



CASE SERIES

Reevaluation of Diagnostic Criteria for Exertional Rhabdomyolysis in Collegiate Wrestlers: A Case Series and Review

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#Equal Contribution



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Abstract

Rhabdomyolysis is a common and potentially fatal condition encountered by athletic trainers, coaches, primary care physicians and sports medicine physicians. Benign, or physiological, Exertional Rhabdomyolysis (ER) may resemble Delayed Onset Muscle Soreness (DOMS) and becomes clinically significant when accompanied by other morphologies including severe muscle pain and swelling, and myoglobinuria. ER is often characterized by a triad of symptoms including 1) Muscle pain, 2) Muscle swelling, and 3) Myoglobinuria. Rhabdomyolysis and ER are associated with a variety of complications including metabolic acidosis, disseminated intravascular coagulation (DIC), hypocalcemia, hyperkalemia, arrhythmias, compartment syndrome, acute renal failure, cardiac arrest, and even death. Risk factors including prolonged repetitive exercise that involves a heavy eccentric component particularly in extreme heat and humidity have been directly linked to the development of ER. Other major factors that have been linked to the development of ER include deconditioning, dehydration, electrolyte imbalances, nutrition and diet, drugs including diuretics, statins, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), recreational drugs, dietary supplements, and high doses of caffeine. ER is often diagnosed as rhabdomyolysis in the emergency setting though this diagnosis may not be interchangeable in the presence of comparing the general population with the athletic population. CK/CPK is one of the most commonly used biomarkers in the diagnosis of rhabdomyolysis though CK/CPK levels ranging from 5 times to 50 times upper normal limits have been proposed in the literature. 5x upper

limits of CK/CPK are often mentioned as being a conservative range for diagnosis, with no definitive pathological value for CK/CPK, healthcare providers should be aware that levels of 20x the upper limit may be seen in those performing repetitive and strenuous exercise(lee), with documented cases of CK/CPK laboratory values in excess of 130,000 IU/L to 244,000 IU/L in literature.

Keywords

Exertional rhabdomyolysis, Exercise induced rhabdomyolysis, Creatine Phosphokinase (CK/CPK)

Introduction

Rhabdomyolysis is a common and potentially fatal condition encountered by athletic trainers, coaches, primary care physicians and sports medicine physicians [1]. When the components of striated muscle such as the myofibrils and sarcolemma are damaged [1-6], cellular components including Creatine Kinase (CK/CPK) [1,2,4,5,7,8], Lactate Dehydrogenase (LDH) [1,7,8], Aspartate Transaminase (AST) [7,8], Alanine Transaminase (ALT) [7,8], calcium [3], potassium [1,3,4], myoglobin [8], and organic acids [3] are released in the surrounding plasma and extracellular space [5,6]. Exertional (exercise induced) Rhabdomyolysis (ER) is often diagnosed as rhabdomyolysis in the emergency setting though this diagnosis may not be interchangeable

in the presence of comparing the general population with the athletic population.

Case Description

Subjects

This study was approved by the Graceland University Internal Review Board. All participants had previously signed a medical record release form and after initial review for continued medical care, informed consents were received from each participant to be included in this study. All cases occurred over two seasons and did not occur at the same time.

Case one

18-year-old Caucasian male presented to the Emergency Department (ED) after having two syncopal episodes and bilateral flank pain while vomiting. Patient reported working out and stated that he had consumed water. Patient later admitted that he had not been eating

or drinking as he had been preparing to lose weight for an upcoming wrestling match. ED workup included an electrocardiogram (EKG), macroscopic urinalysis (UA), and laboratory workup including a CBC with differential, cardiac isoenzymes, and general chemistry panel (Table 1). Based on the diagnostic workup, the patient received 2 liters (L) Normal Saline (NS) and was discharged with the diagnosis of elevated CK and dehydration.

Case two

18-year-old Caucasian male presented to the ED after having three syncopal episodes following strenuous exercise. Patient stated that he had been in the weight room and had felt lightheaded and dizzy and proceeded to prop himself against the wall preparing to pass out. He denied any pain in the ED but did state that he had some muscle cramps and that he was preparing for an upcoming wrestling match and that he had not been eating or drinking much in the days leading up to the event. ED workup included an EKG, macroscopic UA,

Table 1: General chemistry panel.

Test	Patient 1	Patient 2	Patient 3a	3b	Patient 4a	4b
General Chemistry						
CPK	> 1,000 (55-170 IntUnit/L)	848 (55-170 IntUnit/L)	1220* (35-232 U/L)	> 1,000 (55-170 IntUnit/L)	460 (0-135 IntUnit/L)	353 (0-135 IntUnit/L)
BUN	24 (9-20 mg/dL)	19 (9-20 mg/dL)	21 (8-25 mg/dL)	18 (9-20 mg/dL)	26 (9-20 mg/dL)	25 (9-20 mg/dL)
BUN/Creat Ratio	20	16	†	14	21	17
AST	56 (17-59 IntUnit/L)	47 (17-59 IntUnit/L)	†	65 (17-59 IntUnit/L)	45 (17-59 IntUnit/L)	40 (17-59 IntUnit/L)
Na ⁺	144 (136-145 mmol/L)	140 (136-145 mmol/L)	137 (136-144 mmol/L)	140 (136-145 mmol/L)	137 (136-145 mmol/L)	136 (136-145 mmol/L)
K ⁺	4 (3.0-5.5 mmol/L)	3.9 (3.0-5.5 mmol/L)	3.0 (3.6-4.8 mmol/L)	3.3 (3.0-5.5 mmol/L)	4.7 (3.0-5.5 mmol/L)	4.2 (3.0-5.5 mmol/L)
Macroscopic Urinalysis						
UA Color	amber	amber	†	amber	dark yellow	darker
UA Protein	30	3+	†	30	100	+
UA Specific Gravity	>= 1.030	>= 1.030	†	1.02	>= 1.030	
UA Blood	negative	negative	†	small	trace-lysed (A)	Neg
Microscopic Urinalysis						
UA RBC	†	†	†	6-10	0-2	†

* = CK lab value, † = no data available

and laboratory workup including a CBC with differential, cardiac isoenzymes, and general chemistry panel (Table 1). Based on the diagnostic workup, the patient received 2 L of NS and was discharged with the diagnosis of elevated CK and dehydration.

Case three

21-year-old African American male presented to the ED by ambulance after being placed in a chokehold at a wrestling tournament. Patient presented with shortness of breath and difficulty swallowing. Athlete reported cutting weight for several days prior to the tournament but stated that he had not been starving himself. ED workup included a chest X-ray, Computed Tomography (CT) of the neck, EKG, and laboratory workup including a CBC with differential, general chemistry panel, and cardiac isoenzymes (Table 1). Based on the diagnostic workup, the patient received 2 L NS and was discharged with the diagnosis of a choking injury and mild rhabdomyolysis.

The following evening, the patient presented to a different ED via ambulance following a near syncopal episode. Patient stated that he had woken up that morning dizzy and had reported feeling “bad” on and off all day. ED workup included a head and neck CT, EKG, and laboratory workup including a CBC with differential, coagulation panel, general chemistry panel, cardiac isoenzymes, and macroscopic and microscopic UA (Table 1). Based on the ED workup, the patient received 2 L NS and was diagnosed with recurrent rhabdomyolysis, mild hypokalemia, inverted T waves – juvenile persistent pattern, and arachnoid cyst of the pineal gland. Patient was admitted for observation and fluid resuscitation and was discharged the following day.

Case four

24-year-old Caucasian male presented to the ED for an evaluation for rhabdomyolysis after he had presented to a local clinic for vomiting, muscle cramping, and decreased urine output. Patient had received 500 ml NS while at the clinic after he had presented with the inability to urinate. In the ED, patient noted a 17-pound weight loss in a two-day timespan. ED workup included an EKG, a macroscopic and microscopic UA, and laboratory workup including a CBC with differential, general chemistry panel, and a creatine phosphokinase (CPK) (Table 1). Based on the ED workup, the patient received 2 L NS and was admitted for observation and diagnosed with rhabdomyolysis, dehydration, muscle cramping, and low urine output.

Following seven days off of physical activity, the athlete returned to practice where he began to have muscle tightness along with nausea, vomiting, muscle pain and flank pain. Patient returned to the clinic same day where he was referred to the ED for further evaluation. ED workup included a UA and laboratory workup including a general chemistry panel and a CPK

(Table 1). Based on the ED workup, the patient received 2 L Lactated Ringers (LR) and was discharged with the diagnosis of heat exhaustion, hyperuricemia, elevated CPK, acute kidney injury, and dehydration.

Conclusion

Debate revolves around the diagnosis of ER as there is relatively little consensus within the fields of emergency medicine and sport medicine on the overall associated clinical presentation and laboratory findings which may be causing a general misunderstanding regarding appropriate diagnosis [3]. While ER is thought of as an abnormal condition, literature has shown that often times this condition is the result of normal physiological responses in the body as the result of tissue repair and adaptations to physical activity [1,3,8]. Benign, or physiological, ER may resemble Delayed Onset Muscle Soreness (DOMS) and becomes clinically significant when accompanied by other morphologies including severe muscle pain and swelling, and myoglobinuria [8]. It has been theorized that DOMS is a mild form of rhabdomyolysis as it is an indicator of muscle damage post-exercise [9].

Rhabdomyolysis and ER are concerning as they have been associated with a variety of complications including metabolic acidosis [3], Disseminated Intravascular Coagulation (DIC) [5], hypocalcemia [3], hyperkalemia [3,5], arrhythmias [1,3], compartment syndrome [1-3,5,6], acute renal failure [1,2,5,6], cardiac arrest [2], and even death [2,3,6]. While acute renal failure is one of the most well-known and concerning complications of rhabdomyolysis, acute renal failure in ER patients is particularly rare and when it does occur, full recovery is nearly universal [5].

Numerous studies have linked rhabdomyolysis and ER to a variety of sports and professions including trainees in law enforcement [2,4,8], fire fighting and military cadets [2,3,4,8], along with athletes training for and competing in wrestling [2], football [1,2], swimming [1], and long-distance running, and even one reported case in a 12-year-old during physical education class [3].

It has been theorized that sex and ethnicity may increase the risk of experiencing rhabdomyolysis and ER. Due to the increased muscle mass, cases of rhabdomyolysis tend to affect more males than females [5,6,9]. Additionally, African Americans tend to have a greater occurrence when compared to Caucasians and those of South Asian descent [10]. Sickle cell trait, which affects African American males at a higher rate than other ethnicities, has been linked as a potential risk factor for rhabdomyolysis which may help explain this phenomenon [1,5,8].

Prolonged repetitive exercise that involves a heavy eccentric component [1-3,6,8] particularly in extreme heat and humidity [1,2,6,8,9] have been directly linked to the development of ER. Other major factors that

have been linked to the development of ER include deconditioning [2,6,9], dehydration [1,2,7-9], electrolyte imbalances [9], nutrition and diet [2,6], drugs including diuretics, statins [1,5,9], Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) [8], recreational drugs [1], dietary supplements [1,6], and high doses of caffeine [1].

ER can be characterized by a triad of symptoms including 1) Muscle pain [1-6,8], 2) Muscle swelling [2,3,5,6], and 3) Myoglobinuria [1-4,6,8]. Muscle pain is often described as being intense and severe especially during active and passive ranges of motion. The available range of motion, accompanied by the pain is often out of proportion for the amount of fatigue expected following exercise or activity [1-6,8]. Additionally, muscle weakness and general fatigue are prevalent particularly following prolonged and repetitive exercises in novel athletes or in individuals that are unfamiliar with the exertional levels experienced [3,4,8]. Patients experiencing myoglobinuria often have urine described as dark, tea, or cola-colored [1-4,6,8]. The presence of myoglobinuria can be easily detected in the clinical and sideline setting with dipstick analysis being one of the quickest and most easily accessible methods of testing for ER [6,8]. When urinalysis is performed in the emergency department, dipstick urine analysis is positive for the presence of blood, but microscopic analysis reveals no red blood cells [3].

Physicians are aided in the diagnosis of ER by ordering serum creatine phosphokinase (CK/CPK) values. CK/CPK is one of the most commonly used biomarkers in the diagnosis of rhabdomyolysis though CK/CPK levels ranging from 5 times to 50 times upper normal limits have been proposed in the literature [1]. Literature values of 5x upper limits of CK/CPK are often mentioned as being a conservative range for diagnosis [3,5], though other sources mention using 10x upper limits of CK/CPK as being of diagnostic significance [4,5]. Evidence of when renal damage occurs in relation to elevated CK/CPK levels is not well understood further complicating the discussion. Mahmutyazicioglu, et al. [10] discussed that only CK/CPK values over 5,000 U/L should be concerning for renal failure while other sources cite levels of > 10,000 U/L as being diagnostic for ER [6,10]. With no definitive pathological value for CK/CPK, healthcare providers should be aware that levels of 20x the upper limit may be seen in those performing repetitive and strenuous exercise [5].

In the literature, documented cases of CK/CPK laboratory values in excess of 130,000 IU/L in an 18-year-old football place kicker, 146,000 IU/L in a 16-year-old male following two days of practice at wrestling camp, and even one case of a 12-year-old male with a CK value of 244,006 IU/L after performing 250 squat jumps in a physical education class [8]. Knowing when an athlete has moved from a physiological response to a pathological response is difficult to assess and manage

without clinical diagnostic testing [8,9]. Evidence exists that CK/CPK values can range from 2000 IU/L to > 10,000 IU/L following 50 maximal eccentric contractions of the elbow flexors [9]. This expected elevation for CK/CPK may explain why in one study from Oh, et al. [4], the team physician recommended intravenous hydration for athletes with laboratory values >3,000 U/L and hospitalization for athletes over 10,000 U/L [4].

Current laboratory ranges for CK/CPK levels fail to take into account gender, ethnicity, and activity level leaving physicians to use the same laboratory ranges for athletes, as they do for the general population likely leading to incorrect and misguided diagnosis [3,10]. The need for athlete specific reference ranges led Mahmutyazicioglu, et al. [10] to propose a CK reference range for male professional footballers 64.9 U/L to 1971.7 U/L [10].

A similar approach should be taken with athletes competing in highly strenuous activities such as wrestling. Reference ranges for CK/CPK specific to wrestling may prove beneficial when evaluating these patients in the clinical setting. Ozkan and Ibrahim [7] found that wrestlers in a dehydrated state had increased CK levels and experienced a greater degree of damage to skeletal muscle versus wrestlers who were in a euhydrated state. Elevation of key ER biomarkers such as Na⁺, BUN, P_{osm}, AST, CK, and LDH were also noted in the dehydrated athletes with significant statistical correlations of Na⁺ and BUN in relation to dehydration and skeletal muscle damage [7]. When evaluating wrestlers in the emergency setting, evaluation of hydration status is of particular importance as there is added concern that being in a dehydrated state may prevent the athlete from being able to clear the myoglobin and other toxic substances released by the damaged muscle fibers [9].

Traditionally, CK values along with clinical presentation lead emergency medicine physicians to reach the diagnosis of rhabdomyolysis. One challenge facing emergency medicine physicians and sports medicine physicians is determining whether the clinical presentation and laboratory findings are consistent with physiological ER or pathological ER [3]. With the potential for serious consequences that exist with ER, physicians and other healthcare providers must use appropriate risk-stratification to determine what kind of risks the athlete is under when returning to activity [3]. This is further complicated by the fact that there are currently no standardized laboratory markers indicating when recovery has been achieved [1]. Laboratory testing could rely on cellular biomarkers returning to baseline levels as it would demonstrate the ability of the kidneys to function normally and clear these substances from the body [1].

Sports medicine physicians and emergency medicine physicians should be familiar with high-risk patients which is beyond the scope of this case series. High-

risk patients could include those with sickle-cell disease, familial history of rhabdomyolysis, history of hyperthermia, and those with recurrent episodes of ER. Patients deemed high-risk should be referred for further follow-up examination and potential studies [1].

When prompt diagnosis and treatment is initiated, the prognosis for a full recovery with full return to play is often achievable [2]. Treatment often entails intravenous rehydration and re-evaluation of laboratory findings before discharge. While the need for hospitalization and observation may be warranted, this decision is often derived from the physician's intuition and not based on laboratory findings alone [5]. It is imperative to understand that exercise can increase CK/CPK levels in the blood and that for the most accurate diagnosis, research needs to be conducted to establish sport specific reference ranges [10].

Bringing awareness to healthcare providers about the diagnosis, treatment, and management of ER should be of highest importance. As reported by Cleary, et al. [8], many athletic training and exercise physiology textbooks do not provide an adequate clinical picture or rhabdomyolysis and fail to mention ER [8]. Healthcare providers working with athletes should educate themselves along with promoting prevention and practice mitigation techniques, via education and dissemination of appropriate information, as this is the ideal treatment strategy for ER. Teaching athletes the signs and symptoms of ER and the dangers associated with excessive activity is a crucial aspect of clinical practice [2,8].

The purpose of this case series is to accomplish three things 1) Bring awareness to the clinical phenomenon that athletes tend to have higher CK/CPK values than their general population counterparts and may be further complicated dependent on specific sports, 2) Bring awareness to all healthcare providers (physicians, athletic trainers), strength and conditioning coaches, personal trainers, and coaches of the importance of education and prevention, and 3) Show the need for further research to be conducted in an effort to establish reference ranges more suitable for the athletic population and for individual sports. With further research health care providers associated with athletics may find it easier to determine which athletes need to be restricted from activity and aid sports medicine physicians and emergency department physicians in

making better clinical diagnoses, while athletes without clinical complications demonstrating a physiological response to activity can return to play following appropriate evaluation and management. By improving overall awareness, knowledge, along with the diagnostic ability, improvements in evaluation and management of ER in the athletic population may aid in reducing overall complications associated with the condition.

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