

Rhabdomyolysis.

The role of diagnostic and prognostic factors

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Summary

Rhabdomyolysis, literally meaning the breakdown of muscle tissue, is a common syndrome with many causes, acquired ones such as exertion, trauma, infections, temperature extremes, drugs, toxins, electrolyte and endocrine abnormalities, and congenital ones such as myopathies and connective tissue disorders. All results in a common pathophysiologic pathway which ends with the dispersing of muscle tissue content into the circulation. Rhabdomyolysis has characteristic clinical, laboratory and radiologic features, but does require a high index of suspicion so that the diagnosis would not be missed. The sensitivity and specificity of the various characteristics, as well as clinical guidelines, are discussed in this paper. The syndrome may present with several complications, e.g. arrhythmias, electrolyte abnormalities, acute renal injury, acidosis, volume depletion, compartment syndrome and disseminated intravascular coagulation. The prognosis is highly variable and depends on the underlying etiologies and complications, but is in general considered as good. The milestone of treatment is vigorous fluid resuscitation. Treatment options, in practice and in research, are discussed in the following pages.

KEY WORDS: *rhabdomyolysis.*

Introduction

Rhabdomyolysis is a syndrome characterized by breakdown of muscle tissue, followed by dispersing

its intracellular components into the circulatory system. These components include electrolytes, purines, enzymes (such as creatine kinase) and myoglobin. This syndrome is associated with many diseases, drugs, medications, toxins and injuries. The syndrome may be expressed as elevated levels of blood creating phosphokinase (CK) and leading to acute kidney injury and death. Rhabdomyolysis was first reported in Germany in 1881, but the syndrome was characterized in detail by Bywaters and Beall during the Battle of London in the 2nd World War. It is suggested that during the exodus from ancient Egypt, the bible describes a "plague" characterized as similar to rhabdomyolysis among the people of Israel, due to quail consumption, thus intoxication of hemlock herbs consumed by the quail¹.

Pathophysiology

There are many causes for rhabdomyolysis, but they seem to lead to a final common feature, which is the breakdown of muscle tissue, destruction of the myocyte and distribution of its components into the circulatory system. In the normal myocyte, a low level of Calcium is maintained by a Ca²⁺ ATPase pump (concentrating intracellular Calcium in the sarcoplasmic reticulum and mitochondria), and a Na/Ca exchanger ion channel, powered by Sodium influx, due to the gradient created by the Na/K ATPase pump. All these mechanisms depend, directly or indirectly on ATP as a source of energy. The lack of ATP causes the cell's homeostasis to collapse, causing the intracellular level of Calcium to rise. In turn, the rise of Calcium level activates intracellular proteolytic enzymes, thereby degrading the myocyte. As the cell breaks down, large quantities of Potassium, aldolase, phosphate, myoglobin, CK, lactate dehydrogenase (LDH), aspartate transferase (AST) and urate leak into the circulation². When more than 100g of muscle tissue is degraded the plasma's myoglobin binding capacity is overwhelmed and free myoglobin causes renal morbidity by several mechanisms³⁻⁵.

Causes

There is a large variety of causes for rhabdomyolysis, all leading to muscle ischemia and cell breakdown. The most common among adult populations are muscle exertion illicit drugs, alcohol abuse, medications, muscle diseases, trauma, Neuroleptic Malignant Syndrome (NMS), seizures and immobility⁶. Among pedi-

atric patients, the most common are exertion, viral myositis, trauma, connective tissue diseases and drug overdose⁷.

Excessive muscular activity

Sporadic strenuous exercise, especially in trained people (e.g. marathon runners, military recruits)^{8,9}, or involuntary muscle exercise such as seizures¹⁰, status epilepticus, acute psychosis¹¹, status dystonicus¹² or status asthmaticus¹³ may result in acute severe rhabdomyolysis. The mechanism is ATP supply-demand discordance, leading to inability to maintain membrane homeostasis. The more strenuous or prolonged the exercise is, the more damage is incurred¹⁴. Factors increasing the risk of exertional rhabdomyolysis are hypokalemia (often resulting from excessive sweating), sickle-cell trait (especially in combination with high altitude)¹⁵, extreme heat and humidity⁹, exercise-induced asthma, or pre-exertion fatigue. Low intensity exercise induced rhabdomyolysis cases have also been reported, but the mechanism remains unknown¹⁶.

Electrolyte and endocrine abnormalities

Severe electrolyte abnormalities disrupt the cell's membrane homeostasis, mainly by disturbing the Na/K ATPase pump. Hyponatremia¹⁷, hypernatremia¹⁸, hypokalemia¹⁹ and hypophosphatemia (usually as part of diabetic ketoacidosis)²⁰ may result in rhabdomyolysis. It has been suggested that extreme exercise with intense fluid consumption by athletes may cause hyponatremia induced rhabdomyolysis²¹. Polydipsia alone can initiate dilutional hyponatremia followed by rhabdomyolysis as well²². Hypokalemia induced rhabdomyolysis was reported as a complication of hyperaldosteronism or pseudoaldosteronism²³, laxatives²⁴, liquorice ingestion²⁵ and many other etiologies.

Endocrine abnormalities such as hyperaldosteronism^{26,27}, Addison's disease²⁸, hypothyroidism²⁹, hyperthyroidism³⁰, diabetic ketoacidosis^{20,31}, non-ketotic hyperosmolar state³² have been reported occasionally to cause rhabdomyolysis.

Temperature extremes

Excessive heat caused by heat stroke^{33,34}, malignant hyperthermia syndrome³⁵ and neuroleptic malignant syndrome^{36,37} may result in muscle damage, on the cellular level. A body core temperature of 42°C (107.6°F) for 45 minutes to 8 hours was established to be the thermal maximum, meaning the level and duration of heat that muscle cells can endure without being damaged³⁸. The higher the heat a body will absorb, cellular destruction will occur at a higher and faster extent³⁹. Malignant hyperthermia is a condition usually ascribed as a genetic susceptibility to anesthetic drugs, causing hyperthermia, increased metabolic rate, elevated respiratory rate, pulse, rigidity and rhabdomyolysis. It may also be triggered by exer-

cise (exercise induced malignant hyperpyrexia)⁴⁰. In neuroleptic malignant syndrome, the mechanism suggested is that neuroleptic medications induce abnormal calcium availability in muscle cells of susceptible individuals and trigger muscle rigidity, rhabdomyolysis and hyperthermia³⁷.

Although rare, rhabdomyolysis might be induced by exposure to extreme cold (with or without hypothermia), due to direct muscle injury^{41,42}.

Both temperature extremes could be facilitated by exposure and activity during voluntary exercise and exertion.

Muscle ischemia

Muscle ischemia means deprivation of oxygen from muscle tissue, resulting in decreased levels of ATP production. Prolonged ischemia may lead to muscle cells necrosis. Ischemia may be caused by a general condition, such as shock, hypotension, CO intoxication⁴³ and sickle cell trait¹⁵. Alternatively, it may be a result of a localized specific cause, such as blood vessel thrombosis, embolism, compartment syndrome⁴⁴, or compression of a vessel (e.g. surgical tourniquets⁴⁵, tight dressings or casts and vessel clamping^{46,47}). Prolonged immobilization, mainly due to substance or alcohol abuse, coma or anesthesia, is a major cause of compression of blood vessels. Like trauma, pathophysiology actually takes place once pressure is relieved from the damaged tissue, and the necrotic muscles release their components into circulation⁴⁸. Known positions resulting in rhabdomyolysis are lateral decubitus, lithotomy, sitting, knee-to-chest, prone position⁴⁹ and harness hanging⁵⁰. Overweight >30% of ideal body mass, surgery of more than 5-6 hours, circulatory volume depletion and pre-existing diabetes or hypertension are contributing risk factors⁵¹.

Drugs

Rhabdomyolysis may result from substance abuse, prescription and nonprescription medications. Substances that are commonly abused include ethanol, methanol and ethylene glycol^{52,53}, heroin, methadone⁵⁴, tobacco, cocaine, amphetamine, 3,4-methylenedioxymethamphetamine (MDMA, ecstasy), phencyclidine⁵⁵, lysergic acid diethylamide (LSD)⁵⁶, benzodiazepines⁵⁷, barbiturates⁵⁸ and toluene (from glue sniffing)⁵⁹.

Alcohol can induce rhabdomyolysis through a combination of mechanisms including immobilization with muscle compression (due to immobilization), direct myotoxicity (due to inhibition of calcium accumulation by the sarcoplasmic reticulum and alteration of membrane viscosity with derangement of membrane ion transporters), aberration in myocyte carbohydrate metabolism, dehydration and electrolyte abnormalities (hypokalemia and hypophosphatemia)^{55,60}. Cocaine induced rhabdomyolysis is caused by either vasospasm with muscular ischemia, hyperpyrexia, seizures, coma with muscle compression or direct myofibrillar damage⁵⁵. Drug and alcohol abusers are

often malnourished, with resultant diminished glycogen storage and ATP reserve.

Excessive use of barbiturates, benzodiazepines and other sedative and hypnotic drugs causes depression of the central nervous system with prolonged immobilization and muscle compression, resulting in hypoxia, suffering and destruction⁵⁸.

Rhabdomyolysis may also result from both prescribed and over-the-counter medications including salicylates⁶¹, statins (e.g., simvastatin, lovastatin, pravastatin, rosuvastatin, cerivastatin)⁶²⁻⁶⁵, especially simvastatin, statin-fibrate combination⁶⁶, theophylline⁶⁷, cyclic antidepressants, selective serotonin reuptake inhibitors^{68,69}, phenylpropanolamine containing diet pills⁷⁰, fibric acid derivatives (e.g., bezafibrate, clofibrate, fenofibrate, gemfibrozil)^{71,72}, neuroleptics⁷³, anesthetic (e.g. propofol)⁷⁴ and paralytic agents (the malignant hyperthermia syndrome)⁷⁵, quinine⁷⁶, anabolic steroids^{77,78}, corticosteroids⁷⁹. Several mechanisms were related to statin induced rhabdomyolysis. Since cholesterol is an important building block of the cell's membrane, and its synthesis is blocked, the result is also unstable skeletal muscle cell membrane. In addition, mitochondrial respiratory function is interrupted due to coenzyme Q10 deficiency. A third mechanism is the presence of abnormal prenylated proteins which causes an imbalance in intracellular signal transduction⁸⁰.

Toxins

Toxin induced rhabdomyolysis include carbon monoxide (CO)⁴³, snake bites⁸¹, spider venom⁸², massive honey bee and wasps envenomation^{83,84} and quail eating (it nourishes from hemlock herbs)¹. CO gas has a higher affinity to hemoglobin than oxygen, thus combining with it to form carboxyhemoglobin in the blood, preventing the binding of oxygen, causing muscle hypoxia and rhabdomyolysis.

Trauma

Rhabdomyolysis may occur due to traumatic events, such as blunt trauma, crush injury, electrical injury or third degree burns.

Blunt trauma may be due to direct blow or motor-vehicle crush (including acceleration-deceleration mechanism). Crush injuries are associated with mass casualty events and severe trauma, such as terror attacks, bombing, earthquakes and building collapses, train accidents and mining accidents. For instance, earthquakes result in 3% to 20% of crush injuries, of which 74% involve the lower extremity⁸⁵. The rhabdomyolysis pathophysiology actually takes place once pressure is relieved from the damaged tissue, and the necrotic muscles release their components into circulation⁴⁸, for example, once people are extracted from a crushed vehicle. High voltage electrical injury, caused by lightning strike or high voltage power supply, or extensive third degree burns results in rhabdomyolysis due to direct myofibrillar damage⁸⁶. However, extensive thermal third degree burns could

also result in rhabdomyolysis. Regardless of the initial cause, late onset Rhabdomyolysis could occur due to immobilization or circumferential burns constrictures. The treatment of burn induced rhabdomyolysis presents a great challenge because burn treatment itself requires vigorous fluid overload, thus making it difficult to add more fluids for rhabdomyolysis management⁸⁶.

Infections

Several mechanisms are ascribed to infection induced rhabdomyolysis: bacterial invasion of a muscle, low energy related enzymatic activity, tissue hypoxia (due to sepsis, general hypoxia, acidosis, dehydration and electrolyte disturbances)⁸⁷, high lysosomal enzymatic activity⁸⁸ and endotoxins⁸⁹.

Numerous bacterial, viral, fungal and protozoal infections can lead to rhabdomyolysis. Viral infections as a cause of rhabdomyolysis have been described in many reports worldwide, of which influenza types A (including recent reports of H1N1 subtype)^{90,91} and B are the most common⁹². Other viral infections inducing rhabdomyolysis include HIV, Coxsackievirus, Epstein-Barr virus, Echovirus, Cytomegalovirus, Adenovirus, Herpes simplex virus, Parainfluenza, Varicella-Zoster virus⁹² and West Nile virus⁹³. Bacterial infections are often associated with rhabdomyolysis in adults, most commonly Legionella. Other species described as associated with rhabdomyolysis are Streptococcus pneumoniae, Staphylococcus aureus, Streptococcus viridans, Salmonella species, Staphylococcus epidermidis, Francisella tularensis, Streptococcus faecalis, Meningococci, Hemophilus influenza, E.coli, Pseudomonas, Klebsiella, Enterococcus faecalis, Bacteroides⁹⁴, group B streptococcus, Streptococcus pyogenes, Listeria species, Vibrio species, Leptospira species⁹⁵, Brucella species, Bacillus species and Clostridium species⁹².

Myositis and associated rhabdomyolysis has also been reported in patients with fungal or parasitic infections, especially among immunocompromised patients⁹⁶, the most notable being malaria^{97,98}.

Myopathies

Genetic disorders leading to rhabdomyolysis are either inherited myopathies (e.g. Duchene muscular dystrophy and Becker's dystrophy)⁹⁹, metabolic enzymes deficiencies (restricting carbohydrate or lipid metabolism)^{100,101} or mitochondrial function disorders¹⁰². Usually, these disorders will present themselves in early childhood. Careful history taken may reveal these etiologies. Muscle dystrophies were suspected to predispose malignant hyperthermia but relative risk was found to be insignificant¹⁰³. Connective tissue disorders inducing rhabdomyolysis are rare, but have been described. They include polymyositis, dermatomyositis¹⁰⁴ and inclusive body myositis. Inflammatory myopathy can present with very high CK levels, but not as high as those found in muscle dystrophies¹⁰¹ (Tab.1).

Table 1. Causes for rhabdomyolysis (by mechanism).

1. Increased energy demand:
 - 1.1 Exercise (especially strenuous exercise)
 - 1.2 Heat stroke
 - 1.3 Acute psychosis
 - 1.4 Seizures; Status epilepticus
 - 1.5 Status dystonicus
 - 1.6 Status asthmaticus
 - 1.7 Delirium tremens
2. Decreased energy production
 - 2.1 Dystrophies
 - 2.2 Metabolic enzyme deficiencies
 - 2.3 Mitochondrial function disorders
 - 2.4 Hypokalemia
 - 2.5 Hypophosphatemia
3. Direct muscle injury
 - 3.1 Crush injury (trauma)
 - 3.2 Electrical injury
 - 3.3 3rd degree burns
 - 3.4 Inflammatory myopathy
 - 3.5 Temperature extremes (hyper/hypothermia)
 - 3.6 Hyper/hyponatremia
4. Decreased oxygen delivery
 - 4.1 Arterial thrombus; emboli
 - 4.2 Surgery; prolonged immobilization
 - 4.3 Trauma
 - 4.4 Shock
 - 4.5 Sick cell trait/crisis
5. Infections:
 - 5.1 Viral
 - 5.2 Bacterial
 - 5.3 Fungal
6. Endocrine abnormalities:
 - 6.1 Diabetic keto-acidosis; non-ketotic hyperosmolar state
 - 6.2 Addison's disease
 - 6.3 Hyperaldosteronism
 - 6.4 Hypo/hyperthyroidism
7. Drugs & medications:
 - 7.1 Substance abuse (MDMA, Amphetamine, Heroin, Methadone, Cocaine, PCP, LSD)
 - 7.2 Alcohol; ethylene glycol
 - 7.3 Sedative/hypnotic drugs (Barbiturates, Benzodiazepines)
 - 7.4 Anesthetics (malignant hyperthermia)
 - 7.5 Statins; Fibrates
 - 7.6 Neuroleptics
 - 7.7 Anabolic/corticosteroids
8. Toxins:
 - 8.1 Carbon mono-oxide (CO)
 - 8.2 Venom – snake; spider; bee; wasp
 - 8.3 Quail eating

Clinical Presentation

Because of the many possible causes, there is a variety of rhabdomyolysis' presentations. It may be severe when substantial muscle damage has occurred, or, vice versa, subclinical, when the damage is minor. A classic triad was described inclusive of muscle aches, weakness and dark, tea colored urine. Especially when accompanied by clues of muscle damage, this should raise the suspicion of Rhabdomyolysis. This is especially true in pediatrics¹⁰⁵. Some more specific symptoms include muscle tenderness,

swelling, cramping, stiffness, weakness and loss of function of the relevant muscles. The most common muscle groups involved are postural muscles, such as lower back, thighs and calves. Muscle swelling might not be apparent until after intravenous (IV) fluids rehydration. Other symptoms may be of non specific nature, such as fever, malaise, abdominal pain, nausea and vomiting. Change of mental status may occur due to the underlying cause (e.g., trauma, toxins or drugs, infections, electrolyte abnormality, or urea induced encephalopathy).

Physical examination might reveal limb induration or skin changes due to ischemic damage of involved tissues (e.g. blisters, discoloration). However, there may be no signs of muscle involvement.

Rhabdomyolysis could be an incidental finding of a laboratory test. Anyhow, purposeful efforts should be made to identify an underlying cause.

Work-Up

A high index of suspicion is crucial for diagnosing rhabdomyolysis, since classic presentation such as muscular swelling, pain and tenderness may not be eminent, or even be absent. A thorough history must be taken. The definitive diagnosis is made by laboratory tests including serum CK and urine myoglobin. A skeletal muscle biopsy can be used to establish the diagnosis, but is not obligatory.

Serum CK (Creatine Kinase)

Serum CK concentration, mainly the CK-MM subtype, is the most sensitive indicator of damage to muscles. Serum CK begins to rise approximately 2 to 12 hours after the onset of muscle injury, peaks within 24 to 72 hours, and then declines gradually in 7-10 days. A persistently elevated CK level suggests continuing muscle injury, development of a compartment syndrome or continuing muscle stress (e.g. prolonged exercise or infection)². Currently, there is not a clearly agreed level of serum CK that is evident for diagnosis of rhabdomyolysis. However, a CK level higher than 5 times of its normal value is accepted by many authors as diagnostic criteria. Moreover, some studies establish the low specificity of serum CK levels. Kenney et al. found in their contingent of 499 young healthy recruits a CK elevation of 10 times that regarded as normal, none diagnosed as exertional rhabdomyolysis, and suggesting either coexisting myoglobinuria or CK level of 50 folds of normal as a diagnostic threshold¹⁰⁶. Statin induced rhabdomyolysis is commonly defined with marked CK elevation greater than 10 times the upper limit of normality, with muscle symptoms and usually with brown urine with myoglobinuria⁶⁵.

Serum and urine myoglobin

Myoglobin is normally bound to plasma globulins, and is maintained at a low serum level of 0 to 0.003mg/dL³.

Once circulating myoglobin levels have exceeded 0.5 to 1.5mg/dL it overwhelms its protein binding capacity, tubule endocytosis rate and metabolism rate, and is rapidly excreted in the urine¹⁰⁷. Note that myoglobinuria is pathognomonic to rhabdomyolysis, but is not necessarily visible. Elevated serum myoglobin and myoglobinuria are reliable indicators for rhabdomyolysis, but present some limitations. Serum myoglobin levels rise and drop much faster than CK levels (in 1 to 6 hours), thus have a low negative predictive value and may not be used as a ruling out test. Secondly, myoglobinuria is not always visible, or may be resolved early; it takes a urine myoglobin level of 100mg/dL to cause tea or cola colored urine. Moreover, detecting myoglobinuria is commonly done using urine dipstick tests (ortho-toluidine), which also react with the globin fragment of hemoglobin, thus a non-specific test (e.g. in hematuria due to erythrocytes or their fragments). Rodríguez-Capote et al. performed a systemic review which proved a high sensitivity but poor specificity of myoglobinuria as a rhabdomyolysis marker¹⁰⁸. Immunoassay is more sensitive and specific than dipstick, but often not readily available, and it may take days to obtain results. Thus, serum myoglobin and myoglobinuria are not necessarily sensitive or specific parameters, dependant on many factors.

Imaging

Rhabdomyolysis is usually diagnosed as a clinical syndrome, with supporting laboratory tests. However, recent reports claim that, in obscure cases, in which diagnosis is not definite, several imaging tests may prove useful. Bone scintigraphy demonstrates Tc99-labeled diphosphonate reacting with released calcium (due to sarcolemmal disruption) in muscle tissue¹⁰⁹. Magnetic resonance imaging (MRI) may demonstrate an increased signal using T2 weighted images, a decreased signal using T1 weighted images, and a contrast between healthy and damaged muscles using STIR images (which suppresses fat tissue signal). Computerized tomography (CT) images demonstrate diffuse areas of low attenuation in the muscle and muscular swelling due to edema and defined intramuscular hypodense foci suggesting muscle necrosis. Ultra sound (US) may reveal hypoechoic areas attributed to inflammation and fluid infiltration^{110,111}. All techniques could also detect macroscopic findings of the kidney, if affected. None of these techniques is highly specific to rhabdomyolysis, but MRI has proved to be almost 100% sensitive, as other modalities were inferior¹¹².

Often rhabdomyolysis is not diffuse, but is isolated to a specific muscle group. In these cases bone scintigraphy or preferably MRI could demonstrate the affected muscles¹¹³, and serve as a decision making tool, when fasciotomy is considered^{110,114}, to avoid unnecessary interventions.

Investigations for underlying cause

Diagnosing rhabdomyolysis must be followed by a search for the cause. A careful history and physical

examination are crucial, but may not always help in concluding definitively the underlining etiology. In such cases there is not a clear protocol for which tests should be attempted. If drugs or toxins are suspected, toxicological screening should be done. If infection is a possibility, appropriate cultures, complete blood count (CBC) and serological studies should be performed. If an endocrine or a metabolic disorder is suspected, blood chemistry and endocrine assay is to be done to confirm this.

Furthermore, in young patients or in recurrent ER, genetic analysis¹¹⁵, muscle biopsy¹⁰² and the forearm ischemic exercise test¹¹⁶ (revealing myopathies and metabolic disorders) may be indicated, since suspicion of genetic disorders should arise. The susceptibility of any individual to malignant hyperthermia can be detected by performing the caffeine halothane contracture test (CHCT), although currently genetic tests may diagnose it without the need for this invasive procedure¹¹⁷. Magnetic resonance imaging (MRI) had also been proved useful in distinguishing the various etiologies of Rhabdomyolysis.

Other investigations

ECG monitoring is essential to detect cardiac arrhythmias related to hyperkalemia or hypocalcemia¹¹⁸. Electrolyte abnormalities related to rhabdomyolysis (e.g. hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia) may be detected using a simple blood chemistry test. Metabolic acidosis could be detected using arterial blood gas analysis. Raised levels of muscle enzymes such as lactate dehydrogenase (LDH), aldolase, carbonic anhydrase III and aminotransferases (particularly aspartate aminotransferase – AST with normal levels of alanine aminotransferase - ALT) can indicate the occurrence of rhabdomyolysis. Elevated levels of troponin subtype I are found in 50% of rhabdomyolysis cases, while it is normal in inflammatory and chronic myopathies, in which troponin T subtype and CK levels are elevated². In rhabdomyolysis associated kidney injury, the elevation in serum creatinine is often more rapid compared to other causes of kidney injury, especially among muscular young people. In concordance, the blood urea nitrogen (BUN) to creatinine ratio is typically low⁴.

Due to all that, CBC, blood chemistry, liver and kidney function tests, prothrombin time (PT), activated partial thromboplastin time (aPTT), may be useful laboratory tests and should be considered.

Complications

Arrhythmias may occur due to electrolytes abnormalities, chiefly hyperkalemia and hypocalcemia. Since both abnormalities, as well as others described, can present themselves very early in the pathogenesis involving rhabdomyolysis, especially hypocalcemia of the early phase⁴, monitoring and early intervention are indicated in order to prevent arrhythmias and cardiac arrest.

Volume depletion is caused by third spacing of intravascular fluid - an influx into muscle tissue, caused by cellular electrolyte abnormalities. Alternatively, this could be caused by crush injury, due to external and internal bleedings. This process facilitates the depletion of available ATP, creating a viscous circle, resulting in further damage, hypovolemia and even hypovolemic shock. The hypovolemia in extensive rhabdomyolysis is comparable to that occurring in patients with major vessel bleeding or with extensive burns (>60% of body surface)⁴⁸.

Compartment syndrome is caused by the same factors as volume depletion, defined as increased intracompartmental pressure, causing oxygen deprivation of the muscle. The syndrome presents with muscle pain (occasionally out of proportion to observed injury), weakness, paresthesia or hypoesthesia, pallor and tightness of affected muscles. Note that compartment syndrome may present in a milder manner, when concerning a non-acute occurrence, such as chronic exertional compartment syndrome. A compartmental pressure of over 30mmHg (which can be measured using several invasive applications) for more than 8 hours may cause muscular necrosis, or higher pressures for lesser time may cause permanent neuromuscular damage, meaning future dysfunction of the musculoskeletal systems, contractures, posture and gait disturbances¹¹⁹.

Acute kidney injury (AKI) is very common among Rhabdomyolysis patients, although sometimes it presents only several days after the initial impact. About one third to one half of rhabdomyolysis patients will develop acute kidney injury¹²⁰, as 7-10% of all occurring acute kidney injury are due to rhabdomyolysis⁴. The mechanisms are diverse and not fully understood. Firstly, myoglobin has a direct nephrotoxic effect due to its activity as peroxidase-like enzyme, causing uncontrolled oxidation of biomolecules, lipid peroxidation and generation of isoprostanes. The nephrotoxic effect, as cellular damage, is caused also by the unbalanced conversion of the ferrous oxide (Fe^{2+}) of the heme group into ferric oxide (Fe^{3+}), generating hydroxyl radicals¹²¹. Secondly, renal vasoconstriction is caused by renin-angiotensin, vasopressin and sympathetic innervation, activated due to depletion of intravascular volume. Other inflammatory factors such as endothelin-1, thromboxane A2 and TNF- α , and the depletion of nitric oxide also contribute to renal vasoconstriction. Thirdly, myoglobin interacting with Tamm-Horsfall protein creates casts (more vigorously in an acidic environment), obstructing the tubuli, along with sloughed destroyed cells from tubular necrosis^{3-5,120}.

Acidosis is chiefly caused by the depletion of oxygen from involved tissues, resulting in lactic acidosis. However, the kidney injury most probably will advance the situation rapidly⁴⁸. Another mechanism is unmonitored usage of loop diuretics¹²². Acidosis may also be caused directly or secondarily by many of the drugs which cause rhabdomyolysis, as mentioned earlier¹²³.

Disseminated intravascular coagulation (DIC) may be initiated by released components of necrotic mus-

cle tissue, resulting in diffuse internal hemorrhagic complications³⁹.

Treatment & Management

Although there are no sufficient level I evidence studies, meaning randomized controlled trials, regarding management of rhabdomyolysis patients, there are many series of retrospective clinical studies, case reports and animal models. The milestones of treatment are vigorous fluid resuscitation, elimination of the underlying cause and prevention of complications.

Prehospital care

Due to hypovolemia and the danger of acute kidney injury AKI, aggressive fluid resuscitation is required. Using a large caliber catheter, infusion of 1.5L/hr of normal saline is needed, in purpose to maintain a production of 200 to 300mL of urine per hour. No Lactate or Potassium containing fluids should be used, due to the risk of Rhabdomyolysis related hyperkalemia or lactic acidosis. Early fluid resuscitation, once a single limb is accessed (e.g. before extraction of the patient from a crushed vehicle, rubble etc. in case of crush injury)⁴⁸, definitely prior to evacuation to a medical center¹²⁴, or up to 6 hours after admission¹²⁵ is reported to reduce the incidence of AKI. The longer rehydration is delayed, the more likely is AKI to develop^{126,127}. In massive crush disasters, several series showed better results (meaning decreased risk that renal replacement therapy will be required in the future) when intravenous rehydration was applied prior to complete extraction of injured patient from the scene, using sometimes only one available limb^{122,124}.

Hospital care

While starting or continuing fluid resuscitation, thorough history and physical examination are needed to identify and manage the underlining disease. Vital signs, urine output and serum electrolytes and CK levels should be monitored continuously, using intensive care monitoring if needed. A urinary catheter should be inserted and urine output should be monitored carefully. In patients prone to heart condition due to preexisting disease or elderly patients, haemodynamic monitoring might be necessary to avoid fluid overload. The chief objective of treatment is to achieve vigorous diuresis and to dilute the toxic products, using aggressive IV rehydration. A 1.5L/hr infusion of normal saline is required for initial resuscitation, followed by 300 to 500mL/hr once hemodynamic stability had been achieved. Aggressive rehydration is needed especially when concerning crush injury for hypovolemia management, administering both normal saline and blood products. The goals set are urine output greater than 200mL/hr and serum CK levels lower than 1000U/L. Note that the CK level desired is not agreed on by all protocols, and that its serum level will rise only 2-4 hours after the primary injury.

Adding mannitol and bicarbonate with saline hydration is advised in order to prevent acute kidney injury, although yet to be supported by randomized controlled trials. Sodium bicarbonate is used for urinary alkalization, reducing the nephrotoxic affect of myoglobin, cast obstruction, hyperkalemia and lipid peroxidation^{4,124}. Administration is carried out with either one ampoule (44meq) diluted in 1L of half normal saline or 2-3 ampoules (88-132meq) in 1L of 5% dextrose. A rate of 100mL/hr is recommended in order to maintain urine PH>6.5¹²². During treatment, serum bicarbonate, calcium and potassium levels should be monitored, along with urine PH. If symptomatic hypocalcemia develops, or urine PH resists treatment for more than 6 hours, alkalization should be discontinued. In case of iatrogenic metabolic alkalosis (serum PH>7.45), caused by sodium bicarbonate, Acetazolamide administration might prove useful, as it enhances urine alkalization¹²².

Mannitol is suggested to increase renal blood flow and glomerular filtration rate, which helps in preventing obstruction of tubuli by myoglobin casts. Another benefit of osmotic diuresis is the drawing of interstitial fluid back to the intravascular compartment, improving hypovolemia, muscle swelling and nerve compression. It also reduces free radicals' level⁴. Mannitol is to be administrated as 20% infusion, giving a loading dose of 0.5g/kg during a 15 minute period, followed by 0.1g/kg/hr infusion rate. Nevertheless, mannitol is to be administered only once intravascular volume had been restored. It should be avoided with patients with oliguria. Urinary and serum pH levels should be monitored, with acetazolamide added if the serum pH is >7.45 or urinary pH remains lower than 6.0³⁹. However, there are no randomized controlled studies that prove the yield of mannitol in this scenario, and some studies have found no benefit¹²⁸. It should be considered in light of the risk for osmotic nephrosis, due to renal vasoconstriction and tubular toxicity when mannitol serum level exceeds 1000mg/dL¹²⁹. During treatment, plasma osmolality and osmolal gap (the difference between measured and calculated serum osmolality) should be monitored, with mannitol discontinued if sufficient diuresis is not achieved, or serum osmolal gap exceeds 55mOsm/kg (equals to 1000mg/dL serum level)^{4,129}.

The use of loop diuretics (e.g., furosemide) or recombinant B-natriuretic peptide (Neseritide) in Rhabdomyolysis is controversial, with some researchers recommending their use and others opposing it, because loop diuretics acidify the urine and as there is not sufficient evidence of their yield in reducing mortality, reducing the need for dialysis, reducing the number of dialysis sessions applied and shortening the time of hospitalization¹³⁰. However, since it acidifies the urine, it might prove useful in cases of iatrogenic metabolic acidosis caused by excessive use of normal saline infusions¹³¹.

It has been suggested that treatment with corticosteroids might reduce secondary muscle damage due the inflammatory response following initial muscle damage¹³².

Treatment of any reversible cause of muscle damage

The objective is to stop any progressing muscle destruction. Any toxin, infection, trauma or hyperthermia must be diagnosed and treated as early as possible. Drugs and toxins should be eliminated and detoxified (e.g. gastric lavage, antidotes and/or hemodialysis) if possible, and hypoxia must be corrected. Infections should be treated using a broad spectrum antimicrobial regimen until isolated and diagnosed; surgical eradication of infectious foci should be considered (e.g. abscess drainage, soft tissue debridement or removal of infected foreign body). Muscle compartment syndrome is to be treated with fasciotomy. Hyperthermia is treated with external cooling measures and benzodiazepines to control muscular hyperactivity. In malignant hyperthermia, anesthetics should be discontinued, and the patient should be treated with dantrolene sodium; the usual initial dose is 2.5-4.0 mg/kg, followed by a maintenance dose of 1 mg/kg every four hours for up to 48 hours to avoid reoccurrence of the disease³⁹. Electrolyte and metabolic abnormalities that cause rhabdomyolysis (e.g., hyponatremia, hypernatremia, hyperglycemia, hypocalcemia, and hypophosphatemia) should be corrected as soon as possible.

Prognosis

The prognosis of Rhabdomyolysis is heavily dependent upon the underlying etiology, and the associated comorbidities. Despite the lack of any well-organized prospective studies, the available evidence from case reports and small retrospective studies suggests that rhabdomyolysis, when treated early and aggressively, has an excellent prognosis. Moreover, the prognosis for the recovery of full renal function is also excellent.

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