

Acute Kidney Injury and Rhabdomyolysis

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Abstract

Background and objectives: Rhabdomyolysis is clinical syndrome characterized by breakdown of skeletal muscle and the release of intracellular contents into the circulation. Acute kidney injury (AKI) is one of the common systemic complication of rhabdomyolysis. The aim of the study is to report the varied aetiologies of rhabdomyolysis and to study their presentation, clinical profile and outcome in patients with AKI.

Methods: Sixty-four patients are identified with rhabdomyolysis over a period of one year and out of them AKI was seen in 24 patients (37.5%). The association of rhabdomyolysis and AKI was studied retrospectively in eight patients based on the data in our charts.

One patient from different aetiologies of rhabdomyolysis leading to AKI was taken to report the varied aetiologies and presentation of rhabdomyolysis. Hence, eight patients included in the study. Data was expressed as median.

Results: Our results show that AKI associated with rhabdomyolysis was related with comorbidity in all cases (bacterial sepsis, statin induced, chemotherapy induced, herbicide poisoning, cocaine abuse, road traffic accident, strenuous exercise, metabolic myopathy). Most common presenting symptom was myalgia followed by oliguria. Maximum median serum creatinine was 4.7 mg/dl before treatment and 1.7 mg/dl after treatment. Maximum median creatine phosphokinase levels was 2451 IU/L before treatment and 262 IU/L after treatment. Treatment given for rhabdomyolysis and acute kidney injury include either conservative treatment with adequate hydration and alkaline diuresis or invasive treatment such as renal replacement therapy or both. All the patients were treated with hydration and six patients required haemodialysis during hospital stay. Serum creatinine fell simultaneously with the decrease in creatine phosphokinase levels in all cases.

Conclusion: In conclusion, rhabdomyolysis is an uncommon and preventable cause of AKI. It is caused by varied aetiologies, hence high index of suspicion regarding rhabdomyolysis is required in patients with AKI. The presence of rhabdomyolysis associated with AKI is indicative of the presence of comorbidity, as observed in all eight patients studied here. There was an improvement of renal function in all cases as creatine phosphokinase levels decreased. Hence, timely intervention is required to prevent adverse outcomes in rhabdomyolysis.

Keywords: Rhabdomyolysis • Acute kidney injury • Pigment nephropathy • Myoglobinuria • Creatine phosphokinase

Introduction

Rhabdomyolysis is clinical syndrome characterized by breakdown of skeletal muscle and the release of muscle intracellular contents into the circulation [1]. It is a type of pigment nephropathy. It was first reported in Germany in 1881 [2]. Bywaters and Beall described in detail after the London blitz during the second world war in 1941. They described the first association between crush injury and acute kidney injury (AKI) [3]. Details about the global incidence of rhabdomyolysis is limited.

There are eight commonly reported causes of rhabdomyolysis. They are trauma, muscle exertion, muscle hypoxia, genetic defects, infections, body temperature changes, metabolic and electrolyte disorders, drugs and toxins and idiopathic causes [4]. The causes of rhabdomyolysis are different depending on the age. The most commonly reported causes in adults are trauma, drugs and infections [5,6] whereas in children it is trauma, viral infections, drugs and exercise aetiologies [7]. Clinically patients commonly present with triad of symptoms such as myalgia, weakness, and myoglobinuria, classically described as brown-coloured or tea-coloured urine. Systemic complications of rhabdomyolysis are acute kidney injury, hyperkalemia, hypocalcemia, disseminated intravascular coagulation, compartment syndrome and cardiac arrhythmias and cardiac arrest [3].

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Acute kidney injury is the most common systemic complication. AKI incidence in patients with rhabdomyolysis is between 10% to 55% and usually associated with poor outcome in the presence of multiorgan failure [8]. There are three mechanisms postulated to explain rhabdomyolysis causing AKI: 1) intrarenal vasoconstriction, 2) direct and ischemic tubular injury and 3) tubular obstruction. This study evaluates eight patients with AKI associated with rhabdomyolysis and the relation of the latter to causes and outcome after treatment. The aim of the study is to report the varied aetiologies of rhabdomyolysis and to study their presentation, clinical profile and outcome in patients with AKI.

Methods

The data of patients admitted with rhabdomyolysis at Sri Ramachandra Institute of Higher Education and Research, a tertiary care teaching institute situated in the South Indian city of Chennai was collected from the electronic medical records. A total of 11,260 patients admitted in all the departments at our centre were retrospectively analysed, between January 2018 to December 2018. Patients with age > 18 yrs, elevated creatine phosphokinase levels and positive urine myoglobin were included. Patients with chronic kidney disease and acute myocardial infarction were excluded from the study. The demographic, clinical and laboratory data of the patients were obtained by reviewing the hospital electronic medical records in a standard proforma. The clinical data studied included cause of rhabdomyolysis, comorbidities, length of hospital stay, need for renal replacement therapy and outcome. The laboratory data including creatine phosphokinase levels, urine for myoglobin, admission and peak serum blood urea nitrogen and creatine, serum calcium, serum phosphorus, serum electrolytes, serum uric acid and serum albumin levels were recorded. The primary outcome was length of hospital stay and mortality. Secondary outcome were requirement of renal replacement therapy (Figure 1).

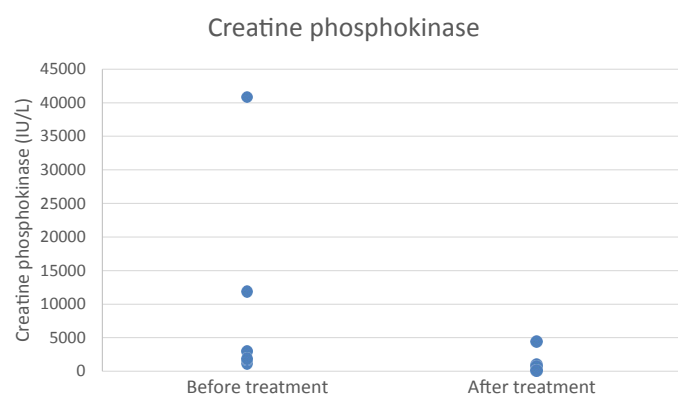


Figure 1. Creatine phosphokinase values before and after treatment of rhabdomyolysis.

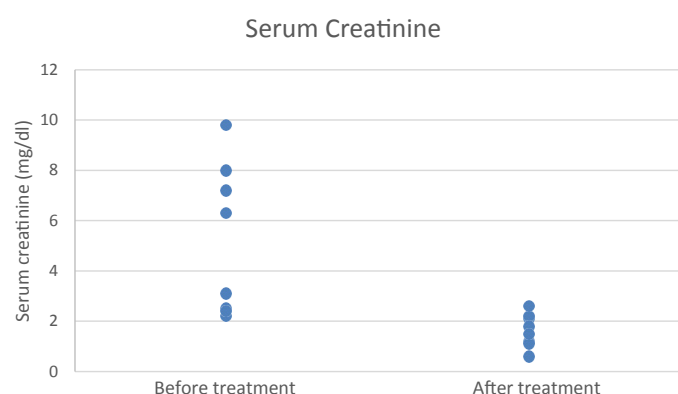


Figure 2. Serum creatinine values before and after treatment of rhabdomyolysis.

Rhabdomyolysis was diagnosed on the basis of medical history and laboratory findings including elevated CPK levels $>1,000$ IU/L with positive urine myoglobin. The definition of AKI was based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. Renal replacement therapy included haemodialysis or continuous renal replacement therapy (CRRT). Data are expressed as median and percentile.

A total of 64 patients with rhabdomyolysis were identified, out of them 24 patients were diagnosed with AKI. All the causes of rhabdomyolysis in these patients were divided into different broad groups. Eight broad groups (Infection, muscle exertion, genetic causes, poisoning, trauma, statin induced, other drugs induced, substance abuse) were identified based on the data. One typical case from each group of rhabdomyolysis leading to AKI was taken to show the varied aetiology profile of rhabdomyolysis and their clinical profile and outcome. Hence, eight patients were included in this study.

Results

Table 1 shows the clinical data of all the eight patients. (age range: 18-86 years, median: 48 years), and Table 2 shows the serum creatinine and CPK levels of the patients. The maximum median serum creatinine were 4.7 mg/dl at admission and 1.7 mg/dl after treatment. Maximum median serum CPK levels was 2451 IU/L and 262 IU/L after treatment. With treatment of rhabdomyolysis by either invasive or conservative approach there is decrease in CPK levels along with decrease in serum creatinine levels. The most common presenting symptom was myalgia followed by oliguria. No mortality recorded. Residual renal failure by the end of 3-months seen on four patients (Figure 2).

One patient with bilateral bacterial pneumonia (patient 1) presented with breathing difficulty and myalgia. Patient was treated conservatively with intravenous antibiotics and hydration. Patient symptomatically improved with decrease in serum creatinine and CPK levels at the time of

Table 1. Age, gender, diagnosis and treatment of eight patients with rhabdomyolysis and acute renal failure.

Patient	Gender	Age (years)	Diagnosis	Treatment given
1	F	86	Respiratory sepsis	H+HD
2	M	24	Heavy weights fitness training	H
3	F	18	McArdle disease	H+HD
4	M	20	Terbutryn poisoning (Herbicide)	H+HD
5	M	75	Road traffic accident	H
6	M	69	Statin induced	H+HD
7	F	72	Oxaliplatin induced (EOX Regimen)	H
8	F	27	Cocaine abuse	H+HD

H: Hydration $\pm$ alkaline diuresis; HD: Haemodialysis; M: Male, F: Female; EOX Regimen: Epirubicin, oxaliplatin and capecitabine regimen.

Table 2. Maximum creatinine and maximum creatine phosphokinase values before and after treatment.

Patient	Maximum serum creatinine levels (mg/dl)	Serum creatinine levels after treatment (mg/dl)	Maximum CPK levels (IU/L)	CPK levels after treatment (IU/L)
1	3.1	2.1	1522	980
2	2.5	1.2	1131	301
3	7.2	0.6	2971	4430
4	8.0	2.2	3011	160
5	2.2	1.1	1680	130
6	6.3	1.8	40860	223
7	2.4	1.5	11840	774
8	9.8	2.6	1930	123
#	4.7	1.7	2451	262

CPK: Creatinine Phosphokinase; #: Values expressed as median

discharge. One young male patient (patient 2) with excessive weight lifting on his first day of gym training presented with decreased urine output and myalgia. Conservative treatment with bed rest and intravenous fluids with alkaline diuresis reduced his serum creatinine and CPK levels. Patient was discharged with normal renal function and CPK levels.

One young female patient (patient 3) with metabolic myopathy presented with cola coloured urine with myalgia and easy fatigability during daily activities. She required one cycle of haemodialysis due to her uremic symptoms along with adequate hydration. Due to her persistently elevated CPK levels even after treatment, patient was suspected to have metabolic myopathy and forearm ischemic stress test was done which showed features suggestive of McArdle disease. DNA analysis for common mutations showed homozygous autosomal recessive mutation in the PYGM gene diagnostic of McArdle disease. Patient was advised to avoid heavy exercise, adequate hydration, high carbohydrate diet with levocarnitine tablets and creatine powder supplementation.

Patient 4 presented with terbutryn (herbicide) poisoning presented with oliguria, cola coloured urine and myalgia. Patient was treated with two sessions of haemodialysis along with intravenous fluids. Patient had decrease in serum creatinine with improvement in urine output and decrease in CPK levels. Patient was discharged with normal CPK levels with residual renal dysfunction which normalised over a 3 month follow-up. One patient (patient 5) presented with road traffic accident with history of fall from running motor bicycle. Patient had multiple fractures and severe abrasions all over the body with elevated serum creatinine and CPK levels. Patient improved with conservative management.

One patient with acute coronary syndrome (patient 6) was started on statins. After 10 days she presented with reduced urine output and severe myalgia. Patient required one session of haemodialysis. CPK levels and serum creatinine reduced gradually after stopping the drug. One elderly

patient diagnosed with carcinoma colon (patient 7) and was given one cycle of chemotherapy with epirubicin, oxaliplatin and capecitabine (EOX regimen). One week after taking therapy patient presented with nausea, and generalised myalgia. On investigating CK levels were 40860 IU/L with worsening renal function. Chemotherapy was stopped and patient was given fluids and five cycles of RRT was done. After 3 weeks patient CK levels reduced and became dialysis independent. At 3 months follow up patient had normal CK levels with serum creatinine of 3.8 mg/dL.

One patient (patient 8) with cocaine abuse presented with generalised myalgia and oliguria for 3 days. Investigations showed elevated CPK levels and deranged renal parameters. Patient required three cycles of haemodialysis, fluid therapy and alkaline diuresis. Patient improved with normal renal profile and CPK levels after a 3 month follow up.

Discussion

In the cases reported in this investigation, rhabdomyolysis was associated with different aetiologies as observed. Incidence of rhabdomyolysis in infections is 5% in the literature 25 years ago [9]. Betrosian et al. in a study on 35 subjects with rhabdomyolysis secondary to bacterial sepsis observed that gram positive pathogens more frequently caused rhabdomyolysis compared to gram negative pathogens [10]. The most common sites of infection in their study was lung followed by urosepsis and gall bladder infection. In the present study, one patient (patient 1) had respiratory sepsis secondary to klebsiella species infection. With adequate hydration, haemodialysis and treatment of the underlying infection, patients become dialysis independent. The incidence of exertional rhabdomyolysis is difficult to define, as most of the patients do not seek medical attention. The largest data by Hill on U.S. Army soldiers reported an incidence rate of 0.2% which translates to a yearly rate of 7-8 cases/10,000 [11]. In the present study, patient 2 presented with one day history of strength training (weight lifting) at gym. Patient improved with hydration and alkaline diuresis and had a normal renal function during a 3 month follow-up.

Genetic disorders presenting with rhabdomyolysis is rare and they usually manifest during childhood. History of recurrent episodes of rhabdomyolysis and family history of recurrent episodes precipitated by mild exertion or starvation should raise the suspicion of genetically determined metabolic myopathy [1]. Patient 3 is diagnosed with McArdle disease or glycogen storage disease type 5 (GSDV) which is a type of metabolic myopathy. Patient CK was still high after a 3 month follow-up with normal renal function. Patient was advised to avoid acute heavy exercise, fluid intake of 3 litres per day, high carbohydrate diet and was started on levocarnitine tablets and creatine powder supplementation.

The incidence of herbicide induced rhabdomyolysis and AKI is not known. A study by Park, Jae-Seok et al. [12] on 93 cases reported 1.8% incidence of rhabdomyolysis secondary to acute pesticide poisoning. In their study 16 patients presented with herbicide subclass poisoning and the amount of chemical ingested was significantly higher in rhabdomyolysis patients compared to non-rhabdomyolysis patients. There is no case reported with acute terbutryn poisoning presenting with rhabdomyolysis and AKI. Our patient (patient 4) presented with ingestion of the herbicide terbutryn. Patient was given gastric lavage and IV fluids. Patient required two cycles of haemodialysis following which patient recovered gradually. Outcome in acute pesticide poisoning depends on the amount ingested and the time lag for admission. Traumatic rhabdomyolysis was first described during world war II by Bywaters during London bombings [3]. High index of suspicion is required to diagnose these patients. On scene treatment and aggressive fluid therapy and early recognition and treatment of complications are required to prevent adverse outcomes. An observational study by M Alezrah et al. on seven patients with post traumatic rhabdomyolysis showed two patient with CPK levels >10,000 IU/L and required RRT. But in their study they concluded that the need for renal replacement therapy was not linked to elevated CPK levels but rather to acidosis due to intra-abdominal complications [13]. Large cohort studies are required to study this association.

Incidence of statin-induced rhabdomyolysis was 0.3-13.5 cases per 1,000,000 statin prescription, according to US Food and Drug Administration adverse event reporting system database. The risk factors that predispose a person to statin-induced rhabdomyolysis are low body mass index, older age, female sex, hypothyroidism, hypertension, alcohol or drug abuse [14]. Our patient (patient 6) was recently diagnosed with coronary artery disease and dyslipidaemia. Patient was started on atorvastatin 40mg. Ten days after starting the drug patient presented with rhabdomyolysis and AKI. Following treatment and follow up after 3 months patient had a normal CK with stable renal function. Identifying patients with risk of statin-induced rhabdomyolysis could prevent complications and further improve the positive benefit-risk ratio of statins. A comprehensive review of case reports by Polyana Mendes et al. [15] reported that rhabdomyolyses was more common in men and in people over 45 years of age, and in those with multiple pre-existing conditions such as cardiovascular disease and dyslipidaemia. Chemotherapy drugs causing rhabdomyolysis is rare. Incidence is not known. Our patient (patient 7) was diagnosed carcinoma colon and was given one cycle of chemotherapy with epirubicin, oxaliplatin and capecitabine (EOX regimen). One week after taking therapy patient presented with severe rhabdomyolysis and AKI. Rhabdomyolysis is one of the less common side effect of EOX regimen, but may be severe or life threatening [16]. There are no case reports of epirubicin and capecitabine causing rhabdomyolysis individually. Oxaliplatin is a platinum-based chemotherapy drug and is commonly used in the treatment of colorectal cancers. There was one case reported by Maruoka et al. [17], where patient presented with myalgia and rhabdomyolysis within few hours after receiving the drug. Patient was treated conservatively with fluids and did not develop any complications of rhabdomyolysis.

Cocaine induced rhabdomyolysis was first reported in 1987 [18]. Rhabdomyolysis is seen in 24% of cocaine users. This is due to direct effect on the muscle tissue, inducing vasoconstriction and tissue ischemia [19]. Our patient (patient 8) presented with generalised myalgia and oliguria for 3 days following cocaine abuse. Patient required three cycles of haemodialysis, fluid therapy and alkaline diuresis. Patient improved with normal renal profile and CPK levels after a 3 month follow up.

The mechanisms postulated to explain rhabdomyolysis causing AKI are intrarenal vasoconstriction, direct and ischemic tubular injury and tubular obstruction.

Intrarenal vasoconstriction is due to intravascular volume depletion caused by fluid sequestration within damaged muscles leading to activation of renin-angiotensin system, vasopressin and also due to vascular mediators that reduced renal blood flow such as endothelin-1, thromboxane A₂, tumor necrosis factor α , f₂-isoprostanes and reduced vasodilator nitric oxide. Direct tubular toxicity is due to uncontrolled release of reactive oxygen species and free radicals by cellular myoglobin release that cause direct cellular injury. It occurs mainly at the level of proximal tubule. Myoglobin gets concentrated in the renal tubules due to volume depletion and vasoconstriction, and after interacting with Tamm-Horsfall protein it precipitates causing tubular obstruction. This is favoured by acidic urine and occurs mainly at the level of distal tubule [4].

Diagnosis of rhabdomyolysis is by measuring creatine phosphokinase (CK) levels (>1000 IU/L) although there is no cut-off value. The risk of AKI is low with low CK values [20]. Myoglobinuria is diagnosed if urinary dipstick test shows a positive result for blood and there are no red cells in the sediment and has a sensitivity of 80% for diagnosis of rhabdomyolysis [8]. Serum myoglobin levels has a rapid and unpredictable mechanism and hence has a low sensitivity for the diagnosis of rhabdomyolysis [21,22]. The electrolyte abnormalities that commonly occur during rhabdomyolysis with AKI are hyperkalemia, hyperphosphatemia, hyperuricemia, high anion-gap metabolic acidosis, hypocalcemia, hypercalcemia and hypermagnesemia [23,24].

Therapeutic approaches in rhabdomyolysis for prevention and treatment of AKI include two approaches: 1) Conservative approach, 2) Invasive approach. Conservative approach includes fluid resuscitation, urine

alkalization and diuretic agents. In severe cases treatment is by invasive approach with intermittent haemodialysis or continuous renal replacement therapy (RRT) based on the hemodynamic stability of the patient. High permeability dialyzer membranes can be beneficial [25].

Conclusion

To conclude, rhabdomyolysis is a clinical syndrome caused by different clinical settings. The potential aetiologies like direct traumatic injury, drugs, toxins, infections, genetic disorders, muscle ischemia, exertion should be considered. It exhibits a triad of symptoms like myalgia, weakness and myoglobinuria. Elevated CK level is the most sensitive test. Prognosis depends on complications resulting from rhabdomyolysis and underlying cause. Early diagnosis and fluid expansion reduces the risk of AKI and has excellent prognosis. This clinical study is done to report the varied aetiologies of rhabdomyolysis. So in patients presenting with acute kidney injury, work up for rhabdomyolysis is required as it may be unnoticed leading to various systemic complications. High index of suspicion with prompt treatment can prevent the risk of AKI and other systemic complications.

Conflict of Interests

All the authors declare no competing interests.

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