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CLINICAL VIGNETTE

Exertional Rhabdomyolysis: Two Case Reports in Untrained and Trained Individuals

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Case 1

A 21-year-old young man with a history of depression and obesity presented to urgent care with complaints of diarrhea and dark brown urine beginning the night before. He was well until that evening, when, within 30 minutes of eating a fully cooked turkey burger in West Hollywood, he had the urge to defecate and produced a voluminous bowel movement with loose, yellowish, nonbloody stool. He denied abdominal pain, fever, or chills. Several hours later, he noticed that his urine was dark brown in the absence of dysuria, flank pain, or reduced urine volume. He denied sick contacts or travel history. On review of systems he recalled experiencing difficulty sleeping that night because of muscle soreness involving his arms and legs, which he attributed to starting an intense workout with a personal trainer for the first time earlier that day.

His past medical history was significant for depression controlled on daily doses of duloxetine 30 mg and dextroamphetamine/amphetamine 20 mg, respectively.

On physical examination he was afebrile with a blood pressure of 140/80 mmHg without orthostatic changes, heart rate 84 bpm, respirations 17/min, height 185 cm, weight 115 kg, and BMI 32.6. Physical exam was unremarkable without notable muscle tenderness.

Laboratory data

CBC: WBC 5.74 6/uL, Hgb 17.3 g/dL, Hct 47.6, plt 259 x 10³/uL.

Coagulation: PT 10.4 seconds, INR 1.0, PTT 30.3 seconds.

Serum chemistries: Na⁺ 139 mmol/L, K⁺ 4.3 mmol/L, Cl⁻ 105 mmol/L, HCO₃⁻ 26 mmol/L, BUN 11 mg/dL (11.8 μmol/L), creatinine 1.0 mg/dL (88.4 μmol/L), glucose 99 mg/dL (5 mmol/L), Ca²⁺ 9.6 mg/dL (2.1 mmol/L), Mg²⁺ 1.8 mg/dL (0.86 mmol/L), CK total 47,162 U/L.

Urine studies: urine specific gravity 1.013, pH 6.0, blood 3+, bilirubin negative, ketones negative, protein 2+, nitrite negative, leukocyte esterase negative, RBC negative, WBC 15 cells/uL, squamous cells 3 cells/uL.

Assessment

The patient was sent to the emergency department (ED) with a diagnosis of exertional rhabdomyolysis based on his history of myalgias after strenuous exercise and dark urine with concomitant elevations in CK and transaminases. In addition, his urinalysis tested positive for blood and protein in the absence of red blood cells, consistent with myoglobinuria. The elevated hemoglobin of 17.3 g/dL likely resulted from hemoconcentration.

Clinical Course

In the ED he was hydrated with 3L of normal saline with 50 mmol bicarbonate added to the first liter. Additionally, he drank 2L of fluid. CK was 37,434 U/L on discharge the following morning. Within 4 days, the CK level decreased to 1407 U/L, and it normalized within 3 weeks.

Case 2

A 25-year-old female presented for follow-up one week after an ED visit for bilateral arm pain. Three days prior to ED presentation, she had experienced right greater than left bilateral upper extremity swelling and soreness. She denied chest pain, shortness of breath, or dark urine. Seven days prior to presentation she had intensified her usual exercise regimen of aerobic exercise and weight training 4-5 days a week with multiple "burpies" (squat thrusts).

Her past medical history was positive for migraine headaches and mitral valve regurgitation. She was taking no medications.

On physical exam, she was afebrile with blood pressure 133/80 mmHg, heart rate 76 bpm, height 152 cm, weight 59 kg, and BMI 25.4.

Laboratory Data

Serum chemistries: Na⁺ 141 mmol/L, K⁺ 3.9 mmol/L, Cl⁻ 104 mmol/L, HCO₃⁻ 25 mmol/L, BUN 11 mg/dL (3.9 μmol/L), creatinine 0.7 (61.9 μmol/L), CK 2717 U/L.

Urinalysis: Specific gravity <1.005, pH <5.0 blood negative, protein negative, RBC 2 cells/μL.

Assessment

The patient was diagnosed with resolving acute exertional rhabdomyolysis because her symptoms of muscle pain and swelling one week prior to presentation were indicative of rhabdomyolysis, at which time she likely would have tested positive for myoglobinuria as well as a more marked increase in CK.

Clinical Course

She received 2 L of normal saline in the ED and was discharged in stable condition. Within 2 weeks of her initial symptoms, CK had decreased to 197 U/L.

Discussion

Both of these cases illustrate exertional rhabdomyolysis in patients who performed vigorous exercise with a personal trainer. In the first case, the patient was untrained, starting a new exercise program. In contrast, the second patient was a trained individual, who regularly exercised, but undertook a more strenuous program compared to her usual routine. This review examines the clinical characteristics and epidemiological aspects of exertional rhabdomyolysis, as well as the risk factors that lead to its development. Finally, preventive measures that can be used to counsel patients are discussed.

Definition

Exertional rhabdomyolysis (ER) is defined as acute reversible or irreversible skeletal muscle injury leading to alterations in cell membrane integrity¹ and resultant myoglobinuria, after intense, prolonged, or repetitive physical exertion². Consequently, cellular contents including the creatine kinase (CK) MM fraction and aldolase are released into the circulation³. Clinically, muscle pain, swelling and

weakness¹, and, in severe cases, compartment syndrome³, are observed in conjunction with myoglobinuria and laboratory evidence of a marked CK elevation to 500 U/L-600 U/L^{1,4}. CK rises 2-12 hours after muscle injury, peaks in 1-3 days, and generally declines within 2-5 days. Myoglobinuria is characterized by the presence of dark or cola colored urine and a heme positive urine dipstick in the absence of urinary RBC's¹.

The spectrum of ER ranges from mild to severe disease. Mild ER may result in hyperkalemia, hypernatremia, lactic acidosis, hyperphosphatemia³, hyperuricemia, and hypocalcemia (when calcium phosphate salts precipitate into necrotic muscle tissue). In severe cases of ER, DIC, renal failure, and death may ensue¹. However, a population-based analysis followed a cohort of 22 military recruits with ER and concluded that ER is associated with lower rates of complications than other causes of rhabdomyolysis⁵.

ER must be distinguished from delayed-onset muscle soreness, in which muscle damage after exercise occurs in unconditioned individuals. Serum CK may be moderately elevated¹ without progression to ER. One study examined the physiologic response to basic training in 499 military recruits. None of the subjects developed clinical ER, despite mean/median serum CK values of 223/157, 734/478, 1226/567, and 667/486 U/L at days 0, 3, 7, and 14, respectively (range 34-35,056 IU/L.) African-American subjects had higher mean CK levels⁶.

In addition to CK elevations, subclinical myoglobinemia and myoglobinuria occur commonly following physical exertion. In one study, myoglobinemia was detected in 25 of 44 participants (57%) in an ultra-marathon race of 99 kilometers⁷. Serum CK levels increased 16-fold from pre-race values to a mean of 2060 U/L. Myoglobinuria was detected in five participants, but acute kidney injury did not develop. Another study demonstrated that 39 percent of 337 military recruits developed myoglobinemia during the first six days of basic training, but none of the participants reported muscle symptoms or demonstrated pigmenturia⁸.

Epidemiology

ER was thought to be a rare entity until 1960, prior to which time only 36 cases of "primary myoglobinuria" had been reported in the twentieth century literature. In 1960, Howenstine reported myoglobinuria in 60 marine recruits undergoing

training¹. Since that time, there have been numerous reports of ER in association with physical training programs for the Marine Corp, law enforcement, and fire departments³. In 1990 Knochel used the term “white collar rhabdomyolysis” to describe rhabdomyolysis occurring in runners because of the prevalence of this entity in well-educated, intelligent individuals with sufficient time and energy after work to commit to running⁹. More recently, there have been case reports of ER occurring in high school¹⁰ and collegiate football athletes¹¹, and in individuals who exercise with a personal trainer¹². In spite of the increased reporting of ER in the literature, both the incidence and risk of recurrence of exertional rhabdomyolysis in young, physically active individuals remain low⁵.

ER occurs primarily in young men. Shumate et al¹³ demonstrated that post-exercise CK was significantly higher in men than in women. These authors postulated that the gender difference might be attributable to the protective effect of estrogen, observing that diethylstilbestrol reduces CK levels in Duchenne muscular dystrophy patients. Animal studies appear to support this theory: Amelink and Bar¹⁴ showed that after oophorectomy, female rats had elevated CK levels; Bar et al¹⁵ further demonstrated that male rats treated with estradiol failed to show post-exertional enzyme elevations.

Risk Factors

Identification of risks factors for ER is essential for early recognition and treatment to prevent the progression to renal failure.

Environmental risk factors include high altitude, high ambient temperature and humidity, and inadequate water consumption at the time of exercise.

Intrinsic occupational risk is conferred upon firefighters, military trainees, and law enforcement officers because of rigorous basic training requirements, and upon farmers, construction workers, and other outdoor laborers, whose work conditions are associated with high temperatures or restrictive clothing and equipment.

High-risk recreational activities include long distance running, high intensity exercise, weight lifting, and football. Sporadic exercise of “weekend warriors” as well as poor physical conditioning also predispose to ER. Consistent with this finding, significantly higher levels of post-exercise CPK are observed in untrained persons or those engaging in high intensity exercise³.

Medical co-morbidities such as renal insufficiency, fatigue, viral illness, prior heat exhaustion³, and sickle cell trait¹⁶ are associated with an increased of ER³. Kark et al¹⁷ showed that recruits in basic training with the sickle-cell trait have a significant increase in age-dependent risk of exercise-related sudden death which could not be accounted for by preexisting causes.

Certain medications and substances that have been identified as increasing the risk of ER include aspirin, anticholinergic agents, cocaine, and alcohol³.

In a small percentage of cases, genetic factors such as (1) **polymorphic variations** and (2) **genetic mutations** also influence the development of ER. **Polymorphisms** that are associated with ER or exercise-induced serum CK elevations characteristic of ER involve variations in genes that code for (a) myosin light chain kinase, (b) α -actin 3, (c) creatine kinase-muscle isoform, (d) angiotensin I-converting enzyme, (e) heat shock protein, and (f) interleukin-6. **Genetic mutations** that result in malignant hyperthermia¹⁸ and the metabolic myopathies (Table 1) have been associated with ER. Metabolic myopathies include disorders of lipid metabolism, (carnitine palmitoyl transferase 2 deficiency), carbohydrate metabolism (myophosphorylase deficiency [McArdle’s Disease]), and purine metabolism (Duchenne’s muscular dystrophy)¹⁹. The myopathic form of CPT 2 deficiency is an autosomal recessive disorder that represents the most frequently occurring metabolic myopathy and the most common cause of hereditary myoglobinuria²⁰. Tonin et al²¹ studied 77 patients with idiopathic myoglobinuria, all of whom had undergone muscle biopsies. Thirty-six patients tested positive for specific enzyme deficiencies of which 17 (47%) were CPT deficiency and 10 (28%) were McArdle’s Disease.

Young patients who exhibit recurrent rhabdomyolysis after low intensity exercise²² or in the setting of fasting or infection, and those with a family history of exercise intolerance should undergo evaluation to exclude metabolic myopathy¹⁹.

Table 1. Metabolic myopathies¹⁹

Disorders of lipid metabolism

Carnitine palmitoyltransferase deficiency
Carnitine deficiency
Short-chain and long-chain acyl-coenzyme A dehydrogenase deficiency

Disorders of carbohydrate metabolism

Myophosphorylase deficiency (*McArdle disease*)

Phosphorylase kinase deficiency
Phosphofructokinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
(creatine kinase level is elevated with
normal lactate dehydrogenase level)

Disorders of purine metabolism

Myoadenylate deaminase deficiency
Duchenne's muscular dystrophy

Prevention

Preventive measures have been suggested to reduce the occurrence of ER in athletic programs. These recommendations include: (1) performing submaximal training over a longer period rather than high intensity exercise over a short period; military data suggests that this strategy reduces the risk for ER, (2) consuming a high carbohydrate load and spacing rest periods to optimize glycogen repletion, (3) ensuring adequate hydration to enhance renal clearance of myoglobin, (4) limiting activity when ambient temperature and humidity are high.³ In 1988 the New York City fire department training program implemented these guidelines, and during the 19 month follow up period, only 32 of 16,506 subjects were hospitalized with rhabdomyolysis or renal impairment.⁴

Case Discussion

In the two cases of exertional rhabdomyolysis presented, the first patient trained intensively with a personal trainer, though he was naïve to all but minimal exercise, and largely untrained. Hours after exercising, he suffered an acute diarrheal illness from food poisoning, which led to dehydration and likely accelerated the development of ER. Of note, the patient was taking dextroamphetamine/amphetamine for depression, and though not evident in this case, amphetamine overdose has been associated with rhabdomyolysis.²³

The second patient was well trained, exercising 4-5 times a week. However, exertional rhabdomyolysis was precipitated after she exercised with a personal trainer, performing an excessive regimen with multiple squat thrusts.

These cases support the findings that substantially higher levels of post-exercise CK occur in untrained persons or those engaging in high intensity exercise and may lead to exertional rhabdomyolysis. Recognition of individual risk factors in trained and untrained persons will assist in counseling patients

regarding preempting the development of exertional rhabdomyolysis.

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