[Primary Care]

Exertional Rhabdomyolysis in the Athlete: A Clinical Review

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Context: Exertional rhabdomyolysis is a relatively uncommon but potentially fatal condition affecting athletes that requires prompt recognition and appropriate management.

Evidence Acquisition: A search of the PubMed database from 2003 to 2013 using the term *exertional rhabdomyolysis* was performed. Further evaluation of the bibliographies of articles expanded the evidence.

Study Design: Clinical review.

Level of Evidence: Level 3.

Results: Exertional rhabdomyolysis (ER) is a relatively uncommon condition with an incidence of approximately 29.9 per 100,000 patient years but can have very serious consequences of muscle ischemia, cardiac arrhythmia, and death. The athlete will have pain, weakness, and swelling in the muscles affected as well as significantly elevated levels of creatine kinase (CK). Hydration is the foundation for any athlete with ER; management can also include dialysis or surgery. Stratifying the athlete into high- or low-risk categories can determine if further workup is warranted.

Conclusion: Exertional rhabdomyolysis evaluation requires a history, physical examination, and serology for definitive diagnosis. Treatment modalities should include rest and hydration. Return to play and future workup should be determined by the risk stratification of the athlete.

Strength-of-Recommendation Taxonomy (SORT): C.

Keywords: exertional rhabdomyolysis, athlete, review

Overuse injuries are common in athletes and present a variety of challenges. For many athletes, the medical management and return-to-sport considerations of overuse injuries involve many variables including the goals of the athlete, medical staff, family, coach, and administration. Although exertional rhabdomyolysis (ER) is relatively rare, the consequences can be fatal, and therefore, appropriate treatment should be initiated to limit morbidity and mortality.

PATHOPHYSIOLOGY

Exertional rhabdomyolysis is characterized by the breakdown and necrosis of striated skeletal muscle after engaging in physical activity.[6] Although there are several different mechanisms that can lead to skeletal muscle cell damage and death, the common final pathway is an increase in intracellular free ionized calcium to a level much higher than normal in the cytoplasm and mitochondria.[6] In rhabdomyolysis secondary to trauma, the increase in intracellular calcium is caused by direct injury and rupture of the cellular membrane.[6] ER also has an overproduction of heat, resulting in increased intracellular calcium via depletion of adenosine triphosphate (ATP).[6] The loss of ATP causes dysfunction of Na/K–ATPase and Ca^{2+}ATPase pumps, leading to an increase of intracellular calcium.[6] This increase in intracellular calcium leads to the activation of proteases and production of reactive oxygen species, eventually

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culminating into the death of the skeletal muscle cells. Necrosis of skeletal muscle cells releases intracellular contents causing pain, swelling, and potential end organ damage in the athlete.[6]

EPIDEMIOLOGY

Rhabdomyolysis is associated with hyper- and hypothermia, sickle cell trait (and other ischemic conditions), exertion, crush syndromes, infection, autoimmune and metabolic disorders, and certain drugs.[19] Stimulants such as phentermine have been associated with exercise-induced rhabdomyolysis.[18] Sports that reported ER include American football, swimming, bodybuilding, and running.[2,4,5,9,16,17] In football, a retrospective cohort of high school football players identified 22 of 43 players at a football camp with ER[16]; 12 were hospitalized and 3 were also diagnosed with compartment syndrome. Repetitive eccentric loading, hyperthermia, and dehydration were contributing factors.

A case series of 7 Division I swimming athletes identified increased activity in well-conditioned athletes as a cause of ER.[5] Urine myoglobin was present in 3 of the 7 athletes. The swimmers underwent an intense pushup routine and body squats the week prior, provoking the syndrome. Not every swimmer developed ER, suggesting additional factors unique to those affected.

A bodybuilder diagnosed with ER and compartment syndrome of the lower extremity overused a supplement, creatine monophosphate; overexertion may have caused ER in this case.[4] A "perfect storm" consisting of bacterial/viral illness, nonsteroidal anti-inflammatory drug (NSAID) use, and latent myopathy can cause renal failure and potentially death in runners.[2]

Athletes may develop a hematologic profile consistent with ER but not develop the clinical condition. A study of ultra-marathon runners demonstrated myoglobinuria in 25 of 44 participants (57%).[17] The mean increase in creatine kinase (CK) was 2400 U/L 48 hours after the race. None of the ultra-marathoners developed clinical symptoms of ER or end organ damage (renal failure). In military personnel, the incidence of ER was 29.9 per 100,000 person-years.[1] Of the 435 US service members that were diagnosed with ER, 48% were hospitalized. Black, non-Hispanic male members younger than 20 years were most affected; the majority of cases occurred between June and August.[1] Common themes surrounding the epidemiology of ER include sudden alterations in training regimen, heat illness, poor conditioning, and dehydration.[2,4,5,9,16,17]

DIAGNOSIS

Exertional rhabdomyolysis may be an extreme continuation of delayed-onset muscle soreness.[12] Affected individuals typically complain of proportional pain, tenderness, weakness, and swelling in the muscles affected following athletic activity. Elevated CK levels 5 times the upper limit of normal with these symptoms are required for diagnosis.[8]

Black football players with sickle cell trait are at a 37 times higher risk of exertional-related death when compared with their non–sickle cell trait counterparts.[7] The cause of this increase in mortality is not completely understood. The depletion of ATP that occurs with ER and the sickling nature of red blood cells may deplete skeletal muscle of oxygen or may represent an autoimmune phenomenon.[7] Elevated levels of CK are normal after exercise in healthy, asymptomatic individuals, and blacks have higher baseline CK levels.[13] In 499 military recruits, peak CK levels occurred at day 7 of initial basic training (mean, 1226 IU/L; range, 56-35,056 IU/L).[8] Recruits did not develop clinically significant ER, but a CK range considering ethnicity should be considered.

A cumulative increase in resting serum CK was noted in 22 Division I football players over the course of a single season.[9] The peak CK range was 119 to 2834 IU/L after the ninth game of the season. A study comparing athletes with nonathletes in Greece noted that athletes have a significantly higher baseline CK level.[12] The range for diagnosis of rhabdomyolysis differs for each laboratory, but traditionally, it includes an increase of CK 5 to 10 times the upper limit of normal.[8] Significantly elevated CK must be present for the diagnosis of ER but should be made in association with the presenting clinical syndrome of muscle weakness, swelling, pain, and occasionally, darkening of the urine to differentiate rhabdomyolysis from other causes. Elevated levels of myoglobin will occasionally lead to darkened urine (tea or cola colored), with positive blood findings on urinalysis without red blood cells.[15] Rapid clearance of myoglobin from the urine makes it a less sensitive indicator for ER, and it should not be used as the sole objective diagnostic marker.[2]

Severe consequences of this condition include disseminated intravascular coagulation, acute kidney failure, hyperkalemia, and cardiac dysrhythmias.[2] Elevated levels of myoglobin in the serum do not necessarily predispose an athlete to renal failure.[17] Of the deaths that occurred in athletes because of this condition, other factors, including recent illness and cardiac ischemia, were listed as potential causes as well. Prompt recognition of these symptoms is paramount.[2]

TREATMENT

In mild cases, ER may go undiagnosed and could be managed on an outpatient basis with oral hydration and rest.[14] For an athlete with severe symptoms (CK greater than 5 times the upper limit of normal or darkening of the urine), hospital admission is indicated for intravenous hydration with normal saline (1-2 L/h) maintaining a urine output of 200 mL/h.[15] Along with intravenous hydration, the tracking of CK levels, kidney function, and electrolyte values is much easier to manage in an inpatient setting where continuous venovenous hemodialysis and other services are readily available. CK levels should be monitored daily. If levels continue to elevate past 48 to 72 hours from the time of injury, consultation of a nephrologist or surgeon should be considered, depending on the severity of

Table 1. Exertional rhabdomyolysis

High-Risk Athlete	Low-Risk Athlete
Delayed recovery (longer than 1 week)	Rapid clinical recovery and CK normalization after exercise restrictions
Persistent elevation of CK despite rest for 2 weeks	Sufficiently fit or well-trained athlete with a history of intense training/exercise
Acute renal injury to any degree	No personal or family history of rhabdomyolysis
Personal or family history of ER	Existence of other group or team-related cases of ER during the same exercise sessions
Personal or family history of recurrent muscle cramps	Suspected or documented concomitant viral illness
Personal or family history of malignant hyperthermia	Ingestion of a drug or dietary supplement that could contribute to the development of ER
Personal or family history of sickle cell trait	
Muscle injury after low to moderate workout activity	
Personal history of significant heat injury	
Serum CK peak of greater than 100,000 U/L	

CK, creatine kinase; ER, exertional rhabdomyolysis.

Table 2. CHAMP guidelines for return to sport following exertional rhabdomyolysis

Phase 1 • Rest for 72 hours and encouragement of oral hydration • 8 hours of sleep nightly • Remain in a thermally controlled environment if the episode of ER was in relation to heat illness • Follow-up after 72 hours with a repeat serum CK level and UA • If the CK has dropped to below 5 times the upper limit of normal and the UA is negative, the athlete can progress to phase 2; if not, reassessment in 72 additional hours is warranted • Should the UA remain abnormal or the CK remain elevated for 2 weeks, expert consultation is recommended
Phase 2 • Begin light activities, no strenuous activity • Physical activity at own pace/distance • Follow-up with a care provider in 1 week • If there is no return of clinical symptoms, the athlete can progress to phase 3; if not, the athlete should remain in phase 2 checking with the health care professional every week for reassessment; if muscle pain persists beyond the fourth week, consider expert evaluation to include psychiatry
Phase 3 • Gradual return to regular sport/physical training • Follow-up with care provider as needed

CHAMP, Consortium for Health and Military Performance; ER, exertional rhabdomyolysis; CK, creatine kinase; UA, urinalysis.

kidney disease or presence of compartment syndrome.[14] Continuous venovenous hemodialysis should be considered if the athlete is not be able to maintain appropriate volume or electrolyte balance.[14] Diuretics (thiazides and loop diuretics) can further deteriorate kidney function in this setting and should be prohibited.[14]

RETURN TO SPORT

There are no evidence-based guidelines for return to play after an episode of ER. Athletes may be at high risk or low risk (Table 1).[15] Athletes at high risk should be evaluated for myopathic disorders.[10,15] Testing may include electromyogram, genetic testing, muscle biopsy, exercise challenge, and caffeine-halothane muscle contracture testing.[15] In low-risk athletes, a gradual return is likely acceptable if the athlete is afebrile, symptom free, and well hydrated and CK levels are normal, myoglobin is no longer present in the serum or urine, the urine is clear, and there is no muscle pain.[3] A conservative return to sport was described at the Consortium for Health and Military Performance (Table 2).[15]

CONCLUSION

Exertional rhabdomyolysis is a relatively uncommon condition but can have very serious consequences if not recognized and managed appropriately. The athlete will typically present with pain, tenderness, weakness, and swelling in the muscles affected after engaging in physical activity. Hyperthermia, changes in workout regimen, sickle cell anemia, certain medications (stimulants and NSAIDs), preexisting illness, and autoimmune or metabolic disorders may predispose an athlete to ER. NSAIDs and illness may predispose the athlete to renal failure, especially long-distance runners. The diagnosis of ER requires serum CK levels 5 times the upper limit of normal. Treatment should include rest and hydration. Further testing may be needed if the athlete is considered high risk.

Clinical Recommendations

SORT: Strength of Recommendation Taxonomy
A: consistent, good-quality patient-oriented evidence
B: inconsistent or limited-quality patient-oriented evidence
C: consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Clinical Recommendation	SORT Evidence Rating
Myoglobinuria by itself is not a good indicator for exertional rhabdomyolysis[14]	C
The diagnosis of exertional rhabdomyolysis requires a serum creatine kinase at least 5 times the upper limit of normal[1,7,8,11]	C
Treatment of exertional rhabdomyolysis should include rest from the provoking activity and hydration[3,12]	C
Return to play should be a gradual phased process only after the clinical syndrome has resolved[3,12]	C

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