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RHABDOMYOLYSIS IN CLINICAL PRACTICE

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ABSTRACT – Rhabdomyolysis is a condition characterized by damage to skeletal muscles and the release of toxic muscle components into the bloodstream, potentially leading to systemic complications affecting mainly the kidneys and the heart. Due to its rarity, only limited evidence is available on the disease, and guidelines and randomized controlled trials on diagnosis, treatment and management are still lacking.

This review summarizes current evidence from the literature on the management of rhabdomyolysis to provide clinicians with an overview of the disease. The review focuses on the pathophysiology of rhabdomyolysis and the different etiological factors, including specifically inherited metabolic myopathies. The review also discusses clinical manifestations and diagnostic clues used to identify rhabdomyolysis, which rely mainly on laboratory testing. Lastly, treatment options are discussed, focusing on acute phase management, which is based on fluid replacement therapy and prevention of renal failure, and the post-acute phase, which consists of rehabilitation and risk prevention measures.

Keywords: Rhabdomyolysis, pathophysiology, diagnosis, inherited metabolic myopathy, acute kidney injury

INTRODUCTION

Rhabdomyolysis is a condition characterized by the breakdown and necrosis of muscle tissue, with consequent leakage of muscle cell content into the bloodstream[1,2]. It typically presents with muscle weakness, pain/myalgia, and local swelling, possibly associated with dark-red color urine[3]. However, severity may vary hugely, from a mild and asymptomatic increase in creatine kinase (CK) to medical emergencies, such as compartment syndrome, intravascular fluid depletion, cardiovascular complications and acute renal failure[3].

The clinical definition of rhabdomyolysis is highly heterogeneous, and no defined diagnostic criteria have been established yet. In addition, many mild cases are underreported, making it difficult to determine the exact global incidence of the disease. Approximately 26,000 cases of rhabdomyolysis are reported annually in the USA[4-6]. Higher prevalence rates have only been reported in certain at-risk populations, including males, individuals under 10 years of age or over 60 years of age, African–Americans, and those with a BMI[1] over 40 kg/m^2 . Overall, given its rarity and the challenge of performing randomized clinical studies, no guidelines are available for treating rhabdomyolysis, and most recommendations come from scattered evidence in the literature[1]. In terms of prognostic factors, there is an absence of well-organized prospective studies. However, the existing evidence from case reports and small retrospective studies indicates that rhabdomyolysis, when promptly and vigorously treated, demonstrates a favorable prognosis[7].

This review aims to provide clinicians with essential updates on the pathophysiology of rhabdomyolysis, diagnostic clues, especially in rhabdomyolysis associated with inherited metabolic diseases, and guidance for its management and treatment.

DEFINITION AND ETIOLOGY

Rhabdomyolysis is most commonly defined by the presence of serum CK levels five-times the upper limit of normal (ULN; >1,000 IU/L)[1]. However, this threshold is not universally recognized, and some physicians may use different CK levels or alternative criteria for diagnosis, including the presence of muscle pain and muscle weakness[1].

Similarly, the etiologic factors underlying rhabdomyolysis are extremely heterogeneous and have been described with alternative classifications, including traumatic/non-traumatic and acquired/inherited (Table 1)[1,8]. Overall, the causes of rhabdomyolysis include trauma, exercise (especially in children), surgery, infections, seizure, drugs (especially in adults) or autoimmune myositis (less common non-traumatic cause)[9-12]. Medications, such as simvastatin, atorvastatin and rosuvastatin, have been reported to be associated with rhabdomyolysis[9], as have recreational drugs and alcohol use[10]. Surgery, especially if requiring lengthy interventions or prolonged immobility, also increases the risk of rhabdomyolysis[11]. In a study that included 475 patients, the most frequent causes of rhabdomyolysis were exogenous toxins (46%), including alcohol and illicit drugs (34%) and medical drugs (11%). Underlying myopathy or muscle metabolic defects were responsible for 10% of cases. Up to 60% of the patients had more than one etiologic factor, and in 7% of the patients, no cause was found[13].

Lastly, inherited diseases, such as metabolic myopathies, characterized by genetic defects in cellular energy metabolism, can lead to muscle weakness, exertional intolerance, and rhabdomyolysis[12].

Table 1. Summary of possible etiologies.

Acquired causes
• Trauma
• Alcohol
• Drugs/Toxin
• Infections
• Surgery
• Prolonged immobility
• Physical excercise
• Electrolyte imbalance
• Malignant hyperthermia
Inherited causes
• Methabolic myopathies
• Dystrophinopathies
• Ryanodine myopathy
• Congenital myopathies
• Limb-girdle muscular dystrophies
• Channelopaties

PATHOPHYSIOLOGY

Regardless of the initial trigger, the pathophysiological cascade of rhabdomyolysis follows a common pathway[1,8]. One of the key events in this pathway is the disruption of intracellular electrolyte balance and myoplasmic calcium overload[1,8]. This is caused by either the destruction of the sarcolemma, the membrane surrounding the skeletal muscle fibers, or by depletion of adenosine triphosphate (ATP): this leads to dysfunction of the ATPase pump, the consequent increase in intracellular Na^+ concentration and activation of the $2Na^+/Ca^{2+}$ exchanger, which ultimately increases calcium influx[14,15].

Excessive intracellular calcium drives the activation of actin–myosin cross-linkage, persistent muscle contraction, and energy depletion[11]. Moreover, elevated cytoplasmic calcium levels activate calci-

um-dependent phospholipases and proteases, such as phospholipase A2 and calpain, promoting the destruction of both cellular and mitochondrial membranes[16]. Lastly, the migration of leukocytes into the damaged muscle stimulates the cascade of cytokines, prostaglandins, and free radicals, further damaging cellular structures, thus perpetrating the electrolyte imbalance and the vicious cycle of cell death[14,15].

As the myocyte degenerates, large quantities of intracellular metabolites (potassium, phosphates and urate) and proteins (myoglobin, CK, aldolase, lactate dehydrogenase, aspartate aminotransferase) are released in the extracellular space and into the bloodstream, leading to potential systemic complications[8,17]. One of the main complications is acute kidney injury (AKI), which is a multifactorial event caused by the combination of hypovolemia, myoglobinuria, and metabolic acidosis[18,19]. Excess myoglobin in the bloodstream can cause direct tubular damage when filtered across the glomerulus, promoting cast formation and tubular obstruction and increased reactive oxygen species production, further damaging renal tubular integrity via lipid peroxidation[20,21].

CLINICAL MANIFESTATIONS

The clinical presentation of rhabdomyolysis is extremely variable, depending on the extent and severity of muscle damage, and can range from an asymptomatic increase in CK levels to life-threatening events, such as AKI and cardiovascular complications[1].

The characteristic triad of rhabdomyolysis includes muscle pain, muscle weakness, and dark-red color urine[1,8]. However, less than 10% of the patients present all of these specific features, and other signs and symptoms may be present, also depending on the disease etiology[1,8]. Patients usually complain of muscle pain, swelling, stiffness, or cramping, especially around the thighs, calves, and lower back[1,8]. Skin changes, such as discoloration and blisters, may be visible due to the ischemic tissue injury[1,8]. Systemic circulation of intracellular muscle components can yield additional general manifestations such as malaise, fever, tachycardia, nausea and vomiting[22,23]. Muscle rigidity, hyperthermia and metabolic acidosis may also occur, especially in drug-induced syndromes associated with rhabdomyolysis[11,24]. Abnormal liver function tests are frequently observed in patients with severe rhabdomyolysis. In some cases (25%), rhabdomyolysis can also lead to acute liver dysfunction. These hepatic derangements are reversible[5,25,26].

Lastly, some patients may report mental issues, either secondary to urea-induced encephalopathy or related to the underlying etiology (e.g., toxic, infection, trauma)[3].

DIAGNOSIS

A thorough evaluation of medical history and physical examination provides important clues to direct the diagnosis of rhabdomyolysis[27]. However, the diagnosis can be confirmed only through laboratory testing revealing elevated levels of CK or other muscle-damage-related enzymes in plasma or higher concentrations of myoglobin in the urine[1,8].

The gold standard is the determination of elevated serum CK levels. Although no specific cut-off has been established, most physicians use a concentration five times the ULN reference range (i.e., 1,000 IU/L)[23]. CK levels are important in the prediction of the likelihood of kidney complications, and levels above 5,000 IU/L are associated with a higher risk of kidney damage[23].

Elevated levels of myoglobin in the urine, also called myoglobinuria, are another sign of rhabdomyolysis. This condition occurs when the release of myoglobin from damaged muscle cells exceeds the plasma protein binding capacity, increasing myoglobin concentration in both the serum (>5.7 nmol/L or >100 µg/L) and in urine (>0.57 nmol/L or >10 µg/L)[15].

Although elevated serum myoglobin and myoglobinuria are reliable indicators for rhabdomyolysis, especially in the early phases of the disease, their practical applicability is limited[15,28]. Firstly, serum myoglobin has a limited half-life (2–4 hours) compared with CK (1.5 days); it increases rapidly after a muscle injury and is quickly cleared through renal excretion, returning to normal levels within 6–8 hours, thus leaving a smaller window of opportunity to detect abnormal levels[15,28]. Myoglobinuria is visible only when the level of myoglobin in the urine exceeds 100 mg/dL, thus making the absence of dark-red color urine insufficient to rule out the diagnosis[29]. Moreover, the urine dipstick test used to detect myoglobinuria also reacts with the globin fragment of hemoglobin, thus limiting the test's specificity[29].

Overall, according to current literature evidence, the diagnosis of mild rhabdomyolysis is based on the presence of acute muscle weakness, myalgia, and swelling combined with a CK value >1,000 IU/L or CK >5 × ULN[2]. The absence of myoglobinuria (either visible or non-visible) should not exclude the diagnosis com-

pletely; conversely, the concomitant presence of visible myoglobinuria and AKI suggest a severe form of rhabdomyolysis[2]. The diagnostic workup should also include an evaluation of potential complications, particularly monitoring renal function for several days after the acute event and determining the underlying condition, which is extremely important for directing treatment beyond the acute phase[2].

RHABDOMYOLYSIS IN INHERITED METABOLIC MYOPATHY

Inherited metabolic myopathies are genetic diseases caused by defects in the enzyme pathways involved in cellular energy metabolism[12]. They can be categorized into three main groups: glycogen storage diseases, fatty acid oxidation defects, and mitochondrial disorders due to respiratory chain impairment[12]. Impairment in cellular energy production leads to variable clinical manifestations, mainly depending on disease onset and the level of residual enzyme activity. Signs and symptoms range from muscle weakness, exercise intolerance, rhabdomyolysis, or even profound multisystem diseases that usually appear in infancy[30].

Given their rarity and the presence of non-specific variable symptoms, the diagnosis is rather challenging[12]. Clinicians usually classify these disorders as either exercise-related, in which patients experience exercise intolerance, cramps, myalgias, and myoglobinuria, or with fixed symptoms, in which patients report frequent muscle weakness associated with systemic manifestations. The former suggests glycogenesis disorder, while the latter usually indicates a defect in fatty acid oxidation, with some exceptions[12]. The occurrence of the "second wind" phenomenon, for example, may indicate the potential presence of McArdle disease; this phenomenon is characterized by an enhancement in exercise tolerance and a decrease in muscle symptoms following a short period of rest during physical activity and is quite typical of patients with glycogenosis type V[31].

Besides various common manifestations of the disease (e.g., muscle weakness, pain, exercise intolerance), specific features in the clinical history and physical examination should be considered to guide the diagnosis[12]. For example, recurrent episodes of myoglobinuria or rhabdomyolysis are suggestive of an inherited metabolic myopathy[3]. Specifically, different types of exercise, fasting, fever, or illnesses can trigger a rhabdomyolysis episode and must be carefully evaluated to reach a differential diagnosis depending on the metabolic pathway primarily involved in the triggering activity[30]. Disorders of fatty acid metabolism usually cause muscle injury and damage after low-intensity or prolonged activity and during periods of fasting or illness, when the main source of energy is through fatty acid β-oxidation. Defects in glycogen metabolism primarily manifest after intense and isometric activity, when muscles rely on anaerobic metabolism and the breakdown of muscle glycogen for energy supply[28]. Lastly, disorders of mitochondrial oxidative phosphorylation present when aerobic metabolic pathways predominate, that is, when ATP is produced via oxidative phosphorylation[28].

Notably, in patients with inherited metabolic myopathy and recurrent rhabdomyolysis, CK levels may return to normal after each event (e.g., in carnitine palmitoyl transferase 2 deficiency) or remain persistently elevated (e.g., in myophosphorylase deficiency)[3].

THERAPEUTIC APPROACH

The first step for successful management of rhabdomyolysis is to identify the underlying cause of muscle damage (traumatic, drug-induced, related to inherited metabolic diseases) to address the emergency phase and to guide long-term treatment[22].

Acute phase

In the acute phase, the main goal is to maintain adequate fluid resuscitation while preserving renal function[22]. This is achieved through immediate and aggressive administration of intravenous fluids, typically isotonic saline, which help maintain adequate renal perfusion and promote the excretion of nephrotoxic compounds[3,22]. According to a systematic review of 27 studies, fluid administration should begin as soon as possible, ideally within 6 hours of the muscle damage, and a urine output of 300 mL/h or more should be targeted[32]. Fluid replacement should be continued until the levels of CK in the plasma decrease to 1,000 IU/L or below[33].

Different saline solutions may be used depending on the causes of rhabdomyolysis. However, the literature evidence on the effectiveness of these options is of low quality overall. Mannitol is commonly added to increase diuresis in patients with a crush injury[8]. It is thought to have multiple beneficial effects, as it acts as a diuretic, increases renal perfusion and excretion of myoglobin, and appears to exert a direct antioxidant effect on renal cells[34,35]. On the other hand, mannitol is associated with adverse events, such as volume overload and hyperosmolality, and, therefore, should be used only in patients with adequate urine output of at least 20 mL/h[8]. Bicarbonate is used to induce alkalinization of the urine, which prevents the precipitation of myoglobin, corrects underlying metabolic acidosis, and reduces the risk of hyperkalemia[8]. However, administration of sodium bicarbonate may also produce paradoxical intracellular acidosis and volume overload[36] and may cause the precipitation of hypocalcemia, triggering tetany and seizures[8].

Beyond fluid resuscitation, specific interventions may be required in the acute phase based on the etiology of rhabdomyolysis. These include discontinuation of any drugs or any other offending agent potentially contributing to muscle damage (e.g., statins or antipsychotics) and decompression surgery in case of muscle injury or compartment syndrome[3]. Compartment syndrome requires emergent fasciotomy[5,37].

Once the patient is under fluid resuscitation, strict monitoring of fluid balance, renal function, and electrolyte levels is essential to prevent dehydration, electrolyte abnormalities, and cardiac and renal complications[3]. Potassium levels should be carefully monitored to prevent hyperkalemia, a condition that is potentially life-threatening when associated with acute renal failure and hypocalcemia[3]. Patients may benefit from intravenous calcium gluconate in case of symptomatic hypocalcemia, such as tetany, seizures, and arrhythmias[8].

Continuous cardiac monitoring is also recommended to detect and manage potential arrhythmias associated with electrolyte abnormalities[3]. Hemodialysis and renal replacement therapy should be introduced in patients with AKI to support kidney function and help remove circulating myoglobin and other toxins. However, this strategy may ultimately not reduce the mortality rate in patients with rhabdomyolysis[38].

Post-acute phase

In the post-acute phase, treatment should focus on promoting muscle recovery and preventing recurrence. Patients can benefit from rehabilitation and physical therapy to regain muscle mass, recover joint function, and prevent long-term complications, such as muscle weakness or contractures. Any underlying condition that caused the initial muscle injury should be addressed to reduce the risk of recurrence. This includes discontinuation of any rhabdomyolysis-inducing drug/agent, modulation of exercise activity, for example, by reducing strenuous exercise and introducing breaks and relaxation, and dietary changes, which may improve symptoms associated with inherited metabolic myopathies[8,39,40].

CONCLUSIONS

Rhabdomyolysis is a rare and complex condition for which only limited evidence is available about diagnosis and management. While the pathophysiology has been overall clarified, the diagnosis is still challenging given the non-specific symptoms (muscle weakness and pain) and the multiple etiologies. High serum CK levels still represent the cornerstone to confirm the diagnosis. However, a careful evaluation of medical history and physical examination provide important clues, especially in patients with inherited metabolic myopathies who may suffer from recurrent rhabdomyolysis episodes.

One of the most important aspects of rhabdomyolysis is the high risk of renal complications that are extremely dangerous and may lead to the death of the patient. This should be addressed in the acute phase through immediate fluid resuscitation, which helps clear out toxic compounds and preserve renal function. Different agents, such as mannitol and bicarbonate, are used in fluid therapy. However, limited evidence shows their effectiveness in improving myoglobin clearance, preventing AKI, and reducing patients' mortality.

Rigorous studies and guidelines need to be developed in the future to better define the criteria for rhabdomyolysis diagnosis and provide further evidence on the effectiveness of different approaches in preventing AKI.

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