

Review Article

Rhabdomyolysis and its pathogenesis

Mei-hua Zhang

Department of Pharmacy, First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou 310006, China

Corresponding Author: Mei-hua Zhang, Email: pharmacistzhang@yahoo.com.cn

BACKGROUND: Rhabdomyolysis may cause severe damage to the human body because of acute renal failure, fatal heart rhythm disturbances, hypovolemic shock, disturbances of electrolyte balance, metabolic acidosis, hyperthermia, disseminated intravascular coagulation, etc. Drugs and toxins are the most common factors for the disease. This article aimed to review the prognosis of rhabdomyolysis.

DATA SOURCES: Based on the reported studies of cell and molecular biology, we reviewed the clinical presentations, laboratory findings, and mechanisms of rhabdomyolysis in the Pubmed.

RESULTS: The clinical symptoms of rhabdomyolysis were dependent on the severity of the condition and whether kidney failure develops. Since the necrosis and dissolution of muscle cells, entocytes such as myoglobin, creatine phosphokinase (CPK), electrolytes, proteins and non-protein substances were released into the plasma, the detection of the entocytes may contribute to the early diagnosis of rhabdomyolysis.

CONCLUSION: Despite the etiology of the disease is multifactorial, the potential causes of rhabdomyolysis share the same pathophysiological pathway involving an increase in intracellular calcium.

KEY WORDS: Rhabdomyolysis; Etiology; Pathophysiological pathway

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INTRODUCTION

Rhabdomyolysis is a condition causing damage to skeletal muscle tissue rapidly. Breakdown products of damaged muscle cells are released into the bloodstream. Laboratory tests have shown that serum creatine phosphokinase (CPK) is elevated in cases of rhabdomyolysis and is accompanied with the high level of serum myoglobin (Mb).^[1] Rhabdomyolysis can cause serious body damage via several mechanisms such as acute renal failure, fatal heart rhythm disturbances, hypovolemic shock, disturbances of electrolyte balance, metabolic acidosis, hyperthermia, disseminated intravascular coagulation, etc. Muscle fiber necrosis may occur as a primary disorder related to inherited or structural abnormalities of muscle cells. In most cases, the necrosis is secondary to an infection, drugs, toxins, an injury, or another external cause.^[2] Drugs and toxins, however, are the most common causes.^[3] Based on the

studies of cell and molecular biology, this article aimed to review the prognosis of rhabdomyolysis.

Clinical presentations

Although the final diagnosis of rhabdomyolysis is mainly dependent on the laboratory test, we should pay more attention to its clinical presentations. The symptoms of rhabdomyolysis depend on the severity of the condition and whether kidney failure develops. Mild forms of rhabdomyolysis may not cause any muscle symptoms, and its diagnosis is based on abnormal results of blood tests and other problems. Severe rhabdomyolysis is characterized by pain, tenderness, weakness and swelling of the affected muscles. If the swelling is very rapid, as it happens after someone is released from a collapsed building; the movement of fluid from the bloodstream into damaged muscle

may cause low blood pressure and shock. Other symptoms are nonspecific and result either from the consequences of muscle tissue breakdown or from the condition that led to the muscle breakdown. Release of the components of muscle tissue into the bloodstream causes disturbances in electrolytes, which can lead to nausea, vomiting, confusion, coma or abnormal heart rate and rhythm. The urine may be dark, often described as "tea-colored", due to the presence of myoglobin. Damage to the kidneys may give rise to decreased or absent urine production, usually 12 to 24 hours after the initial muscle damage.^[4]

Swelling of the damaged muscle occasionally leads to compartment syndrome, i.e. compression of surrounding tissues, such as nerves and blood vessels, in the same fascial compartment, leading to the loss of blood supply and damage or loss of function in part of the body supplied by these structures. Symptoms of this complication include pain or reduced sensation in the affected limb.^[5] A second recognized complication is disseminated intravascular coagulation (DIC), a severe disruption in blood clotting that may lead to uncontrollable bleeding.^[5]

Laboratory findings

Because of the necrosis and dissolution of muscle cells, entocytes, such as myoglobin (Mb), CPK, electrolytes, protein and non-protein substances, are released into the plasma. Thus the detection of these entocytes may be helpful in the early diagnosis of rhabdomyolysis.

Myoglobin is composed of globin (a polypeptide chain of 135 amino acids) and a molecule of heme. The molecular weight of myoglobin is approximately 18 kD, one-fourth of hemoglobin.^[6] During rhabdomyolysis, a portion of the myoglobin from skeletal muscle cells enters the plasma. The low binding affinity of serum for myoglobin and the small molecular weight of myoglobin contribute to the increased filtering of the molecule. When the concentration of myoglobin in the preurine exceeds the reabsorbing capacity of glomerular cells, an excessive amount of myoglobulin appears in the urine. The half-life of myoglobin is particularly short, about 2-3 hours. In rhabdomyolysis, the level of myoglobin in the serum increases within 1-3 hours, peaks within 8-12 hours, and then returns to normal within 24 hours after the onset of the injury. Thus, the detection of myoglobin in the blood or urine is specific for the diagnosis of rhabdomyolysis. This is helpful in

the early diagnosis of rhabdomyolysis (i.e., within the first 24 hours).^[7]

Increased level of serum CPK is a marker for the diagnosis of rhabdomyolysis. CPK is active in skeletal muscles, and catalyzes the transportation of one phosphate group from creatinine (CP) to ADP, resulting in ATP and creatinine (C).^[8] There are three isoenzymes of CPK: muscle-type creatine phosphokinase (CPK-MM), myocardial isoenzyme of creatine phosphokinase (CPK-MB), and brain-type creatine phosphokinase (CPK-BB). CPK-MM is mainly found in skeletal muscles, but it is less in the myocardium; CPK-MB is mainly seen in the myocardium; CPK-BB is observed in the brain and kidneys. CPK-MM is often increased in rhabdomyolysis.^[8] CPK elevates in the first 12 hours after the onset of rhabdomyolysis, peaks within the first 3 days, and returns to the baseline level at 3-5 days after the injury. The half-life of CPK is 1.5 days. Therefore, CPK and more specifically CPK-MM isoenzyme is a more reliable marker than myoglobin in the diagnosis of muscular damage because it remains at high levels for a longer period compared to serum myoglobin.

During rhabdomyolysis, electrolyte imbalance and hyperkalemia develop. Whereas, hyperkalemia is aggravated by coexistent metabolic acidosis and renal dysfunction, thus causing fatal ventricular arrhythmias.^[6] Therefore, some clinical risk factors can be avoided in advance by observation of changes of serum potassium.^[9]

During the disruption of muscle cells, inorganic and organic phosphoric components are dissolved and a large amount of inorganic phosphorus is released into the plasma, leading to hyperphosphatemia. Hyperphosphatemia causes the deposition of calcium phosphate on the destroyed muscle cells and other tissues, resulting in early hypocalcemia during rhabdomyolysis. During cellular necrosis, calcium, initially combined with muscle cells, is released back into the plasma. Following combination with the secondary hyperparathyroidism that takes place because of early hypocalcemia and high levels of vitamin D (produced in great quantities by the glomerular cells), late hypercalcemia occurs.

In addition, hyperuricemia is observed in rhabdomyolysis. Increased levels of carbonic anhydrase III, heavy-chain myosin fragment and other proteases [e.g. such as lactate dehydrogenase, aspartate aminotransferase], are commonly seen in rhabdomyolysis. Hypoalbuminemia, anemia, and contraction of intravascular volume can also be used for the diagnosis of rhabdomyolysis.

Mechanisms of rhabdomyolysis

Etiology of rhabdomyolysis

Balance of intracellular calcium

The concentration of free ionized calcium in the extracellular space (Ca^{2+}) is 10 000 times higher than that in the intracellular space. Hence, minimal changes of the Ca^{2+} permeability in the cellular membrane may result in significant changes in its intracellular concentration and cause unfavorable consequences for the functional integrity of the cell,^[10] which has to maintain the balance of intracellular calcium within the normal range. For this purpose, it is equipped with a group of special regulatory proteins including: non-membrane proteins soluble in the cytoplasm, and transmembrane proteins as regulators of calcium concentration.^[10] The transmembrane proteins consist of a series of carrier proteins located either at the plasma membrane of the muscle cell (sarcolemma) or at the membranes of intracellular organelles, notably the sarcoplasmic reticulum and mitochondria. The plasma membrane carrier proteins include Ca^{2+} channels, $2\text{Na}^+/\text{Ca}^{2+}$ exchanger, and Ca^{2+} ATPase pump. The Ca^{2+} channels and the $2\text{Na}^+/\text{Ca}^{2+}$ exchanger facilitate the energy-consuming entrance of Ca^{2+} into the cytoplasm, whereas the Ca^{2+} ATPase pump facilitates the energy-consuming transportation of Ca^{2+} to the extracellular space.^[10] In the sarcoplasmic reticulum, the Ca^{2+} ATPase pump is responsible for the entrance of Ca^{2+} .^[11] The Ca^{2+} is brought into the mitochondria with the Ca^{2+} uniporter, and the release of Ca^{2+} into the cytoplasm is primarily accomplished by the $2\text{Na}^+/\text{Ca}^{2+}$ exchanger. Despite the fact that the causes of rhabdomyolysis are numerous, the final pathogenetic pathway is commonly characterized by an increase in free ionized calcium in the cytoplasm. The increased Ca^{2+} initiates a chain of downstream reactions that eventually lead to the destruction of the muscle cell.

Causes of increased concentration of intracellular calcium

The major causes of increased concentration of intracellular calcium share a common pathogenetic basis involving either energy depletion in the muscle cell or (sarcolemma) rupture of the plasma membrane.

The reduction in energy production is mirrored by a decrease in adenosine triphosphate (ATP) and causes the dysfunction of energy-dependent ion pumps such as Na^+/K^+ ATPase and Ca^{2+} ATPase in the sarcolemma as well as in other intracellular membranes.^[12] Na^+/K^+ ATPase pump dysfunction results in an increase in intracellular Na^+

concentration. Following an intracellular Na^+ increase, the cell increases the activity of the $2\text{Na}^+/\text{Ca}^{2+}$ exchanger, which removes the excess intracellular Na^+ from the cytoplasm by exchanging it with Ca^{2+} , ultimately increasing the concentration of cytoplasmic calcium. As the $2\text{Na}^+/\text{Ca}^{2+}$ exchanger requires energy to function properly, the energy deficit of the cell is accentuated.^[13] In this situation, Ca^{2+} ATPase releases any surplus of intracellular Ca^{2+} into the extracellular space, turns to be dysfunctional, and further increases Ca^{2+} .

The sarcoplasmic reticulum and mitochondria constitute the most important intracellular depots of free ionized calcium. Their role is to deposit the excess cytoplasmic calcium so that its concentration in the cytoplasm can be kept at a low level. As mentioned, these organelles are equipped with special mechanisms of transmembrane calcium transportation (Ca^{2+} ATPase and Ca^{2+} uniporter) that hydrolyze ATP for proper functioning.^[14, 15] The decreased energy production in rhabdomyolysis hinders the function of the organelles, thereby sustaining high levels of Ca^{2+} .

Several factors directly affect the membrane of muscle cell and cause interruption of its continuity, resulting in a massive influx of extracellular calcium into the cytoplasm driven by its chemical gradient. In addition, the progressive damage of the sarcoplasmic reticulum and mitochondria during cellular death promotes the release of stored calcium ions into the cytoplasm.^[16] This phenomenon leads to the overloading of the muscle cell with Ca^{2+} . Once Ca^{2+} exceeds a critical limit, the cascade of cellular death is activated.^[17]

Pathophysiological mechanisms of rhabdomyolysis

Activation of phospholipase A_2

Increased concentration of Ca^{2+} activates phospholipase A_2 and various neutral proteases (e.g., calpain)^[18] that degrade the cellular phospholipid membranes (e.g., plasma membrane, mitochondrial membrane) and various intracellular organelles. Following the enzymatic dissolution of membrane phospholipids, the resultant lysophosphatides and free fatty acids lead to direct toxic damage to the sarcolemma and other intracellular membranes or dysfunction of cell membrane carrier proteins and finally to the entry of Ca^{2+} into the cytoplasm.

Persistent contractility of muscular cell

Increased concentration of Ca^{2+} keeps muscle cell contract continuously, resulting in severe ATP depletion and progressive exhaustion of the cellular energy reserves.

Mitochondrial dysfunction

The rapid increase of Ca^{2+} concentration contributes to an increase of $[\text{Ca}^{2+}]_m$ in mitochondrial calcium because of its chemical gradient between the cytoplasm and mitochondrion. As mentioned above, the mitochondrion acts as a "safety reservoir" that succeeds in depositing a large quantity of Ca^{2+} when its concentration in the cytoplasm is excessively increased.^[19] In this way, the cell saves time in order to confront the actual cause of $[\text{Ca}^{2+}]_c$ increase. If the cause persists for a long time, the overloading of the mitochondrion with Ca^{2+} adversely affects its structural and functional integrity (e.g., dysfunction of oxidative phosphorylation), eventually impairing the production of ATP. Such a reduction in ATP worsens the dysfunction of Ca^{2+} carrier proteins in the sarcolemma and intracellular organelles, thereby initiating a self-perpetuating, vicious circle.

Free radical production-oxidative stress

Increased mitochondrial calcium $[\text{Ca}^{2+}]_m$ leads to increased production of reactive oxygen species (ROS, e.g. $\text{O}_2\cdot$, $\text{OH}\cdot$, H_2O_2).^[20] Human body has its own powerful endogenous antioxidant systems, such as superoxide dismutase, catalase and glutathione.^[21] When the endogenous antioxidant capacity of the system is weakened, body cells will suffer from ROS attack, resulting in oxidative stress.^[22] ROS oxidates various biomolecules of the cell such as proteins, lipids and nucleic acids, leading to structural and functional impairment of the cell. Because proteins and lipids are basic structural components of biological membranes and intracellular organelles, their destruction influences the integrity of the sarcolemma and intracellular membranes as well as the function of various intracellular organelles such as mitochondria and sarcoplasmic reticulum. Ultimately, cytoplasmic calcium increases. Moreover, ROS induce mutations in both nuclear and mitochondrial DNA. The modification of nuclear DNA leads to functional disorganization of the muscle cell, whereas mutations of mitochondrial DNA which contains the coding sequences for the respiratory chain proteins leads to structural and functional degeneration of the electron transport system, resulting in reduced ATP production. It is reported that myoglobin causes oxidative stress, increase of NO production, and dysfunction of kidney mitochondria.^[23]

Cell death

The results of the aforementioned complex and self-reinforcing reactions can cause the lysis of muscle cells

and the release of their toxic content into the extracellular space. The concentration of toxic substances in the microenvironment of the muscle cell causes damage to the adjacent capillaries, inducing local edema, increase of intracompartmental pressure, and regional ischemia. The ischemia further augments the energy depletion, resulting in damage of more capillaries. The circulating leukocytes adhere to the damaged capillaries, become activated, and transmigrate to the damaged muscle cells. Thus released ROS and proteolytic enzymes from the cells aggravate cellular impairment.^[24,25]

Conclusion

Although the etiology of rhabdomyolysis is multifactorial, their potential causes share the same pathophysiological pathway involving an increased concentration of intracellular calcium. Since rhabdomyolysis is critical in clinical practice, it is important for physicians to recognize its pathogenesis, clinical manifestations, and laboratory data, and to make a timely decision for the prevention or treatment of serious complications of the disease.

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