filtration rate and proximal intratubular urine flow and stimulates the release of prostaglandins E and I. It also stabilizes renal perfusion by increasing intravascular volume and stimulating atrial natriuretic factor. Muscle swelling is decreased and contractility is restored. On the other hand, some studies were unable to show a renoprotective effect of mannitol when used in patients with rhabdomyolysis, and other studies suggested that mannitol can cause AKI, especially at high doses, due to renal vasoconstriction [70]. This resultant renal vasoconstriction may be due to the fact that mannitol diuresis increases sodium reabsorption, which depletes ATP stores due to the increase in energy demands. Also, solvent drag caused by the increase in plasma osmolarity may exacerbate hyperkalemia. Prospective randomized multicenter trials may be needed to determine if bicarbonate and mannitol therapy is of any benefit in patients with elevated CK levels.

Role of hemodialysis As the incidence of AKI in rhabdomyolysis depends on etiology and the severity of the condition, the need for hemodialysis (HD) also varies widely. In one study, HD was required in only 4% of cases [6], while in another study, 8% of patients went on to require HD [3]. One of the indications for HD in these patients was severe hyperkalemia and prolonged oligo-anuric renal failure. Continuous veno-venous hemofiltration may be more effective than HD in removing larger molecular-weight substances, such as myoglobin (17,000 Da) [73]. There is currently no role for plasmapheresis in the treatment of myoglobinuric renal failure.

Management of hereditary rhabdomyolysis

To date, prevention is the main tool in patients with inherited forms of rhabdomyolysis, as well as the avoidance of fasting and strenuous exercise. A low fat diet supplemented with medium even-chain triglycerides, which allow it to be metabolized by mitochondria, independently of carnitine, is the current prescribed treatment of CPT. Some studies have suggested that a triheptanoin diet may be of value. Triheptanoin, medium *odd*-chain fatty acids (precursors of acetyl-CoA and anaplerotic propionyl-CoA) could restore energy production in these patients. Early recognition and prompt treatment of VLCAD deficiency may not only prevent rhabdomyolysis but possibly prevent severe multi-organ involvement and reverse the cardiomyopathy. Severe infantile sepsis-like episodes can be controlled with intravenous glucose, while long-term management should involve frequent meals that are high in carbohydrates, low in long chain triglycerides (palmitate and oleate) and supplemented with medium-chain triglyceride oil, which bypass the block in the oxidation of long-chain fatty acids [27, 56, 74, 75]. Some animal and a few human studies have revealed that calcium channel blockers and dantrolene provide protection from exercise and hyperthermic-induced rhabdomyolysis by blocking cellular calcium influx and calcium release from the sacroplasmic reticulum, respectively.

Future direction

Animal studies examining the role of free-radical scavengers and other interventions to treat ischemia-reperfusion injury are in progress. As we develop a better understanding of the pathophysiology of rhabdomyolysis and myoglobinuric kidney injury as well as genetic linkages to the disease, one would expect more novel therapies to be developed. For example, gene therapy is a promising route to cure metabolic muscle disease. Adenovirus has been used to express and transfer glycosidase, resulting in the correction of abnormal glycogen storage in glycosidase knockout mice [76]. Similar studies have yet to be conducted for lipid myopathy and in humans.

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