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CASE REPORTS

RHABDOMYOLISYS AS A CAUSE OF ACUTE RENAL INJURY

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Abstract. *Rhabdomyolysis (RM) is defined as striate muscle-cell damage with disintegration of skeletal muscles and release of intracellular constituents to the circulation, with or without subsequent kidney injury. RM is one of the leading causes of acute kidney injury and is associated with substantial morbidity. The major signs of acute kidney injury in rhabdomyolysis are: pain, weakness and swelling of the injured muscle or muscle groups and myoglobinuria with reddish discoloration of the urine and decrease in urine output to anuria. The authors describe three cases of rhabdomyolysis with acute renal injury and discuss the current knowledge on the etiopathogenesis, clinical manifestations, diagnosis and treatment of this condition.*

Key words: *rhabdomyolysis, acute kidney injury, diagnosis, treatment*

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INTRODUCTION

The term “rhabdomyolysis” describes striate muscle-cell damage and refers to disintegration of skeletal muscles with release of intracellular constituents to the circulation, with or without subsequent kidney injury [1-4]. The key markers of striate muscle damage that are released and detected in the extracellular fluid and the circulation are myoglobin, creatin phosphokinase (creatin kinase) and lactate dehydrogenase [1-5]. Myoglobin is an 18.8 kDa oxygen-binding protein that binds plasma proteins and small amounts reach urine. In massive skeletal muscle damage the plasma protein binding capacity is exceeded and myoglobin reaches the tubuli where it can cause tubular obstruction and toxicity with subsequent development of acute renal failure [1, 5]. Moreover, the muscle swelling in rhabdomyolysis can lead to interstitial and muscle cell edema with decrease in effective circulating volume and renal hypoperfusion [1, 2, 3]. Rhabdomyolysis (RM) is one of the leading causes of acute kidney injury accounting for 7-10% of the cases of acute renal injury per year [3]. The prevalence of RM is unknown and probably significantly underestimated [3], as in most of the cases the condition subsides spontaneously. In the US approximately 26 000 new cases are reported every year [3]. The incidence of acute kidney injury among RM patients is also unclear but is assumed to develop in between 4% and 33% of all RM patients [3]. RM could be classified as traumatic and non-traumatic (associated with seizures or strenuous physical activity, muscle compression, alcohol and/or drug abuse, dehydration, and inborn metabolic de-

fects). The major signs of acute kidney injury in rhabdomyolysis are: pain, weakness and swelling of the injured muscle or muscle groups and myoglobinuria with reddish discoloration of the urine and decrease in urine output to anuria [1-4].

RM has accompanied mankind since the dawn of history. Cases of toxic rhabdomyolysis after the consumption of quail in spring time have been described in the Bible (Book of Numbers 11:31-35) [6]. This condition is known to develop due to the myotoxic effect of hemlock alkaloids in humans, as the quails consume hemlock herbs in spring [7]. In war time and during disasters and cataclysms (i.e., earthquakes, floods, volcano eruptions, etc.), RM can develop as a consequence of traumatic muscle injury [1-4]. The first detailed description of RM as a complication of military traumatism was first published in the English literature by Bywaters and Beall in 1941 [8] who described four victims of the bombings in London in 1940 and suggested an association between the muscle injury and the acute renal failure. Subsequently this link has been proven in experimental model [9] and other, non-traumatic causes of RM have been recognized [1-7, 10-17].

ETIOLOGY

RM can be classified in two major types – traumatic and non-traumatic (Table 1). Traumatic rhabdomyolysis develops as a result of direct muscle trauma and/or compression and non-traumatic – as a result of toxic, ischemic or metabolic striate muscle-cell injury. Many over-the counter, prescriptional and illicit drugs and other toxic substances are known to cause RM (Table 2).

Table 1. Causes of traumatic and non-traumatic rhabdomyolysis [1-5]

Traumatic	Non-traumatic
Trauma (crush injury: war, cataclysms) disasters, collapsed buildings, traffic accidents, etc.	Strenuous physical exercise, seizures Thermal injury: hyper- or hypotermia Autoimmune myopathies Muscle hypoperfusion: shock, prolonged systemic vasoconstriction or vasodilation
Sports traumatism and assault, including martial arts	Drugs and toxins (statins, illicit drugs, plant toxins, snake and insect venoms, fish poisoning – carp fish, buffalo fish, burbot, etc.)
Electrocution – lightning, electric current	Infections: influenza, EBV, HIV, Coxsackie virus, herpesvirus, Gram positive cocci, Legionella, Salmonella, tularemia, malaria, etc.
Compartment syndromes – prolonged immobilization, perioperative trauma, prolonged tourniquet use, forced body position in coma or drug overdose	Metabolic and electrolyte disturbances –acquired and inherited: hypo- and hyperosmolarity, severe acidosis, dyselectrolitemia (hypokalemia, hypo- and hypernatremia, hypocalcemia), hypothyroidism, hyperaldosteronism, diabetic ketoacidosis and hyperosmolarity state; inherited dysmetabolic conditions – impaired glycogen, fatty acid, pentoso-phosphate or purine metabolism, impaired mitochoindrial metabolism, (glycogen storage diseases, mitochondrial respiratory chain enzyme deficiencies, carnitine palmitoyl transferase deficiency, phosphofructokinase deficiency, myoadenylate deaminase deficiency, etc.) and congenital muscle dystrophies and myopathies
	Idiopathic

Table 2. Drugs and substances known to cause rhabdomyolysis [1, 7, 10-18]

Drugs	Illicit drugs	Toxins
Amphothericin B Antipsychotics, lithium	Amphetamines	Alcohol
Antimalarials	Cocaine	Licorice
CO (carbon monoxide)	Heroin and opioids	Alkaloids
Colchicine	Ecstasy	Fish poisoning
Corticosteroids	Methadone	Insect venoms
Diuretics	Phencyclidine	Mercury
Fibrates Isoniazide Laxatives Statins		Plant poisoning: brucine, buckthorn, hemlock, strychnine, thorn apple, pokor ipoh and akar ipoh blowpipe dart poisons
Tenofovir, zidovudine and other anti-HIV medications		

MOLECULAR MECHANISMS

The development of RM is associated with direct striate muscle cell injury (physical trauma, electrocution, thermal trauma, changes in plasma electrolyte levels or osmolarity) or with adenosine triphosphate (ATP) depletion (due to ischemia, metabolic disturbances, drugs and toxins) [1-4, 17, 18]. The low ATP levels lead to decreased activity of membrane ATPase pumps with persistent myofibril contraction, further decrease in energy levels, activation of calcium-dependent intracellular enzymes within the striate muscle cells and subsequent cell degradation with liberation of myoglobin to the interstitial spaces and systemic circulation. Moreover, the direct blocking of sarcolemic ATPases by toxins could lead to additional striate muscle cell damage.

To make the long story short, in direct muscle injury myofibrils undergo rapid physical damage, and in ATP-depletion-dependent myolysis the damage develops more slowly due to blockage of energy sources. Subsequently, independent of the etiology, striate muscle cells are disintegrated and large quantities of intracellular constituents (myoglobin, enzymes, potassium, nuclear material, etc.) are released in the circulation and finally reach renal parenchyma. The underlying mechanisms of renal damage are described below.

Metabolic changes leading to systemic and renal effects of rhabdomyolysis

The molecular mechanisms underlying systemic and renal damages and RM are associated with [1-3]: oxidative stress; inflammation and apoptosis; decreased circulating volume, vasoconstriction and dyselectrolytemia; acute tubular obstruction in myoglobinuria.

The myoglobin released by the striate muscle cells in RM enters the systemic circulation and is filtered through the glomerulus filter and reaches the tubular spaces. Then myoglobin undergoes endocytosis by the tubular epithelial cells and within the latter the Fe^{2+} is oxidized to Fe^{3+} leading to the formation of reactive oxygen species (ROS). These ROS lead to lipid peroxidation, protein and DNA changes with subsequent induction of inflammatory response and cell apoptosis (mainly due to mitochondrial damage). Moreover, the ferrymyoglobine in the urine of RM patients acts as nitric oxide scavenger and leads to endothelial dysfunction, vasoconstriction and promoter of platelet aggregation. One should not forget that the oxidative changes in myoglobin molecule are pH-dependent – alkaline environment stabilizes Fe^{2+} and decreases myoglobin reactivity.

Vasoconstriction in RM is induced by two main factors – urine ferrymyoglobine and volume depletion due to the marked swelling of the affected muscles, decreased circulating volume, systemic hypotension and rennin-angiotensin-aldosterone system activation.

The hyperkaliemia in muscle damage can lead to rhythm disturbances.

The filtered myoglobin can precipitate within the tubular spaces and cause acute obstruction of renal tubules with acute renal failure, especially in lower urine pH. Moreover, the hyperuricemia, caused by massive tissue degradation, can also lead to acute tubular obstruction.

The main protective mechanisms of the body, counteracting the adverse systemic and renal effects of RM, are hemeoxygenase and re-uptake of the released iron by ferritin [3]. Hemeoxigenase is an antioxidant enzyme that takes part in the degradation of heme to carbon monoxide, free iron and biliverdin. The free iron is then bound to ferrin that decreases iron levels and oxidative stress and has antiapoptotic effect. Carbon monoxide and biliverdin are well-known ROS scavengers and biliverdin has additional anti-inflammatory effects.

CLINICAL PICTURE

The clinical manifestations of RM are variable, ranging from asymptomatic increase in muscle enzymes (creatin kinase, lactate dehydrogenase and transaminases) and myoglobin serum levels to a very painful condition with marked muscle swelling, weakness and pain, and reddish discoloration of the urine with oligo-anuria [18]. In the majority of cases the patient can identify a clear provoking factor – muscle trauma, drug intake, etc.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis is usually based on the patient's history of trauma, drug intake, intoxication, surgery, etc., in combination with typical muscle pains with or without swelling, urine discoloration and decreased urine output. The laboratory investigations usually reveal increased serum levels of muscle enzymes (creatin kinase > 1000 U/l, lactate dehydrogenase – LDH, alanin aminotransferase – ALAT, aspartate aminotransferase – ASAT), hyperkaliemia, hyperphosphatemia with or without hypercalcemia, acidosis with increased anionic gap (due to release of organic acids from the disintegrated muscle cells), initially hyperalbuminemia due to edema of the affected muscles with subsequent hypoalbuminemia due to capillary leak of albumin, hyperuricemia, increased urea and creatinine levels [3, 18]. The urine investigations usually reveal increased specific gravity, myoglobinuria,

increased creatinine, uric acid, amino acid and glucose excretion (markers of tubular damage).

Some novel markers of acute kidney injury in RM patients include: neutrophil gelatinase-associated lipocalin (NGAL, shoes positive correlation with mortality) and kidney injury molecule-1 (KIM-1, positively correlates with the need of extrarenal depuration) [3]. These parameters are sensitive markers of kidney injury but are not routinely investigated.

Muscle biopsy, autoantibodies and genetic analysis are used to rule out some rarer forms of rhabdomyolysis.

Differential diagnosis should be made between the different types of RM (i.e., traumatic and non-traumatic) and in patients with acute renal injury all efforts should be made to identify the possible causes.

JR Nance and AL Mammen [18] propose the following algorhythm for the diagnosis of RM:

- Step 1: look for acquired causes of rhabdomyolysis: alcohol/drug intake, medications and illicit drugs, poisoning, metabolic or electrolyte disturbances, autoimmune myopathy.
- Step 2: if all causes in step 1 are ruled out, consider inherited metabolic cause: disorders of glycogen metabolism, disorders of lipid oxidation or mitochondrial diseases.
- Step 3: if all causes in steps 1 and 2 are ruled out, consider muscular dystrophy or congenital myopathy or LIPN1 mutation.
- Step 4: if all other causes are ruled out, consider idiopathic benign RM (a diagnosis of exclusion).

TREATMENT AND PROGNOSIS

The treatment of patients with RM depends on the underlying cause and on the presence or absence of acute kidney injury. General supportive measures include: rehydration / correction of water and electrolyte balance, alkalization of urine (intravenous saline infusions and sodium bicarbonate to reduce protein precipitation in the tubules), supportive treatment (gastroprotection, prophylaxis of thromboembolism, antibiotics if needed, etc.). Once euvolemic state is achieved diuretic medications can be added. The administration of mannitol remains disputable. As osmotic diuretic, it increases urinary flow and can prevent myoglobin precipitation. Moreover, mannitol has ROS scavenging properties. Still, no randomized controlled trials on the use of mannitol in RM with or without acute kidney injury are available.

Renal replacement therapy is indicated in the cases of massive RM with refractory anuria, severe metabolic disturbances (life-threatening hyperkaliemia, hypercalcemia, acidosis). Moreover, in patients with acute renal failure myoglobin can be removed from circulation with the use of high-flux dialysers with large pore size [3]. Plasma exchange has also been reported to be beneficial [3]. The Cystosorb® filter is known to effectively remove cytokines (including tumor necrosis factor alpha, interleukins) and is known to have beneficial in sepsis model in mice, but whether it will have anti-inflammatory effect in RM-induced renal injury remains unknown.

Newer therapeutic strategies in RM with acute kidney injury include [3]: anti-inflammatory medications (including corticosteroids), iron helators, antioxidants (N-acetyl cystein, flavonoids, vitamin E, L-carnitine, suramine, pentoxyphylline), vasoconstriction inhibitors (L-arginine, moldosine). Recombinant human erythropoietin can reduce renal damage and improve renal tubular function by increase of nuclear factor kappa-b activation but no studies on its effects in humans with acute renal injury due to RM have been performed.

Mesenchymal stem cells are known to reduce RM-induced kidney injury in mice but no large-scale studies have been performed in humans.

Concerning the prognosis of RM patients, the overall mortality in this population is between 2% and 46% [5], depending on the etiology, timing and type of treatment and accompanying diseases. The majority of patients with RM-induced acute kidney injury recover within several months with some degree of renal impairment due to the development of interstitial fibrosis and glomerular sclerosis caused by macrophage activation. There are no studies on the long-term outcome of RM in humans [3].

CLINICAL CASES

Patient 1

A 39 years-old male athlete was admitted to the Clinic of Nephrology for acute renal failure after active sports. The patient took part in a martial arts fight and about 2 days after the fight noticed decrease in urine output and reddish discoloration of the urine. The laboratory investigations at the admission revealed: marked increase in serum creatinine levels (1051 mcmol/l), urea 17.6 mmol/l, hyperuricemia (880 mcmol/l), hyperkaliemia (5.89 mmol/l), increased prosphate levels (1.79 mmol/l) with normocalcemia (2.29 mmol/l), increased creatinkinase (4026 U/l), ASAT (91 U/l) and ALAT (53 U/l) levels, increased LDH (604 U/l), decreased serum albumin (34 g/l) and total protein levels (53 g/l). Urinalysis revealed pH 5, specific gravity 1025, positive protein, sediment: 2-3 RBC/pf, 4-5 WBC/pf. Proteinuria 0.06 g/24 hours.

Abdominal ultrasound revealed normal kidney size 110-113 mm, renal parenchyma 20-23 mm, diffusely increased parenchymal echogenicity of 2 gr., with contrasting hypoechogenic pyramids (the image of diffuse renal parechymal disease) (Figure 1).

The patient was started intravenous infusions of 1000 ml saline plus 1000 ml 5% glucose solution, intravenous sodium bicarbonate, low-dose intravenous corticosteroids (20 to 40 mg methylpredisolon per day), intravenous furosemide 40 mg a day, gastroprotection with intravenous omeprazole 20 mg a day, heparin. The diuresis improved and reached 3 000 ml per 24 hours, serum creatinine levels fell to 760-310-110 mcmol/l, creatin kinase – to 325 U/l, LDH, ASAT and ALAT, serum potassium and phosphates returned to normal levels. The acute renal failure was interpreted as associated with rhabdomyolysis.

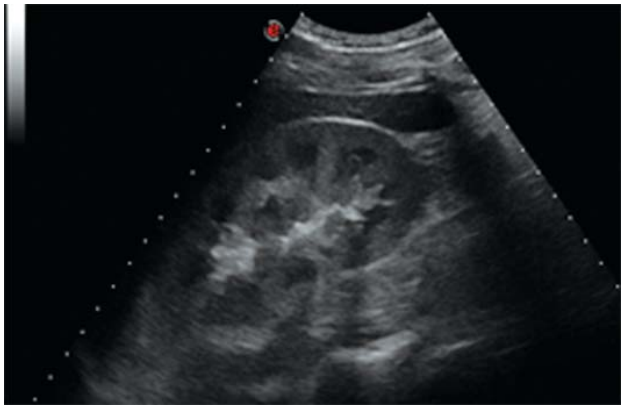

Fig. 1. Abdominal ultrasound of patient 1 revealing diffuse renal parenchymal disease – normal kidney size with thick hyperechogenic parenchyma and contrasting hypoechogenic pyramids

Patient 2

A 24-years old male heroin-addict was admitted to the Clinic of Nephrology for acute renal failure (serum creatinine of 500 mcmol/l, urea of 24.1 mmol/l) with anuria after an episode of heroin overdose with coma and rhabdomyolysis (creatin kinase 5500, LDH 1200, ASAT 280, ALAT 124, potassium 6.8 mmol/l, calcium 3.01 mmol/l, prosphates 2.02 mmol/l), proteinuria 1.12 g/l. The patient developed deep-vein thrombosis of vena femoralis. The ultrasound investigation again revealed diffuse renal parenchymal disease with medullary nephrocalcinosis (Figure 2). The immunological investigations revealed positive IgG anticardiolipin antibodies, suggesting the presence of antiphospholipid syndrome. HIV, HBV and HCV tests were negative. RF, cryoglobulins, C3 and C4 were within the normal limits. The patient was started on intravenous infusions, alkalization with sodium bicarbonate, intravenous furosemide 40 mg a day and intravenous corticosteroids (methylprednisolon 20 to 40 mg per day), gastroprotection and heparin infusion. Within 4 days diuresis improved and reached 2500 ml per day, serum creatinine fell to 220-90 mcmol/l, urea, cytolytic enzymes, potassium, calcium and phosphates fell to normal levels. Renal biopsy showed chronic tubulo-interstitial nephritis. The episode of acute renal failure was interpreted as acute kidney injury associated with rhabdomyolysis at the background of chronic tubulo-interstitial nephritis of toxic origin. The patient continued low-dose corticosteroids for 6 months and ceased heroin intake. Anticardiolipin antibodies returned to normal levels within 6 months suggesting heroin-induced antiphospholipid syndrome. The patient had had no further thrombotic episode.

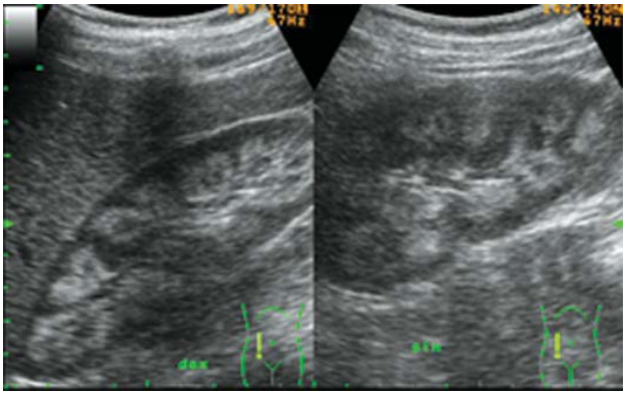

Fig. 2. Abdominal ultrasound of patient 2 revealing medullary nephrocalcinosis

Patient 3

A 21 years-old male patient was admitted to the Clinic of Cardiology for chest pain, tachycardia of 138 bpm and hypertensive crisis of 170/115 mm Hg. The ECG revealed ST-segment depression in II, III and aVF leads. The clinical laboratory investigations showed normal troponin T (0.01 ng/ml), marked increase in creatin kinase (10 000 U/l), initially normal serum creatinine (90 mcmol/l) with mild increase on the following day (150 mcmol/l). The patient had normal urine output. Abdominal ultrasound revealed normal image of both kidneys. The urine test for amphetamine came positive and the patient reported amphetamine intake the previous night. The patient was started on intravenous infusions, intravenous sodium bicarbonate, heparin infusion, sedation, beta-blocker. Serum creatin kinase returned back to the normal limits within 7 days, serum creatinine fell to the normal levels within 3 days, pulse rate and blood pressure remained within the normal limits without further medication after the cessation of amphetamine intake. ECG normalized within 3 days and was interpreted as subendo-

cardial ischemia due to vasospasm in amphetamine use. The acute renal injury was interpreted as associated with rhabdomyolysis and generalized vasospasm due to amphetamine intake.

Patient 4

A 42-years male patient with heroin overdose was started on dialysis due to therapy-resistant anuria and azotemia (serum creatinine 281 mcmol/l, urea 29 mmol/l) with extreme elevation of cytolytic enzymes (creatin kinase 171 340 mcmol/l, ASAT 1 830 U/l, ALAT 666 U/l). After awakening from heroin-induced coma the patient reported severe diffuse muscle pain. The patient reported heroin and marijuana use for the past 10 years. Creatin kinase levels gradually fell within the normal limits within three weeks but despite the renal depuration, infusions of saline and sodium bicarbonate, intravenous corticosteroids and supportive treatment the patient never regained spontaneous diuresis and remained on chroniohemodialysis.

CONCLUSION

Rabdomyolysis is a severe condition, frequently associated with renal damage. The proper and timely diagnosis and treatment are the keys to the favorable outcome. The therapeutic strategy in RM, especially with acute kidney injury, aims at elimination of the cause of RM, correction of electrolyte and metabolic abnormalities, restoration of renal function and prevention of systemic complications. Proper hydration, urine alkalization, anti-inflammatory and anti-oxidant treatment can minimize the need for dialysis but still extrarenal depuration remains one of the therapeutic modalities. In three of the described patients renal function returned to normal after conservative treatment started early. In patient 4 extrarenal depuration was initiated due to resistant anuria. The patient did not restore renal function despite adequate treatment – conservative plus dialysis. In three patients RM was caused by illicit drug abuse. The intake of recreational and illicit drugs should be suspected in all patients with renal disease and RM of unknown origin.

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