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Review article

The syndrome of rhabdomyolysis: Complications and treatment

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Abstract

Rhabdomyolysis is a syndrome of skeletal muscle cell damage that leads to the release of toxic intracellular material into the systemic circulation. The pathogenesis of rhabdomyolysis is based on an increase in free ionized calcium in the cytoplasm. Its main complications include (a) acute renal failure, which is triggered by renal vasoconstriction and ischemia, (b) myoglobin cast formation in the distal convoluted tubules, and (c) direct renal toxic effect of myoglobin on the epithelial cells of proximal convoluted tubules. Other major complications include electrolyte disorders, such as hyperkalemia, which may cause cardiac arrhythmias, metabolic acidosis, hyperphosphatemia, early hypocalcemia, and late hypercalcemia. Compartmental syndrome and disseminated intravascular coagulopathy may also emerge. The management of myoglobinuric acute renal failure includes aggressive fluid administration to restore the hypovolemia and urine alkalization. The concomitant electrolyte and metabolic disorders should also be treated appropriately; hemodialysis should be considered when life-threatening hyperkalemia and metabolic acidosis exist. In the case of compartmental syndrome, it is important to monitor the intracompartmental pressure and to perform fasciotomy, if required. When diagnosed early and if the appropriate treatment is initiated promptly, the complications of rhabdomyolysis are preventable and the syndrome has a good prognosis.

Keywords: Rhabdomyolysis; Acute renal failure; Metabolic acidosis; Electrolyte disturbances; Compartmental syndrome

1. Introduction

Rhabdomyolysis refers to the traumatic, ischemic, pharmaceutical, toxic, metabolic, or infectious skeletal muscle cell damage that influences the integrity of plasma membrane (sarcolemma) and leads to the release of toxic intracellular material into the systemic circulation [1–4]. The causes of rhabdomyolysis are divided into hereditary and acquired ones. The hereditary causes are mainly related to a lack or insufficiency of enzymes that participate in the catabolism of different energy macromolecules (e.g., carbohydrates, lipids) [1]; the most frequent cause in this category is McArdle's disease [5]. The acquired causes are classified as traumatic and non-traumatic. The traumatic ones, such as crush syndrome, accidents, natural disasters, or intense exercise, cause direct muscle injury and rupture of the sarcolemma [6–8]. The non-traumatic causes are the most common ones during peacetime and include alcohol abuse, medicines (e.g., statins, amphetamines, anti-psychotics, diuretics), seizures, and coma [9–15].

Despite the great diversity in the etiology of rhabdomyolysis, the final pathogenetic pathway is common and includes an increase in free ionized calcium in the cytoplasm (sarcoplasm) [3,4,6]. The increased cytoplasmic calcium initiates a complex network of intracellular processes, such as the activation of phospholipase A_2, prolonged contraction of muscle cells, mitochondrial dysfunction, and production of reactive oxygen species, which eventually promote muscle cell damage and the release of various substances (e.g., myoglobin, creatine phosphokinase, potassium, organic acids, and other enzymes and electrolytes) into the systemic circulation, thereby leading to the clinical manifestation of rhabdomyolysis [16–20]. Typically, rhabdomyolysis presents with muscle

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pain, weakness, and reddish-brown urine due to myoglobinuria [21]. Nevertheless, more than half of the patients do not report muscular symptoms. In more severe cases of rhabdomyolysis, general symptoms, such as malaise, fever, tachycardia, nausea, and vomiting, may also occur [22]. The severity of rhabdomyolysis varies from an asymptomatic increase in creatine phosphokinase to heavy complications, such as acute renal failure (ARF), cardiac arrhythmias, compartmental syndrome, and disseminated intravascular coagulopathy [21,23].

In this review, we summarize the existing literature regarding the major complications of rhabdomyolysis, as well as their treatment. An enhanced understanding and awareness of these complications is necessary to enable the clinician to recognize and treat them promptly and successfully.

2. Complications of rhabdomyolysis

2.1. Acute renal failure

Baywaters and Beall [24] first described rhabdomyolysis-induced ARF in 1941 after they followed the progress of four victims who had developed ARF during the London bombardment in 1940. Although the authors attributed the ARF to rhabdomyolysis as a result of compression, they did not reveal the actual pathogenetic mechanism underlying this observation. A few decades later, it was found that the nephrotoxic effect of myoglobin, which is released by the disrupted muscle cells, is responsible for the renal damage [21]. It is estimated that roughly 10–40% of cases of rhabdomyolysis leads to ARF, while 5–15% of ARF cases is attributed to rhabdomyolysis [9,25,26].

Myoglobin plays a dominant role in the pathogenesis of rhabdomyolysis-induced ARF. The basic mechanisms involved in the pathophysiology of myoglobinuric ARF are presented in Fig. 1 and include [27–29]: (a) renal constriction and ischemia, (b) myoglobin cast formation in the distal convoluted tubules, and (c) direct cytotoxic action of myoglobin on the epithelial cells of the proximal convoluted tubules. The coexisting hypovolemia and acidic pH of urine, due to the metabolic acidosis, are regulating factors that intensify the nephrotoxic action of myoglobin [29–31].

2.1.1. Renal vasoconstriction and ischemia

The necrosis of muscular tissue creates a “third space” in which a large amount of intravascular fluid accumulates and causes hypovolemia [32]. The hypovolemia activates the sympathetic nervous system and the rennin–angiotensin–aldosterone system, increases the production of vasoconstricting molecules (e.g., endothelin I, vasopressin), and inhibits the production of vasodilatory prostaglandins [13,20,33–35]. Muscle damage provokes the release of endotoxins and cytokines into the systemic circulation, which also promote vasoconstriction [36–38], whereas the myoglobin that is released by the dead muscle cells degrades nitric oxide (NO), which is the most potent endogenous vasodilatory factor [39–41]. Ultimately, the abovementioned processes lead to renal vasoconstriction, renal ischemia and, subsequently, decreased ATP production due to decreased oxygen supply in the renal tubular cells.

2.1.2. Myoglobin cast formation

The presence of myoglobin casts inside the distal convoluted tubules constitutes a common finding in myoglobinuric ARF. Depletion of ATP causes epithelial cell necrosis, accumulation of dead cells in the tubular lumen, and subsequent precipitation of myoglobin and creation of casts [32,42,43]. The formation of these casts is dependent on the concentration of filtered myoglobin in the preurine. The larger the extent of muscular damage, the higher the concentration of myoglobin in the serum and, consequently, the amount of myoglobin that is filtered at the renal glomeruli [44]. An increased concentration of myoglobin in the preurine, in combination with an acidic pH, enhances the

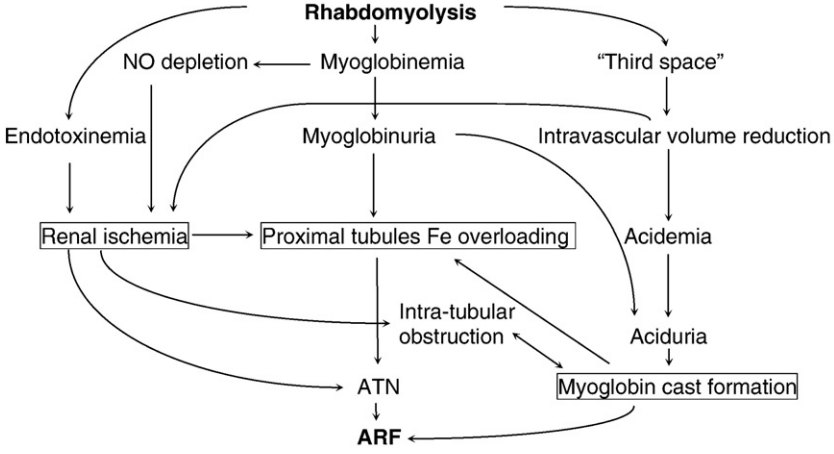

Fig. 1. Renal ischemia, formation of myoglobin casts at the distal convoluted tubules, and the cytotoxic effect of iron (Fe) on the epithelial cells of the proximal convoluted tubules are the principal pathogenetic mechanisms of myoglobinuric acute renal failure (ARF). Coexisting hypovolemia and acidic urine pH further intensify these processes. Acute renal failure is induced by the combination of a decreased oxygen supply at the tubular cells, tubular obstruction, and acute tubular necrosis (ATN). NO, nitric oxide.

accumulation of myoglobin inside the distal convoluted tubules, resulting in myoglobin cast formation [20,43]. Obstruction of distal convoluted tubules by myoglobin casts reduces blood flow and glomerular filtration rate, thereby promoting the accumulation and aggregation of necrotic epithelial cells and proteins and the creation of casts [28].

2.1.3. Direct cytotoxic effect of myoglobin

Besides the formation of casts, myoglobin exerts a direct cytotoxic effect through enhancement of local oxidative stress in the tubular cells of the proximal convoluted tubules [32,45]. Once the concentration of myoglobin that is filtered at the glomerulus exceeds the normal level, the tubular cells of the proximal convoluted tubules increase their reabsorbing capacity in order to limit the excretion of myoglobin into the urine and to protect the kidney from its nephrotoxic effect. The increased reabsorption of myoglobin through endocytosis and its subsequent intracellular degradation to proteins, heme and iron, which mainly occurs at a urine pH below 5.6 [45], leads to free iron overloading of tubular cells. Free iron is an oxidative metal that either facilitates the production of free oxygen radicals ($Fe^{2+}+H_2O_2 \rightarrow Fe^{3+}+OH^-+OH^{\cdot}$) or acts as a free radical by itself [46–49]. The oxidative stress generated in the cytoplasm of tubular cells promotes the peroxidation of lipids, proteins, and DNA, leading to acute tubular necrosis (ATN) [45,50,51]. Heme itself can also enhance cellular oxidative stress [52,53]. ATP reduction further facilitates the toxic effect of myoglobin on the epithelial cells of the proximal convoluted tubules as it causes morphologic and functional changes in the cells, which alter membrane permeability, allowing heme to enter into the cell [28,37]. On the other hand, the distal tubule obstruction caused by the myoglobin casts increases the intra-tubular concentration of nephrotoxic myoglobin and its reabsorption by the tubular cells of the proximal convoluted tubules and intensifies ATN.

2.1.4. Other mechanisms

In the setting of acidic pH in blood and urine, hyperuricemia provokes the deposition of uric acid crystals in the lumen of distal convoluted tubules, intensifying tubular obstruction [21,32]. Also, the release of tissue thromboplastin from the dead muscle cells triggers the cascade of disseminated intravascular coagulopathy and results in the formation of multiple microthrombi within the renal parenchyma and onset of renal ischemia [54].

2.2. Electrolyte disorders and metabolic acidosis

Hyperkalemia, which is defined as a potassium level greater than 5.0 mEq/L (normal range: 3.5–5.0 mEq/L), causes serious cardiac arrhythmias that may lead to cardiac arrest [55,56]. Ninety-eight percent of potassium is in the intracellular space, whereas 60–70% of the total cellular mass of the human body consists of skeletal muscle cells; consequently, even an acute necrosis of only 100 g of muscular mass could increase serum potassium by 1.0 mEq/L [4]. Hyperkalemia is further aggravated by metabolic acidosis induced by the release of various organic acids (e.g., lactic acid, uric acid) from the disrupted muscle cells [21,57,58]. The hypocalcemia that occurs in the initial stages of rhabdomyolysis further enhances the cardiotoxic effect of potassium [20]. Therefore, the cardiotoxic potential of hyperkalemia should always be considered in the setting of coexisting metabolic acidosis and decreased calcium levels [21]. Hyperkalemia lower than 6.0 mEq/L is usually asymptomatic, whereas levels of potassium above 6.0 mEq/L require urgent treatment. Electrocardiographic follow-up is mandatory for the diagnosis of hyperkalemia: acute, peaked T waves, decreased QT interval and, in more severe hyperkalemia, low P waves, extension of QRS interval, and ventricular arrhythmias, are the most frequent electrocardiographic findings.

Furthermore, during the destruction of muscle cells, the release of inorganic phosphorus into the plasma causes hyperphosphatemia [22,58] and subsequent hypocalcemia through deposition of calcium phosphate onto the destroyed muscle cells and other tissues [32]. Inhibition of kidney 1a-hydroxylase, which results in downregulation of the production of the active form of vitamin D [$1,25(OH)_2D_3$], can further promote hypocalcemia [14]. However, in the course of rhabdomyolysis, the calcium that is entrapped in the cytoplasm of muscle cells is released back into the plasma after their destruction, resulting in late hypercalcemia [59,60].

2.3. Compartmental syndrome

Compartmental syndrome is not a rare finding in rhabdomyolysis [2,9]. Most skeletal muscles are enfolded in confined, inflexible compartments created by bones, fascia, and other structures. Compartmental syndrome develops more often in the compartments of the extremities, such as the anterior compartment (containing the biceps-brachialis muscle) and the posterior compartment (containing the triceps muscle) of the upper arm, the volar compartment (wrist and finger flexors) and dorsal compartment (wrist and finger extensors) of the forearm, the three gluteal compartments, the anterior and posterior compartments of the thigh, and the four compartments of the lower leg [61,62]. The impairment of muscle cells during rhabdomyolysis and the massive influx of calcium and sodium promote the accumulation of large amounts of extracellular fluid into the cells, resulting in the formation of local edema and an increase in intramuscular pressure [8,62]. The increased intramuscular pressure impedes blood perfusion of the region as well as the venous return of the blood, thereby intensifying the local edema [8]. Furthermore, the local ischemia increases the permeability of the capillaries, thus worsening the edema and establishing a self-perpetuating vicious cycle [43]. The clinical symptoms of compartmental syndrome include local pallor and pain, weakening or complete absence of pulse, and sensory and motor disturbances in the case of severe ischemia [8,20].

2.4. Disseminated intravascular coagulopathy

The release of various prothrombotic substances (mainly thromboplastin) from the destroyed muscle cells activates the coagulation cascade and triggers the syndrome of disseminated intravascular coagulopathy, which is usually asymptomatic [55,56,63]. Seldom does the insult of respiratory muscles, especially in severe forms of rhabdomyolysis, lead to ARF [20,64].

3. Management of rhabdomyolysis

The major therapeutic interventions in rhabdomyolysis are conservative and include treatment of the underlying cause, prevention of ARF, early correction of potentially lethal electrolyte disorders (e.g., severe hyperkalemia), treatment of metabolic acidosis, and management of other coexisting complications (Table 1). Upon failure of conservative treatment and onset of ARF, patients should undergo hemodialysis.

3.1. General measures

Patients should be encouraged to report to their care provider every inexplicable muscle pain, sensitivity, or weakness, especially if it is accompanied by fever or fatigue. On the other hand, the care provider must be aware that early recognition of the symptoms of rhabdomyolysis constitutes the cornerstone in the diagnosis of the syndrome.

3.2. Prevention of ARF

3.2.1. Fluid replacement

According to experimental and clinical data, early (i.e., before the formation of casts, increased endocytosis of myoglobin from the epithelial cells, and onset of ATN) intravascular volume expansion by intravenous administration of NaCl 0.9% is crucial for the prevention of myoglobinuric ARF as it increases renal blood flow and, consequently, glomerular filtration and urination [32]. The pace of fluid replacement is dependent on the severity of myoglobinuria; the treatment objective is to achieve at least 300 ml/h urine excretion [64]. Early recognition of the onset of ATN is essential as it may prevent excessive administration of crystalloid and other fluids that can lead to non-cardiac pulmonary edema [65].

Table 1
Management of myoglobinuric acute renal failure and other complications of rhabdomyolysis

1. General preventive measures
2. Prevention of acute renal failure
a. Fluid replacement
b. Alkaline diuresis
3. Correction of electrolyte disorders (e.g., hyperkalemia) and metabolic acidosis
4. Hemodialysis
5. Treatment of other complications

3.2.2. Urine alkalization

Alkalization of urine is achieved through intravenous administration of sodium bicarbonate ($NaHCO_3$) and appears to be particularly effective in the prevention of ARF [6,32]. The alkaline pH of urine increases the solubility of myoglobin and uric acid and limits the formation of myoglobin casts and uric acid crystals, respectively, while it impedes the degradation of myoglobin into heme and free iron and the accompanying nephrotoxic effect [13,48]. In addition, $NaHCO_3$ corrects the metabolic acidosis and, subsequently, hyperkalemia. The treatment objective of urine alkalization is to reach a urine pH above 6.5 and a serum pH between 7.40 and 7.45 [21].

3.2.3. Diuresis

After hypovolemia is corrected and satisfactory hourly excretion of urine is achieved, the patient should be subjected to forced diuresis, which is achieved through intravenous administration of mannitol and/or one of Henle's loop diuretics, such as furosemide or bumetanide [28,34]. Mannitol is an osmolar diuretic that acts through the following mechanisms [7,54]: (a) provokes vasodilation on the renal parenchyma, improving renal perfusion and glomerular filtering; (b) acts on the proximal convoluted tubules and contributes to the excretion of myoglobin, heme, and iron, minimizing the probability of myoglobin cast formation and its direct cytotoxic effect on epithelial cells; and (c) exerts antioxidative action, thereby decreasing the oxidative stress in the tubular cells. Nevertheless, recent studies have shown that administration of NaCl 0.9% in combination with mannitol is not more effective in the prevention of ARF than the administration of NaCl 0.9% alone. Hence, there is strong skepticism regarding the need for mannitol administration in rhabdomyolysis [66,67]. However, it is considered beneficial when there is suspicion of compartmental syndrome [32].

Furosemide, which causes more intense diuresis, thereby preventing the accumulation of myoglobin in distal convoluted tubules, has also been used in myoglobinuric ARF. However, it has the disadvantage of producing low pH urine [23]. Furthermore, studies have not shown any advantage of the administration of Henle's loop diuretics in patients with ARF, and their contribution to the treatment of ARF remains uncertain [34].

3.2.4. Prevention of nephrotoxicity

Avoidance of exposure to nephrotoxic substances, such as non-steroidal anti-inflammatory drugs, nephrotoxic antibiotics, and radiocontrast media, is essential for the recovery of patients presenting with rhabdomyolysis [68]. Studies have shown that the administration of antioxidant substances, such as desferrioxamine, a chelating agent that binds nephrotoxic free iron, glutathione, and vitamin E, may protect the renal epithelium from the toxic effect of myoglobin

[45,66,69]. Allopurinol may also act beneficially, as it restricts the production of uric acid crystals [23]. Dantrolene, which blocks calcium channels in the sarcoplasmic reticulum, has also been proposed for the treatment of rhabdomyolysis [70].

3.3. Treatment of electrolyte disorders and metabolic acidosis

3.3.1. Hyperkalemia

When the level of potassium exceeds 6.0 mEq/L, urgent treatment is needed. Intravenous administration of glucose and insulin solution (12–14 IU of insulin in 1000 ml dextrose 5%) or NaHCO3 (50–100 nmol daily) can restore the normal levels of intracellular potassium [71]. Since both approaches have a temporary effect, especially when ARF is well established, they should be accompanied by more effective therapeutic strategies, such as per os or per anus administration of sorbitol solution, which contains the cation-exchange resin disodium polysterene sulphonate that binds the excess potassium in the intestines [23,72]. Great caution is needed with medications that have negative inotropic, antihypertensive, or hyperkalemic properties, such as angiotensin-converting enzyme inhibitors, calcium channel blockers, and β-blockers [7]. The administration of calcium chloride or calcium gluconate should be avoided unless it is absolutely necessary, e.g., in the case of lethal cardiac arrhythmias [72]. Finally, hemodialysis, which constitutes the ultimate solution, is recommended only when life-threatening hyperkalemia emerges [9,72].

3.3.2. Metabolic acidosis

It is not recommended to treat metabolic acidosis unless the concentration of serum bicarbonate is lower than 15 nmol/L or the blood pH is lower than 7.2 [32,73]. In such a case, the correction of acidosis is achieved through intravenous administration of $NaHCO_3$, and, upon failure of conservative treatment, with hemodialysis. Following $NaHCO_3$ administration, the patient should be watched for the emergence of possible complications, such as hypervolemia, metabolic alkalosis, hypokalemia, or hypocalcemia.

3.3.3. Hypocalcemia

Normally, hypocalcemia is automatically corrected and no intervention is required [74]. The administration of calcium chloride or calcium gluconate would intensify the accumulation of calcium in the muscular tissue and consequently reinforce the mechanism of rhabdomyolysis [32]. However, calcium should be administered in cases of severe hyperkalemia (potassium > 6.0 mEq/L) associated with potentially lethal cardiac arrhythmias or intense muscular convulsions [71,75].

3.3.4. Hyperphosphatemia

Correction of hyperphosphatemia is achieved by per os administration of agents that bind phosphorus, such as calcium carbonate or calcium hydroxide [71]. Along with hyperphosphatemia, hypocalcemia is also regulated [74].

3.4. Hemodialysis

The indications for hemodialysis include severe and resistant hyperkalemia, an abrupt increase in potassium levels, persistent metabolic acidosis, and ongoing ARF despite conservative treatment [2,68,72].

3.5. Management of compartmental syndrome

The intra-compartmental pressure should be monitored either invasively, with the use of a special catheter, or non-invasively, with Doppler ultrasound, in order to avoid potential infections [61]. When the intra-compartmental pressure exceeds 40 mm Hg, direct surgical decompression with fasciotomy should be performed in order to avoid necrosis of the region and subsequent amputation [2,43]. Intravenous administration of mannitol also reduces the intra-compartmental pressure [21].

3.6. Management of disseminated intravascular coagulopathy

The treatment of disseminated intravascular coagulopathy is mainly supportive and the overall treatment for rhabdomyolysis is the essential treatment for disseminated intravascular coagulopathy. Nevertheless, in cases of severe hemorrhagic predisposition, the administration of fresh frozen plasma is required [13].

4. Prognosis of rhabdomyolysis

Acute renal failure and hyperkalemia are the major complications that worsen the prognosis of rhabdomyolysis and require special attention. However, in most cases, ARF is completely reversible [55,75]. Due to the fact that rhabdomyolysis is a rather rare syndrome and that few studies with large series of patients exist, it is difficult to reveal the true prognosis of the syndrome and its complications. Patients with severe injury who develop rhabdomyolysis-induced ARF have a mortality of approximately 20%, and this percentage increases in patients with multiple organ failure syndrome [55]. According to some clinical series, the mortality rate in patients who develop ARF ranges from 7% to 80% [43]. Dialysis is required in about 85% of patients with oliguric ARF and in 30% of patients with non-oliguric ARF, whereas the mortality rate in patients with ARF who require dialysis is between 50% and 80% [65,68].

5. Conclusions

Rhabdomyolysis is a rather rare syndrome with serious potential complications. Although the prognosis of the syndrome is generally good, complications such as ARF and hyperkalemia are accompanied by high mortality. With regard to

treatment, it is crucial that there is prompt and aggressive fluid replacement in combination with urine alkalization and close clinical follow-up of the patient. As rhabdomyolysis is the cause of ARF in a considerable percentage of cases, physicians should be well informed and prepared to recognize the signs of the syndrome in order to provide immediate and proper treatment.

6. Learning points

- Rhabdomyolysis is a syndrome of skeletal muscle cell damage that leads to the release of toxic intracellular material into the systemic circulation.
- The main complications of rhabdomyolysis include acute renal failure, electrolyte disorders such as hyperkalemia, hyperphosphatemia, early hypocalcemia, and late hypercalcemia, metabolic acidosis, compartmental syndrome, and disseminated intravascular coagulopathy.
- The management of myoglobinuric acute renal failure includes aggressive fluid administration to restore the hypovolemia and urine alkalization.
- The concomitant electrolyte and metabolic disorders should also be treated appropriately, whereas hemodialysis should be considered only when life-threatening hyperkalemia and metabolic acidosis emerge.
- In the case of compartmental syndrome, it is important to monitor the intra-compartmental pressure and to perform fasciotomy, if required.
- When there is an early diagnosis and prompt initiation of the appropriate treatment, the complications of rhabdomyolysis are preventable and the syndrome has a good prognosis.

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