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Extremely High Creatine Kinase Activity in Rhabdomyolysis without Acute Kidney Injury

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Male, 22-year-old
Final Diagnosis: Rhabdomyolysis
Symptoms: Myalgia
Medication: —
Clinical Procedure: —
Specialty: Nephrology

Objective: Unusual clinical course

Background: Elevation of creatine kinase (CK) activity has been shown to be predictive of acute kidney injury (AKI) in rhabdomyolysis. Patients with extremely high CK activity with preserved renal function are uncommon. This report describes a case of non-traumatic rhabdomyolysis, with a markedly elevated CK activity, without associated AKI.

Case Report: A 22-year-old male presented with severe generalized myalgias and darkened urine for 1 week prior to his admission. The patient presented to the Emergency Department with initial CK activity of >40 000 U/L and a serum creatinine level of 0.77 mg/dL. Urinalysis was positive for myoglobinuria. Serum cystatin C confirmed an estimated glomerular filtration rate of 144 mL/min/1.73 m^2. Several causes of rhabdomyolysis, including viral infections, Lyme disease, viral hepatitis, hypothyroidism, and cocaine abuse were investigated; however, all were negative. He was given a bolus of 2 liters of normal saline and continued on intravenous normal saline at 250 mL/hour throughout his hospital stay. Urine output remained adequate. We were able to quantify his serum CK activity by dilution method, which revealed a serum CK activity of >150 000 U/L. His CK levels consistently trended down with treatment.

Conclusions: An extremely high CK activity in rhabdomyolysis may lead to AKI. However, preserved kidney function is possible. Young age, no concurrent cocaine use, and adequate oral fluid hydration may prevent AKI in rhabdomyolysis. Physicians need to remain vigilant for cases of rhabdomyolysis that have not yet caused renal compromise.

MeSH Keywords: Acute Kidney Injury • Creatine Kinase • Myoglobinuria • Rhabdomyolysis

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Background

Rhabdomyolysis is a medical condition that results from rapid breakdown and dissolution of damaged skeletal muscle fibers [1]. This condition is commonly secondary to physical trauma but can also be due to other etiologies such as muscle ischemia, toxin exposure, and muscle enzyme disorders [2]. Clinical indicators for rhabdomyolysis include myoglobinuria, fatigue, and myalgia, while laboratory indices for rhabdomyolysis include elevated creatine kinase (CK), lactate dehydrogenase (LDH), and serum myoglobin, and electrolyte imbalances such as hyperkalemia [2].

Patients demonstrate complications from rhabdomyolysis in a myriad of forms such acute kidney injury (AKI), electrolyte abnormalities, and disseminated intravascular coagulation [3]. While AKI is one of the most common and serious complications, patients with rhabdomyolysis require careful and thorough management to prevent it. Treatment modalities focus on AKI prevention by providing aggressive fluid resuscitation with either isotonic normal saline solution or sodium bicarbonate solution [3].

It is extremely rare for patients with severely high CK activity to have preserved kidney function. It is generally accepted that increasing CK activity in rhabdomyolysis is associated with higher incidence of AKI. This concept was adopted from at least 2 major observational studies of patients with rhabdomyolysis [4,5]. In these studies, patients with AKI had significantly higher CK activity compared to non-AKI patients with the highest peak CK activity of 55 000 U/L. Here, we present a rare case of a young patient with severe rhabdomyolysis and an exceptionally high CK activity (almost 3 times higher than in these studies) without AKI.

Case Report

A 22-year-old African American male without a significant past medical history presented to the Emergency Department (ED) with upper respiratory tract symptoms for 4 days. He reported having rhinorrhea, sore throat, and non-productive cough which worsened from onset to the date of visit. He also endorsed subjective fever and generalized "muscle cramping" which had been present for 2 days. He did not receive an influenza vaccination but denied close contact with any sick individuals. On the day he presented to the ED, he noticed that his urine was very dark brown (almost black) without associated dysuria. He denied prior history of urinary tract infections, abdominal pain, nausea, vomiting, or diarrhea. He stated that he had been hydrating himself well with oral fluids. Initial examination showed body temperature 37.3°C, heart rate 94 beats per minute, respiratory rate 20 breaths per minute, blood pressure 135/72 mmHg, and oxygen saturation 97%. Physical examination was only significant for nasal congestion, and dry oral mucosa. Complete blood count (CBC) suggested viral illness with white blood cell count of 4700/uL, 71% neutrophils, 22% lymphocytes, 5.4% monocytes, platelet count 168 000/uL. Comprehensive metabolic panel (CMP) was notable for serum potassium 3.4 mEq/L, serum bicarbonate 30.6 mEq/L, serum creatinine 1.02 mg/dL, aspartate transaminase (AST) 582 U/L, alanine transaminase (ALT) 89 U/L. A computed tomography of abdomen and pelvis was obtained and revealed no liver pathology or other intra-abdominal lesions. Given his low severity of symptoms, he was discharged with supportive therapy for viral upper respiratory infection. He was advised to keep hydrated and return to the ED if his symptoms worsened.

Three days after discharge, he returned to the ED complaining of worsening generalized muscle pain. He reported that his cough resolved, however, the myalgias had worsened to the point that he had to stay in bed and was being woken up by pain during the night. He stated that his urine appeared darker despite adequate hydration at home. He had been taking ibuprofen 800 mg every 8 hours for the pain, along with one dose of 5-mg cyclobenzaprine, without improvement. He denied fever, chills, shortness of breath, chest pain, abdominal pain, nausea, vomiting, dysuria, or diarrhea at this time. He works as a waiter at a restaurant and denied history of trauma or strenuous exercise. He denied any recent domestic or international travel and did not have any pets. He endorsed tobacco smoking and recreational marijuana use 5 times a week. He denied alcohol use or other substance abuse. Family history was unremarkable, including history of myopathies. Vital signs: body temperature 37°C, heart rate 109 beats per minute, respiratory rate 24 breaths per minute, blood pressure 152/87 mmHg, and oxygen saturation 100%. Physical examination revealed an obese male (body mass index 33.82 kg/m^2) who was not in distress. Most of the examination was unremarkable except for poor skin turgor and tenderness of proximal muscles (arms and thighs). The patient was admitted to the hospital for further investigation and management.

Investigations

CBC showed white blood cell count 8700/uL, hemoglobin 16.2 g/dL, hematocrit 46.2%, platelet count 180 000/uL. CMP showed serum sodium 134 mEq/L, serum potassium 4.2 mEq/L, serum chloride 98 mEq/L, serum bicarbonate 38.8 mEq/L, serum creatinine 0.77 mg/dL, blood urea nitrogen 14 mg/dL, serum magnesium 2.3 mg/dL, serum calcium 8.9 mg/dL, serum phosphate 3.5 mg/dL, AST 2299 U/L, ALT 404 U/L, CK >40 000 U/L, and LDH >12 000 U/L. Venous blood gas was sent due to elevated serum bicarbonate; pH of 7.411, and pCO_2 45.2 mmHg, suggesting chronic metabolic alkalosis with respiratory compensation due to intravascular volume contraction. Serum thyroid

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Table 1. Daily laboratory investigation.

Admission Day	0	1	2	3	4	5	6	7
CK (U/L)	>40 000	>40 000	>40 000	>150 000*	123 414*	80 914	55 662*	32 042*
LDH (U/L)	>12 000	–	–	–	–	–	1609*	–
Sodium (mEq/L)	134	137	136	134	137	136	136	138
Potassium (mEq/L)	4.2	4.9	4.9	4.4	4.7	4.5	4.5	3.9
Chloride (mEq/L)	98	105	104	101	102	100	103	106
CO_2 (mEq/L)	38.8	35.2	30.4	27.7	28.1	27.8	27.6	25.2
Blood urea nitrogen (mg/dL)	14	14	13	10	12	14	16	13
Creatinine (mg/dL)	0.77	0.65	0.60	0.53	0.53	0.49	0.52	0.46
eGFR African American (mL/min/1.73 m^2)#	204	218	226	237	237	245	239	252
Alkaline phosphatase (U/L)	58	44	43	37	57	61	60	55
ALT (U/L)	404	312	378	407	440	461	515*	405
AST (U/L)	2299	1695	1710	1355	1123	884	725	465
Total bilirubin (mg/dL)	0.8	0.6	0.6	0.6	0.6	0.6	0.5	0.5
Direct bilirubin (mg/dL)	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Total protein (g/dL)	6.4	5.1	5.3	5.1	5.2	5.5	5.2	5.3
Albumin (g/dL)	4.1	–	–	–	–	–	–	–

* Confirmed by dilution; # eGFR is calculated using CKD-EPI formula. CK – creatine kinase; LDH – lactate dehydrogenase; eGFR – estimated glomerular filtration rate; ALT – alanine transaminase; AST – aspartate transaminase; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration.

stimulating hormone (TSH) was insignificantly elevated at 5.655 uIU/mL. Urinalysis showed clear, dark amber urine, specific gravity 1.030, pH 6.3+ occult blood, 2+ protein, urine white blood cells 0–5, urine red blood cell 0–5. Daily laboratory results are illustrated in Table 1. With elevation of AST, ALT activity, an ultrasound of the liver was obtained and was negative for liver pathology. Elevation of AST and ALT activity were thought to be secondary to rhabdomyolysis.

Given the high suspicion for non-traumatic rhabdomyolysis, multiple studies were performed to identify the etiology. Urine drug screen was positive for cannabinoid and tricyclic agent. The latter could be a false positive from the cyclobenzaprine that he took prior to being hospitalized. Troponin I was 0.03 ng/mL (normal range, <0.03 ng/mL). Lyme IgG and IgM were negative. Hepatitis A antibody (HAV-IgM), hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc, IgG and IgM), and hepatitis C antibody (anti-HCV) were all negative. Human immunodeficiency virus (HIV) antibody was negative. Real-time polymerase chain reaction (PCR) of nasopharyngeal swab for influenza A/B virus was negative. Quantitative PCR for cytomegalovirus (CMV) was <200 IU/mL and for Epstein-bar virus (EBV) was <200 IU/mL. Screening anti-nuclear antibodies (ANA) by immunofluorescent assay was negative. Serum cystatin C level was sent as patient might have acute kidney injury with normal serum creatinine level. His serum cystatin C level was 0.57 mg/L with estimated glomerular filtration rate (eGFR) of 144 mL/min/1.73 m^2. Erythrocyte sedimentation rate (ESR) was normal at 6 mm/hour but C-reactive protein (CRP) was slightly elevated at 2.12 mg/dL (normal range, 0 to 1 mg/dL). Blood cultures showed no growth for 5 days. At this point, it was presumed that his rhabdomyolysis might be associated with marijuana abuse or a non-specific viral illness.

Treatment

Patient was initially given 2 liters of normal saline solution followed by a maintenance infusion at 250 mL/hour. He was given 650 mg of acetaminophen every 8 hours as needed for severe myalgias. Fifteen mg of intravenous ketorolac was given with caution due to concern for renal impairment. He had

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been afebrile throughout hospital stay. CK activity and basic metabolic panel were followed daily as he was at high risk for acute kidney injury. On day 5 of hospitalization, elevated CK activity was confirmed by dilution method as >150 000 U/L. His myalgia had improved over the course of treatment. He did not require the use of acetaminophen and ketorolac within the 24 hours prior to discharge. His CK activity and LDH level slowly trended down to 32 042 U/L and 1609 U/L, respectively upon discharge. His serum creatinine level was 0.46 mg/dL on discharge.

Outcome and follow-up

Patient was discharged after being hospitalized for 8 days. He was advised to continue taking oral fluid intake and follow up with his primary care physician.

Discussion

This report presented a rare case of rhabdomyolysis with preserved kidney function despite an extremely high CK activity. AKI is the most common complication of rhabdomyolysis with an incidence ranging from 10% to 55% [6]. The correlation of CK activity elevation and increased risk of AKI was confirmed by previous meta-analysis [7]. Some studies suggest that incidence of AKI is usually low if CK activity on admission is less than 15 000 to 20 000 U/L [4,5]. In 2003, de Meijer et al. conducted a 5-year prospective observation study of 7500 patients who were admitted to intensive care unit and found that only 71 patients were diagnosed with severe rhabdomyolysis with CK level >10 000 U/L [5]. In this cohort, AKI occurred in 65% of these patients. Patients with AKI had significantly higher CK activity on admission and peak CK activity. The CK activity on admission and peak CK activity were 47 194±37 600 U/L and 55 366±33 240 U/L, respectively. This study concluded that serum CK activity correlated with the onset of AKI. Similarly, a single-center observational study reported a significant trend of increasing AKI with increasing CK activity [8]. However, despite previous evidence, there is at least one newer study that suggests that CK activity does not correlate with occurrence of AKI in rhabdomyolysis. Nonetheless, this study is limited to its single-center design and low initial CK activity on admission [9].

There are only a few cases of rhabdomyolysis with exceptionally high CK activity reported to date. However, none had preserved kidney function. Runnstrom et al. reported an unusual case of influenza-induced rhabdomyolysis with peak CK activity of 34 176 U/L and initial serum creatinine of 8.48 mg/dL [10]. Another case was reported by Luckoor et al. [11]. This patient presented with combined etiology of rhabdomyolysis with initial CK activity of 701 400 U/L. Unfortunately, this patient had AKI requiring continuous renal replacement therapy. These findings emphasize that preserved kidney function with extremely high CK activity is uncommon.

This case presentation adds more information toward the understanding of protective factors for AKI in rhabdomyolysis and serves as a reminder to health care providers that significant muscle breakdown may occur without renal impairment. Several factors, including self-hydration and low complexity of the etiology leading to rhabdomyolysis were shown to be protective against AKI in rhabdomyolysis [6]. One retrospective cohort showed that the common causes of rhabdomyolysis were cocaine, strenuous exercise, and immobilization [12]. This is consistent with a previous case report by Luckoor et al. in which a patient was a cocaine user with Legionella co-infection. We believe our patient had the following protective factors against AKI: younger age, African American race, no history of cocaine use, and adequate oral hydration. With the same serum creatinine level, patients of African American race have higher eGFR compared to other races [13]. Further observational studies are needed to confirm the protective factors against AKI in rhabdomyolysis patients.

Conclusions

Extremely high CK activity in rhabdomyolysis can lead to AKI. However, preserved kidney function is possible in such a patient. Young age, no concurrent cocaine use, and adequate oral fluid hydration may prevent AKI in rhabdomyolysis.

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