Original Article

An Observational Epidemiological Study of Exercise-induced Rhabdomyolysis Causing Acute Kidney Injury: A Single-center Experience

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Abstract

Exercise-induced rhabdomyolysis (EIR) is an uncommon cause of severe rhabdomyolysis and a very rare cause of acute kidney injury (AKI). A prospective observational study of 25 patients diagnosed with EIR was conducted in a multispecialty hospital in Dubai, from 2009 to 2015. Five out of 25 patients experienced AKI necessitating temporary renal replacement therapy. The initial presentation, biochemical parameters, and clinical course of patients were monitored, to understand epidemiology and risk factors for the development of AKI. There was male preponderance (4 out of 5 patients), higher rate of systemic symptoms (all 5 patients) versus 60% in NRAKI), oligo-anuria (all 5 patients), compartment syndrome (3 out \of 5) and severe dehydration seen in patients with RAKI group. On laboratory evaluation, there was higher rise in creatinine kinase (CK) enzyme, serum and urine myoglobin levels impaired renal function on presentation, hyperuricemia, high D-dimer level, PCV of more than 55%, found to be associated with RAKI as compared to NRAKI group. Hematuria by positive urine dipstick with absent red blood cells on urinalysis, is an insensitive tool as was present in only 62% and 43% of RAKI and NRAKI groups, respectively. It was also observed that delayed pesentation for medical care, metabolic acidosis, were commonly associated with AKI. All patients with RAKI required RRT for a comparable period of time (3–4 weeks). In all of them, no deterioration or relapse reported on follow-up of 3 months.

Keywords: *Acute kidney injury, exercise-induced rhabdomyolysis, rhabdomyolysis*

Introduction

Exercise-induced rhabdomyolysis (EIR) requiring medical attention is a rare complication of any form of exercise. The manifestations of EIR are mostly nonspecific and can delay medical attention most of the time; however, complications of EIR are serious. EIR can cause acute kidney injury (AKI), hepatic dysfunction, compartment syndrome, dysarrhthymia, heart failure, electrolyte imbalance, and in severe cases even death.[1] AKI is one of the most serious complications associated and only very few prospective studies published on the characteristics, risk factors, and prognosis of severe EIR with AKI.[2,3] In this prospective observational study, we observed the characteristics of patients, with EIR admitted to the hospital from 2009 to 2015, elucidating the risk factors, investigations, complications, and prognosis of EIR.

Materials and Methods

A prospective observational study was conducted in a tertiary care hospital in Dubai, from 2009 to 2015, to evaluate the clinical and the investigation parameters of all the patients who presented with EIR. The inclusion criteria were evidence of rhabdomyolysis (creatinine kinase [CK] ten times above the upper limit of normal) with a history of strenuous activity in the last 5 days.[1] The patients with other risk factors for rhabdomyolysis were excluded from the study.

The Kidney Disease Improving Global Outcome (KDIGO) clinical practice guideline 2012, criteria for diagnosing AKI was considered. The sequential organ failure assessment score was used for the diagnosis of other organ failures. The investigations included serum CK, lactate dehydrogenase (LDH), urinalysis, serum and urine myoglobin level, complete blood count, liver function tests, serum electrolytes, blood urea and serum creatinine, blood gas analysis, and serum uric acid.

Results

There were 25 patients in this study as per the inclusion criteria, all of them

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were male patients, with age ranged between 21 and 36 years and median of 29 years. Myalgia was the most common presentation (25 patients; 100%). Swelling and tenderness involving two major groups of muscles were present in upper limbs bilaterally in seven patients (28%), quadriceps bilaterally in ten patients (40%), and generalized in eight patients (32%). Dark (cocoa)-colored urine was present in 25 (100%) patients and 5 (20%) patients were oligoanuric on presentation. The patients were further classified according to renal dysfunction into AKI on presentation (RAKI) and no renal injury on admission (NRAKI) [Table 1].

RAKI patients

Five patients presented with AKI according to KDIGO criteria on presentation. Three patients had a history of long distance running (more than 5 km), two others were engaged in outdoor sports in the last 5 days. All of these patients had systemic symptoms on admission such as fever, nausea, vomiting, and altered mental status. All of them had dark-colored urine and were oligoanuric on presentation. The median duration of presentation from inciting exercise was 78 h. Three patients (60%) had extensive lower limbs swelling, which evolved into compartment syndrome. An urgent fasciotomy was performed in all the three patients. All the patients presented without hypotension (systolic blood pressure <90 mmHg). All patients with RAKI were managed with targeted fluid hydration using mainly crystalloids (ringer lactate and 0.9% normal saline) using hemodynamic tools such as central venous pressure and ultrasound, monitoring of electrolytes, renal functions, arterial blood gas, CK, and urine output. The investigations of these patients are mentioned in Table 2. All five patients had abnormal electrolytes such as hyperkalemia, hypocalcemia, and hyperphosphatemia associated with severe rhabdomyolysis [Table 3]. All patients required renal replacement therapy (RRT). The mean packed cell volume (PCV) and mean D-dimer on presentation were 57% and 1624 ng/ml, respectively. The median duration of RRT was 3.4 weeks and all of the five patients recovered renal function in 8–12 weeks.

Table 1: Comparison of initial presentation, laboratory features, and clinical course of patients with exercise-induced rhabdomyolysis in renal dysfunction (RAKI) and without renal dysfunction groups (NRAKI)

Variables	RAKI	NRAKI
Number of patients	5	20
Oligoanuria	5	None
Metabolic acidosis	5	None
CS	3	None
Systemic manifestation	5	12
AKI on presentation	5	None
D-dimer (mean), ng/ml	1624	560
DIC	None	None
PCV (%)	57	42
Urgent fasciotomy	3	-
Hemodialysis	5	0
Urine analysis (positive urine dip and absent RBC) (%)	62	43

AKI: Acute kidney injury, DIC: Disseminated intravascular coagulation, PCV: Packed cell volume, RBC: Red blood cell, CS: Compartment syndrome

NRAKI patients

There were twenty patients who present with EIR without AKI on admission. Eleven patients had a history of long distance running (more than 5 km), seven patients were engaged in outdoor sports, and two were laborers working at outdoor construction. The systemic symptoms were present in 12 (60%) and local symptoms such as myalgia and swellings of lower limbs were present in 18 patients (90%). No compartmental syndrome was reported in any of these patients with NRAKI. All of these patients have dark-colored urine but were nonoliguric and presented within 24 h of the insult. The CK enzyme ranging from 5000 to 35,000 ng/ml and serum and urine myoglobin levels ranging between 8000–15,000 ng/ml and 17,000–25,000 ng/ml, respectively, were abnormal laboratory investigations. PCV (mean 42%) and D-dimer (mean 560 ng/ml) was normal in all twenty patients. The patients were managed similarly with balanced and target hydration as like RAKI patients and none of the patients required RRT. The hydration was targeted and continued till CK was <1000 U/L and clinical

Table 2: Clinical and investigational features of patients with rhabdomyolysis-induced acute kidney injury

Patient	Systemic symptoms (+: Present, -: Absent)	Hemodialysis (+: done, -: Not done)	Metabolic acidosis (+: Present, -: Absent)	Myoglobin urine (ng/ml)	Uric acid (mg/dl)	Myoglobin serum (ng/ml)	CK (U/L)	AKI (KIDGO stage)	CS	LDH (ng/ml)	D-dimer (ng/ml)	PCV (%)
1	+	+	+	10,500	10	14,000	17,080	3	+	37,000	1500	56
2	+	+	+	12,000	11	16,000	19,500	2	+	41,000	1550	59
3	+	+	+	11,000	30	14,500	23,200	3	-	35,750	1670	55
4	+	+	+	15,000	10.5	16,000	25,600	3	-	51,000	1804	57
5	+	+	+	55,000	9.8	19,450	33,030	3	+	50,115	1595	58

CK: Creatinine kinase, AKI: Acute kidney injury, KIDGO: Kidney Disease Improving Global Outcome, LDH: Lactate dehydrogenase, PCV: Packed cell volume, CS: Compartment syndrome, +: Present or absent

Table 3: Serum electrolytes and renal function tests of patient with acute kidney injury

Patient	Urea/creatinine (mg/dl)	Serum sodium/potassium/ calcium/phosphorous (mmol/L)
1	48/2.2	139/5.7/6.8/4.7
2	29/2.4	146/5.9/6.9/4.3
3	40/3.7	145/6.1/7.0/5.1
4	62/4.3	141/5.5/6.6/4.7
5	54/4.1	143/5.9/7.1/4.9

improvement, which was attained within 3–5 days in all of the patients. The follow-up of the patients for 4 weeks confirmed the sustained improvement.

Discussion

There is still an ongoing debate, regarding the risk of AKI in the context of rhabdomyolysis in general and EIR in particular.[1] Rhabdomyolysis can be defined as a syndrome caused by injury to skeletal muscle fibers and involves leakage of potentially toxic contents into plasma.[2] Rhabdomyolysis is associated with many inciting etiologies such as trauma, alcohol or illicit drug use, prescribed medicine such as statins, infections, toxins, extreme physical exertion, heat stroke, hereditary and acquired metabolic disorders, and inflammatory myopathies.[2] There are many serious complications of rhabdomyolysis such as life-threatening electrolyte abnormalities (hypokalemia, hyperkalemia, hypocalcemia), hyperuricemia, liver dysfunction, compartment syndrome, AKI, and disseminated intravascular coagulation (DIC). The pathophysiology of rhabdomyolysis-associated AKI (RAKI) is disruption of various pumps on skeletal muscle cell membrane (sarcolemma) because of adenosine triphosphate depletion.[1,3]

The Na-K-ATPase and Na-Ca pumps are main pumps resulting in impaired sodium and calcium extrusion from myocytes. This leads to activation of various intracellular cytolytic enzymes and release of potassium, phosphates, and potential toxins such as myoglobin, CK, LDH, and aldolase into the blood circulation. Excess myoglobin may cause nephrotoxicity by renal vasoconstriction, formation of intratubular casts, and direct toxicity.[1,4]

Due to increasing awareness about positive effects of exercise on physical and mental health, more people are participating in organized or random physical activities. EIR is still an uncommon cause of hospitalization and RAKI by EIR is very rare.[1-4] In our study, we found only 25 cases of EIR requiring hospitalization over 7 years and only five cases (20%) developed AKI. Exercise is an uncommon cause of RAKI with studies showed an incidence varying 10%–30%. The primary factors that may affect the incidence of EIR include the exercise experience of an individual, level of physical fitness, intensity, duration, or types of exercises. The novice exercisers are more prone as compared to regular athletes also intense physical activity and/or longer duration is more likely to cause EIR.[4-8] There are some secondary factors that may contribute to EIR such as hot temperatures, male sex, coexisting electrolyte imbalance (hypokalemia, hyponatremia), nutritional deficiencies (low protein diet), and use of creatinine supplements and/or drugs use.[9-17]

Our study, to our knowledge, is one of the largest cohorts of patients with EIR and RAKI. In our study, there was an apparent disparity between the two groups, in terms of clinical presentation and investigations. All patients had local symptoms; however, systemic symptoms were vague and present only in 60% patients with NRAKI group. The tropical desert climate of our country with its urban and mainly expatriates' population not adjusted to the hot and humid conditions may have contributed to EIR. In addition, like other studies, there was male preponderance and four patients were on protein supplements. The clinical symptoms, biochemical parameter between the groups showed patients with RAKI had higher rate of systemic symptoms, renal function impairment on presentation, oligoanuria, hyperuricemia, compartment syndrome, high D-dimer level, elevated PCV of more than 55%, and dehydration more commonly than NRAKI group. Hematuria by positive urine dipstick with absent red blood cells on urinalysis, a surrogate marker of rhabdomyolysis, however, is insensitive tool as was present in only 62% and 43% of RAKI and NRAKI groups, respectively. Similar results were seen in other studies.[1,3] The delayed presentation (median duration after inciting event more than 24 h), metabolic acidosis, oligoanuria and renal impairment (100% of patients with RAKI), and compartment syndrome on presentation were only associated with RAKI group. In RAKI patients, there was marked hemoconcentration with mean PCV 57%, which could be attributed to the massive destruction of muscles with subsequent evolvement of compartment syndrome leading to consequent profound extravasation of fluid into extravascular space. No overt hemoconcentration (mean PCV 42%) was found in NRAKI patients. The markedly elevated PCV, as a surrogate marker for the plasma volume contraction, might also exacerbate the muscular injury because of its heightened vulnerability to provoke vascular thrombosis. This hypothesis was fostered by the other distinctive finding of very high D-dimer (mean 1624 ng/ml) that was peculiar to RAKI patients, suggesting a concurrent thrombotic process consequent to the blood hyperviscosity, in addition to endothelial dysfunction and vasoconstriction provoked by the myoglobinuria. Despite the fact that DIC is a known complication of rhabdomyolysis secondary to the massive liberation of tissue thromboplastin activator, it was not detected in any of our patients.[1] Therefore, the high D-dimer in RAKI patients might be marker of *in situ* venous thrombosis. This was agreed by proposition drawn

by other studies, suggesting compartment syndrome as the major risk factor for AKI in the context of rhabdomyolysis secondary to intense hypovolemia.[1,4,15]

In all five patients of RAKI, there was associated hyperuricemia (>7 mg/dl) [Table 1]; in patient 3, it was 30 mg/dl on admission. There was no significant past or family history of hyperuricemia and it was unclear whether any predisposing factor had provoked the development of marked hyperuricemia in this patient. Early visit to healthcare (median duration of presentation <24 h) and intensive management may had prevented the progression to AKI in twenty patients of NRAKI group who presented with normal renal function in concurrence with other studies.[1-3] On the contrary, in all patients with RAKI (5 out 25) on admission, who presented late, required RRT for a comparable period of time (3–4 weeks). In all of them, no deterioration or relapse reported on follow-up of 3 months.

There are few limitations of our study, long duration and small number of cases with AKI, but being a rare clinical condition, these confounding variables are acceptable.

Conclusion

EIR is the uncommon but preventable cause of AKI. The markedly elevated PCV of more than 55% and high-level D-dimer on presentation were most commonly associated with RAKI and RRT requirement. It was also observed that delayed presentation, metabolic acidosis, compartment syndrome, the renal impairment, and the oligoanuria on presentation were commonly associated with AKI. CK can be used as a monitoring tool for hydration in these patients for the prevention of AKI. There is need of awareness among the public about the risk of EIR and seeking medical help early in case of discomforting symptoms after strenuous exercises. We recommend larger studies to further verify our findings.

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Conflicts of interest

There are no conflicts of interest.

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