

Recurrent Exertional Rhabdomyolysis: Coincidence, Syndrome, or Acquired Myopathy?

Danit Atias, PhD¹; Amit Druyan, MD¹; and Yuval Heled, PhD, FACSM^{1,2}

Abstract

The purposes of this report are to review and discuss the issue of recurrent exertional rhabdomyolysis (ER), the return to physical activity after ER, and the possible causes of recurrence, with special consideration to metabolic myopathies and the possibility of an acquired post-ER myopathy. We discuss the medical investigation required prior to return to physical activity after an episode of ER and suggest two possible mechanisms for recurrence of ER in the absence of a known cause: premature return to activity and an acquired post-ER muscular disorder. We also emphasize the need to create proper guidelines for return to physical activity after ER and, for further investigation, the possible mechanisms of ER recurrence in patients without a known metabolic myopathy.

The laboratory diagnosis of ER usually is based on elevation of CPK activity to more than five times the upper limits of normal (10,18). However this cutoff is controversial since it does not take into consideration baseline differences, and mostly since the normal CPK values are not defined clearly (3,21). Moreover serum CPK activities after physical exercise vary widely between individuals and have been suggested to correlate with gender, race, and fitness (3,21). One possible explanation for these differences may be found in muscle predominance of type II muscle fibers (8). This mechanism also has been

Introduction

Rhabdomyolysis is a syndrome characterized by muscle necrosis and release of intracellular muscle content (creatine phosphokinase (CPK), myoglobin, calcium, potassium, organic acids, proteases, etc.) into the circulation (27). The common causes of rhabdomyolysis are listed in Table 1. Serious complications of rhabdomyolysis include acute myoglobinuric renal failure, disseminated intravascular coagulation, arrhythmias, and death (14,27). Exertional rhabdomyolysis (ER) occurs in response to excessive, prolonged, or repetitive exercise (21). Key clinical features of ER include severe muscle pain during active and passive movements, muscle swelling, and muscular weakness within the first 24 to 72 h after extreme and/or unfamiliar physical exercise. Patients' urine during an ER episode may be described as dark, red, tea, or "cola" colored. Nonetheless parts of the symptoms that are associated with ER, especially the pain, are similar to delayed onset of muscle soreness after exercise that is not associated with ER (5), a fact that makes early diagnosis difficult.

suggested in heat stroke patients who developed significant rhabdomyolysis (9,13). Clarkson and Ebbling (6) classified subjects as "high responders," "low responders," or "no responders" based on their CPK activity after exercise. The presence of myoglobin in urine (urine dipstick positive for blood) and/or serum also may be found in patients with ER (19,27).

Although there are no clear guidelines for treatment of ER or for hospitalization criteria, we recommend that ER patients with highly increased CPK activity, decreased creatinine clearance (elevated serum creatinine), myoglobinuria, metabolic abnormalities, or signs of compartment syndrome should be hospitalized. These general recommendations for hospitalization may be strengthened by a recent study by Delaney *et al.* (7) that found a significant correlation between known markers of rhabdomyolysis and acute kidney injury with the RIFLE (risk, injury, failure, loss, end stage) categories of renal impairment in emergency department patients. Similar recommendations have been given by George *et al.* (11). Treatment should include rest, rehydration, and monitoring for serious or life-threatening sequelae (acute renal failure, electrolyte, and acid-base disturbances) (14,21,24).

ER may occur as an isolated episode or as recurrent episodes, mostly (when other precipitating factors are excluded) in adults with hereditary metabolic myopathies (15). In a recent epidemiological report on the natural history of ER, Alpers and Jones (1) noted a relatively low recurrence rate

¹Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer, Israel; and ²The IDF Institute of Military Physiology, Tel Hashomer, Israel

Address for correspondence: Yuval Heled, PhD, FACSM, The IDF Institute of Military Physiology, Heller Institute of Medical Research, Sheba Medical Center, Tel Hashomer 52621, Israel; E-mail: yuval.heled@sheba.health.gov.il.

1537-890X/1206/365-369

Current Sports Medicine Reports

Copyright © 2013 by the American College of Sports Medicine

Table 1.
The most common causes to rhabdomyolysis (summarized from Ref. (14,17,27,28)).

Causes of Rhabdomyolysis	Examples
Traumatic or direct injury	
Multiple trauma	
Crush injuries	
Vascular or orthopedic surgery	
Coma/immobilization	
Nontraumatic	
<i>Exertional</i>	
Extreme exertion, overexertion	
Environmental heat illness	
Malignant hyperthermia	
Sickle cell trait	
Seizures	
Hyperkinetic states	
Neuroleptic malignant syndrome	
Metabolic and mitochondrial myopathies	See Table 1a
<i>Nonexertional</i>	
Illicit drugs and alcohol	Heroin Cocaine Amphetamine Methadone D-Lysergic acid diethylamide Alcohol
Drugs	Antipsychotics and antidepressants Sedative hypnotics Antilipemic agents (statins, fibrates, etc.) Antihistamines Others
Toxins	Heavy metals Insect venoms Snake venoms
Infections	HIV Coxsackievirus Falciparum malaria Herpes viruses Legionella Salmonella Streptococcus

Table 1.
(Continued)

	Tularemia
Electrolyte abnormalities	Hyperosmotic conditions Hypernatremia Hypocalcemia Hyponatremia Hypokalemia Hypophosphatemia
Endocrine disorders	Hyperaldosteronism Hypothyroidism Ketoacidosis Hyperaldosteronism
Autoimmune diseases	Polymyositis Dermatomyositis
Inflammatory myopathies	
Shock states	
Idiopathic	

of ER. In their work, however, they described 44 cases of ER among basic military trainees from the U.S. Air Force, of which only 22 were followed for recurrence over a mean time period of 31.2 months, and 1 recurrence has occurred in that group (recurrence risk of 0.08% per person per year). It should be emphasized however that although the recurrence rate demonstrated was low, the number of participants in this study was small and included a population from the U.S. Air Force only that has been reported to have a relatively low occurrence of ER compared to the other military units (20).

ER may be caused by various genetic myopathies (Table 1a), where the most common hereditary causes are carnitine palmitoyltransferase II (CPT II) deficiency and muscle phosphorylase deficiency (McArdle disease) (15). Although metabolic myopathies represent a very small percentage of ER cases, they should be suspected in patients with recurrent episodes of ER (25,26,27). Tonin *et al.* (26) reported a series of 77 patients with “idiopathic” myoglobinuria in whom muscle biopsies were performed and specific enzyme deficiencies were identified in 36 of the patients (47%). CPT II deficiency was the most common disorder, occurring in 17 of the 36 patients, followed by muscle phosphorylase deficiency in 10 patients. Exercise was stated as the main precipitating factor, both in patients with and without detectable myopathies. In another study (16), 23% out of 22 patients with recurrent ER had enzyme defects, from which the most common disorder was muscle phosphorylase deficiency. Other muscle diseases, muscular dystrophies, or myopathies were detected in 18% of these patients. In both studies, more than 50% of the recurrent ER cases had no known biochemical cause. Yet it should be emphasized that some less common enzyme deficiencies also were described as causing recurrent ER (Table 1a) (16,22,23,26).

Table 1a.**Metabolic myopathies associated with ER (summarized from Ref. (16,22,23,25,26,27,29,30)).**

Disorders of glycogenolysis/glycolysis
Myophosphorylase deficiency (McArdle disease)
Phosphorylase kinase deficiency
Phosphofructokinase deficiency
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Abnormal hexokinase activity
Disorders of lipid metabolism
CPT II deficiency
Short/medium/long/very long-chain and multiple acyl-CoA dehydrogenase deficiency
Mitochondrial trifunctional enzyme deficiency
LIPN1 gene (phosphatidic acid phosphatase) mutations
Disorders of purine metabolism
Myoadenylate deaminase deficiency (MAD)
Pentose phosphate pathway
Glucose-6-phosphate dehydrogenase (G6PD) deficiency
Mitochondrial respiratory chain
Microdeletion in cytochrome c oxidase subunit I III
Succinate dehydrogenase/complex II deficiency
Krebs cycle
Lipoamide dehydrogenase deficiency
Others
Sarcoplasmic calcium adenosine triphosphatase (Ca-ATPase) deficiency (Brody myopathy)

In another study, 475 medical records of patients with an acute neuromuscular illness/rhabdomyolysis were analyzed for a possible etiology. This study showed that the most common reasons for recurrent ER were found to be muscle diseases, illicit drug use, alcohol, medication, and idiopathic reasons (18).

Discussion

ER is a dangerous, life-threatening syndrome. In many cases, the cause to recurrent ER can be explained, but in some cases, the existence of possible inherent, unfamiliar causes should be considered. Moreover recurrent events due to acquired myopathies have not been looked at scientifically as far as we know. This manuscript emphasizes the need to further investigate this assumption.

Reasons for recurrent episodes of ER often remain unknown, but we can point to a few possible causes and mechanisms for a recurrent injury.

The first possible explanation is the existence of an undiagnosed metabolic disorder; since less common enzymatic deficiencies are usually not tested for (Table 1a), we

cannot completely rule out this possibility (16,26). Nevertheless the presence of a hereditary disorder might be argued against when patients had no prior episodes of ER despite being highly physically active. On the other hand, some metabolic disorders may be expressed only under certain conditions such as prolonged exercise, cold, fasting, a low-carbohydrate and high-fat diet, and infections (15). Krivickas (15) reported on a collegiate athlete with recurrent ER, without any prior history of ER, who was diagnosed finally with a mutation in the CPT II gene. In that case, the trigger for the initial episode seemed to be a combination of prolonged exercise and fasting.

Another potential explanation for recurrent ER may be premature return to physical activity. Returning to physical activity before complete recovery may lead to recurrent episodes of ER due to incomplete regeneration of the injured muscle tissue despite clinical recovery. Indeed a lag between clinical recovery and morphological recovery from ER, diagnosed by MRI, has been recently reported (2).

Another theoretical explanation may be a post-ER acquired myopathy. Such a disorder may be caused, for example, by dysregulation of the muscle repair mechanism. There is evidence that exercise increases plasma concentration of transforming growth factor-beta (TGF- β -1), probably due to mechanical load on the muscle tissues (12). In dysregulated muscle regeneration, there is a persistent inflammatory response and overexpression of proteins, such as TGF- β -1 and myostatin, which promote the formation of fibrotic tissue to replace damaged myofibers (4). Such dysregulated muscle regeneration may occur following ER and may lead to the formation of a weakened muscle tissue (possibly through the TGF- β -1 pathway), which may be more vulnerable to recurrent muscle breakdown and ER. This hypothetical mechanism, as well as other mechanisms, needs further investigation.

Return to physical activity after an episode of ER should include a thorough medical investigation (21). When no known etiology for the acute episode is found, evaluation for metabolic myopathies should be considered. Recurrent episodes of ER increase the level of suspicion for existing metabolic disorders (15), but in many cases, the recurrent injury is not associated with any known pathology. From a practical point of view, we suggest that even if no positive findings are found during the medical investigation of post-ER patients, they should be educated about the causes, signs, and symptoms of ER prior to return to physical activity.

Currently proper guidelines for return to physical activity after ER still are needed. It is recommended however that patients who have experienced ER should be evaluated and risk stratified as high or low risk prior to returning to activity (Table 2) (21). The evaluation may include severity of the injury, time for recovery, type of activity that caused the injury, personal and familial history, suspicion of metabolic myopathies, malignant hyperthermia, and sickle cell trait. High-risk patients will require further medical evaluation prior to return to physical activity, such as genetic testing for metabolic myopathies (Table 1a).

Conclusions

Several possible mechanisms for recurrence of ER in the absence of a known cause have been discussed in this report

Table 2.

Suggested parameters for defining high- and low-risk ER patients signs (adapted from (21)).

Suspicious for high risk ^a
Delayed recovery (more than 1 wk) when activities have been restricted.
Persistent elevation of CK (greater than 5 times the upper limit of the normal lab range) despite rest for at least 2 wk.
ER complicated by acute renal injury of any degree.
Personal or family history of ER.
Personal or family history of recurrent muscle cramps or severe muscle pain that interferes with activities of daily living or sports performance.
Personal or family history of malignant hyperthermia, or family history of unexplained complications or death following general anesthesia.
Personal or family history of sickle cell disease or trait.
Muscle injury after low to moderate work or activity.
Personal history of significant heat injury (heat stroke).
Serum CK peak >100,000 UL ⁻¹ .
Suspicious for low risk ^b
Rapid clinical recovery and CK normalization after exercise restrictions.
Sufficiently fit or well-trained athlete with a history of very intense training/exercise bout.
No personal or family history of rhabdomyolysis or previous reporting of debilitating exercise-induced muscle pain, cramps, or heat injury.
Existence of other group or team-related cases of ER during the same exercise sessions.
Suspected or documented concomitant viral illness or infectious disease.
Taking a drug or dietary supplement that could contribute to the development of ER.

^a To be considered "suspicious for high risk," at least one of the following conditions must exist or be present.

^b To be considered a "low risk" athlete, none of the "high-risk" conditions should exist, and at least one of the following conditions must exist or be present.

including less common hereditary metabolic myopathies, premature return to activity due to incomplete recovery of the muscle tissue despite clinical recovery, and an acquired post-ER muscular disorder. Further investigation is required in order to determine the exact mechanism of recurrent ER in patients without known metabolic myopathies. This investigation should include proper consideration of the possibility for temporary or permanent higher susceptibility to recurrent events after severe ER due to an acquired myopathy in the damaged muscles. Furthermore the level of medical investigation required for patients experiencing single or recurrent episodes of ER is not well established in the literature and varies from meticulous investigation of the medical history to an extensive genetic and metabolic investigation and muscle biopsy. Accordingly proper guidelines

for treatment and return to physical activity after ER are needed. It should include a thorough medical investigation along with risk stratification, and when no known etiology for the acute episode is found, evaluation for metabolic myopathies should be considered. Moreover the guidelines should include the length of time required before return to physical activity.

Acknowledgments

This study was not funded by any source. None of the authors has any professional relationships with companies or manufacturers who will benefit from the results of the present study. In addition, the results of the present study do not constitute endorsement by *Current Sports Medicine Reports* or the American College of Sports Medicine.

References

- Alpers JP, Jones LK Jr. Natural history of exertional rhabdomyolysis: a population-based analysis. *Muscle Nerve* 2010;42:487–91.
- Boni R, Rabitti PG. Spinning-induced rhabdomyolysis: importance of MRI for patient's outcome. A case report. *Reumatismo* 2011;63:44–8.
- Brewster LM, Mairuhu G, Sturk A, van Montfrans GA. Distribution of creatine kinase in the general population: implications for statin therapy. *Am. Heart J.* 2007;154:655–61.
- Burks TN, Cohn RD. Role of TGF-beta signaling in inherited and acquired myopathies. *Skelet. Muscle* 2011;1:19.
- Cheung K, Hume P, Maxwell L. Delayed onset muscle soreness: treatment strategies and performance factors. *Sports Med.* 2003;33:145–64.
- Clarkson PM, Ebbeling C. Investigation of serum creatine kinase variability after muscle-damaging exercise. *Clin. Sci. (Lond).* 1988;75:257–61.
- Delaney KA, Givens ML, Vohra RB. Use of RIFLE criteria to predict the severity and prognosis of acute kidney injury in emergency department patients with rhabdomyolysis. *J. Emerg. Med.* 2012;42:521–8.
- Echegaray M, Rivera MA. Role of creatine kinase isoenzymes on muscular and cardiorespiratory endurance: genetic and molecular evidence. *Sports Med.* 2001;31:919–34.
- Epstein Y. Predominance of type II fibres in exertional heat stroke. *Lancet* 1997;350:83–4.
- Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. *Medicine (Baltimore)* 1982;61:141–52.
- George M, Delgaudio A, Salhanick SD. Exertional rhabdomyolysis — when should we start worrying? Case reports and literature review. *Pediatr. Emerg. Care* 2010;26:864–6.
- Heinemeier K, Langberg H, Kjaer M. Exercise-induced changes in circulating levels of transforming growth factor-beta-1 in humans: methodological considerations. *Eur. J. Appl. Physiol.* 2003;90:171–7.
- Hsu YD, Lee WH, Chang MK, et al. Blood lactate threshold and type II fibre predominance in patients with exertional heatstroke. *J. Neurol. Neurosurg. Psychiatry* 1997;62:182–7.
- Huerta-Alardin AL, Varon J, Marik PE. Bench-to-bedside review: rhabdomyolysis — an overview for clinicians. *Crit. Care* 2005;9:158–69.
- Krivickas LS. Recurrent rhabdomyolysis in a collegiate athlete: a case report. *Med. Sci. Sports Exerc.* 2006;38:407–10.
- Lofberg M, Jankala H, Paetau A, et al. Metabolic causes of recurrent rhabdomyolysis. *Acta Neurol. Scand.* 1998;98:268–75.
- Mannix R, Tan ML, Wright R, Baskin M. Acute pediatric rhabdomyolysis: causes and rates of renal failure. *Pediatrics* 2006;118:2119–25.
- Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. *Medicine (Baltimore)* 2005;84:377–85.
- Milne CJ. Rhabdomyolysis, myoglobinuria and exercise. *Sports Med.* 1988;6:93–106.
- MSMR. Update: exertional rhabdomyolysis, active component, U.S. Armed Forces, 2011. *MSMR* 2012;19:17–9.
- O'Connor FG, Brennan FH Jr, Campbell W, et al. Return to physical activity after exertional rhabdomyolysis. *Curr. Sports Med. Rep.* 2008;7:328–31.
- Poels PJ, Wevers RA, Braakhekke JP, et al. Exertional rhabdomyolysis in a patient with calcium adenosine triphosphatase deficiency. *J. Neurol. Neurosurg. Psychiatry.* 1993;56:823–6.

23. Rosa R, George C, Fardeau M, *et al.* A new case of phosphoglycerate kinase deficiency: PGK Creteil associated with rhabdomyolysis and lacking hemolytic anemia. *Blood* 1982;60:84–91.
24. Sayers SP, Clarkson PM. Exercise-induced rhabdomyolysis. *Curr. Sports Med. Rep.* 2002;1:59–60.
25. Tein I, DiMauro S, DeVivo DC. Recurrent childhood myoglobinuria. *Adv. Pediatr.* 1990;37:77–117.
26. Tonin P, Lewis P, Servidei S, DiMauro S. Metabolic causes of myoglobinuria. *Ann. Neurol.* 1990;27:181–5.
27. Miller ML. Causes of rhabdomyolysis. UpToDate Web site [Internet]. Waltham (MA). Available from: <http://www.uptodate.com/>
28. Vanholder R, Sever MS, Ereke E, Lameire N. Rhabdomyolysis. *J. Am. Soc. Nephrol.* 2000;11:1553–61.
29. Warren JD, Blumbergs PC, Thompson PD. Rhabdomyolysis: a review. *Muscle Nerve.* 2002;25:332–47.
30. Zeharia A, Shaag A, Houtkooper RH, *et al.* Mutations in LPIN1 cause recurrent acute myoglobinuria in childhood. *Am. J. Hum. Genet.* 2008;83:489–94.