Unmasking of Carnitine Palmitoyltransferase Deficiency during an Acute Exacerbation of Asthma Complicated by Rhabdomyolysis in a Soldier

Guarantor: CAPT Jacob Gilad, MC IDF
Contributors: CAPT Jacob Gilad, MC IDF*†; MAJ Avinoam Pirogovsky, MC IDF†‡; LT COL Carmi Bartal, MC IDF*†

Rhabdomyolysis is a life-threatening condition that may result from various etiologies. We report a rare case of severe rhabdomyosis in a soldier after a mild acute asthma exacerbation. Further work-up revealed an underlying deficiency of type II carnitine palmitoyltransferase. The case is discussed along with a review of the literature. It is concluded that acute asthma exacerbations may be a unique precipitating factor of rhabdomyolysis and may therefore unmask underlying metabolic myopathies. Asthma may cause rhabdomyolysis through several different mechanisms, and thus the occurrence of rhabdomyolysis in the context of asthma exacerbations should warrant a work-up for metabolic diseases, especially in the presence of high creatine kinase levels. Given the high incidence of asthma, especially among young adults, a high index of suspicion is needed in order that rhabdomyolysis be promptly diagnosed and treated.

Introduction

Rhabdomyolysis is a life-threatening condition that may result from various etiologies, the most important of which are congenital or acquired metabolic disorders, trauma, infection, exertion, and drug adverse events.[1] Rarely, rhabdomyolysis may complicate the course of an acute exacerbation of asthma by either of several pathophysiologic mechanisms.

We report a case of severe rhabdomyosis in a soldier who presented with an acute asthma exacerbation. Laboratory analysis revealed a deficiency of carnitine palmitoyl-transferase (CPT) type II. The case is discussed along with a review of the literature regarding the association of asthma and rhabdomyolysis in the context of congenital metabolic myopathies.

Case Report

The patient was an 18-year-old soldier in basic training. Past history included bronchodilator-responsive mild intermittent asthma that did not require regular drug therapy. A lung function test was reportedly normal 1 year before recruitment. No past difficulty in performing physical exercise, including muscular aches or cramps, was reported.

Six weeks after the beginning of training, the patient complained of dyspnea that began during routine exercise, which included walking a distance of 3 miles, and did not resolve after β2 agonist inhalation. The patient participated fully in all endurance training over the previous 6 weeks. There was no recent history of an intercurrent febrile illness, dehydration, stress reaction, fasting, or exposure to extreme cold. Physical examination was unremarkable, and β2 agonist therapy was continued.

On the following day, the dyspnea recurred and the patient complained of severe and diffuse muscle aches. No strenuous physical activity was performed that day. On examination, there were no signs of respiratory distress or dehydration. His pulse was 92 beats per minute, his oxygen saturation was 98%, and his blood pressure and temperature were normal. Bilateral wheezes where noted on auscultation. Inhaled β2 agonists and budesonide were administered at standard dosages.

Inhalation therapy resulted in clinical improvement of dyspnea and wheezing, but the patient still complained of muscle aches and also of muscle fasciculations. Vital signs were normal. A urine sample disclosed dark brown urine, and the dipstick was positive for blood. An intravenous infusion of lactated Ringer's solution was started, and the patient was transferred to the emergency room because of suspected rhabdomyolysis.

On hospital admission, his pulse was 83 beats per minute, his respiratory rate was 18 per minute, his blood pressure was 134/75 mm Hg, he had a rectal temperature of 36.9°C, and his oxygen saturation was 99% while breathing room air. Laboratory studies revealed the following: hemoglobin, 14.5 g/dL; leukocyte count, 10,800/mm^3; platelets, 264,000/mm^3; glucose, 96 mg/dL; creatinine, 1.8 mg/dL; urea, 61 mg/dL; sodium, 137 mEq/L; potassium, 5.2 mEq/L; chloride, 102 mEq/L; calcium, 9.0 mg/dL; phosphate, 5.8 mg/dL; and magnesium, 2.7 mEq/L. Serum creatine kinase (CK) was 159,920 IU/L (muscle-brain isoenzyme fraction <1%) and serum myoglobin was 938 ng/mL.

Hydration and alkalinization were achieved by continuous infusion of intravenous saline and bicarbonate. Over the following days, serum creatinine levels peaked at 5.1 mg/dL. Marked improvement was noted after therapy, and the patient was discharged with a residual renal dysfunction (creatinine, 1.7 mg/dL).

A postdischarge work-up for possible etiologies of rhabdomyolysis revealed a type II CPT deficiency with residual enzyme activity of 13% compared with normal controls by means of the isotope exchange test of the patient's lymphocytes.

Discussion

We report a case of rhabdomyolysis in a patient with late-onset type II CPT deficiency, the most common inherited disorder of lipid metabolism affecting skeletal muscle. There are two

*Division of Internal Medicine, Soroka University Medical Center, Beer-Sheva, Israel 84101.
†Medicine Branch, Ground Forces Command, Israeli Defense Forces.
‡Department of Radiology, Kaplan Medical Center, Rehovot, Israel.
This manuscript was received for review in January 2003. The revised manuscript was accepted for publication in September 2003.

distinct forms of type II CPT deficiency—the rare, severe, and fatal infantile form and the benign, muscular, adult-onset form.[2]

The hallmark of adult-onset CPT deficiency myopathy is myoglobinuria. The classic manifestation includes recurrent myoglobinuria and rhabdomyolysis, which are typically precipitated by various factors including stress, fasting, cold exposure, strenuous exercise, and acute infections such as influenza.[3] Uncommonly, this condition may manifest as chronic myopathy with limb pain and stiffness without myoglobinuria. The phenotypic heterogeneity in CPT type II deficiency is related to the type and extent of enzymatic defect as well as to precipitating factors.[3] That rhabdomyolysis occurred during the course of an acute asthma exacerbation in this case is intriguing and deserves further discussion.

Rhabdomyolysis is in itself a rare complication of acute asthma exacerbation. Several mechanisms have been implicated in the pathogenesis of this condition in asthmatic patients, mostly based on case reports or small case series. Drug therapy appears as the most prominent cause, and several drug classes have been reported to cause muscle injury in asthmatic patients, including corticosteroids, β2 agonists, theophylline, and neuromuscular-blocking agents.

Theophylline therapy is a major cause of asthma-related muscle injury. Elevated CK levels have been described after concomitant therapy with theophylline and other CK-elevating drugs for asthma even with normal plasma drug levels because of a synergistic effect.[4] The combination of theophylline and clarithromycin has been reported to cause rhabdomyolysis,[5] as did theophylline toxicity in asthmatic patients, with more than 10 reported cases.[6]

Steroid therapy may also cause muscle injury or rhabdomyolysis in asthmatic patients. The combination of neuromuscular-blocking agents and steroids has been claimed to cause a heterogeneous myopathic disorder ranging from asymptomatic CK elevation to myopathy with weakness[7] and even rhabdomyolysis.[8] Douglass et al.[9] found that 76% of patients admitted to the intensive care unit with severe asthma requiring mechanical ventilation had elevated CK levels, with the highest being 7,430 IU/L. Moreover, acute steroid myopathy in asthmatic patients may occur with various intravenous steroid preparations.[10] However, inhaled steroids, such as those administered to our patient, are currently not considered a risk factor for rhabdomyolysis.

Nevertheless, therapy with 400 μg per day of inhaled beclomethasone with or without salmeterol may be associated with asymptomatic elevation of CK-MB levels in children.[11] The clinical significance of this finding has been long debated,[12] but recent data show that elevated CK-MB levels in patients with severe asthma do not result from myocardial injury as evidenced by the normal troponin levels in such cases.[13]

Albuterol may rarely result in CK elevation when an underlying primary myopathy exists.[14] However, even in the absence of myopathy, β-2 agonists have been implicated in muscle injury. Continuous albuterol nebulization caused elevated CK in 3 of 17 pediatric patients in one study.[12] Another study detected CK elevations during subcutaneous rather than nebulized terbutaline therapy.[15] An experimental model has demonstrated that salbutamol-induced muscle injury can be abolished by administration of β blockers, suggesting that an adrenergic mechanism is involved.[16]

Several authors have reported the occurrence of rhabdomyolysis in patients with severe asthma, including a 15-year-old boy with prolonged and severe asthma exacerbation,[17] a 71-year-old man with status asthmaticus,[18] and a 25-year-old man with status asthmaticus in whom rhabdomyolysis was attributed to vigorous contraction of respiratory muscles.[19] Indeed, elevated CK levels have been shown to correlate well with disease activity on long-term follow-up as well as acute exacerbations and have been attributed to an increased stress of breathing.[20]

In the case under discussion, there were no clinical or laboratory signs of myopathy before army recruitment or after physical exertion during the first weeks of basic training, despite type II CPT deficiency. Severe rhabdomyolysis developed during a mild exacerbation of asthma, though no vigorous respiratory effort was observed and despite inhaled salbutamol being the only possible therapeutic risk factor. No other extrinsic risk factors, which are common in the military setting, such as strenuous exertion, cold exposure, dehydration, or heat stroke, were present. We believe that the asthma exacerbation, salbutamol therapy, or their combination may have been sufficient to trigger rhabdomyolysis given the underlying metabolic myopathy, and that rhabdomyolysis would have probably not occurred under similar conditions but in the absence of a metabolic myopathy.

In conclusion, acute asthma exacerbations may be a unique precipitating factor of rhabdomyolysis and may therefore unmask an underlying metabolic myopathy such as type II CPT deficiency. Asthma may cause rhabdomyolysis by several different mechanisms, and thus the occurrence of rhabdomyolysis in the context of asthma exacerbations should warrant a work-up for metabolic diseases, especially if high CK levels are present. Given the high incidence of asthma exacerbations among young adults, including military personnel, a high index of suspicion is needed in order that rhabdomyolysis be promptly diagnosed and treated.

References

1. Warren JD, Blumberg PC, Thompson PD: Rhabdomyolysis: a review. Muscle Nerve 2002; 25: 332–47.
2. Roe CR, Coates PM: Mitochondrial fatty-acid oxidation. In: The Metabolic and Molecular Bases of Inherited Disease, Ed 7, pp 1501–33. Edited by Scriver CR, Sly WS, Valle D. New York: McGraw-Hill, 1995.
3. Kelly KJ, Garland JS, Tang TT, Shug AL, Chusid MJ: Fatal rhabdomyolysis following influenza infection in a girl with familial carnitine palmitoyltransferase deficiency. Pediatrics 1989; 84: 312–6.
4. Iwano J, Nakamura Y, Izumida T, et al: Synergistic effect of combining theophylline and drugs that potentially elevate serum creatine kinase. J Med Invest 2000; 47: 9–13.
5. Shimada N, Omuro H, Saka S, Ebihara I, Koide H: A case of acute renal failure with rhabdomyolysis caused by the interaction of theophylline and clarithromycin. Nippon Jinzo Gakkai Shi 1999; 41: 460–3.
6. Aoshima M, Kameyama S, Murai Y, Yamazaki M, Kamiay T, Miyazaki T: A case of theophylline-induced rhabdomyolysis following therapy of bronchial asthma. Nihon Kyobu Shikkan Gakkai Zasshi 1991; 29: 1064–9.
7. Blackie JD, Gibson P, Murree-Allen K, Saul PW: Acute myopathy in status asthmaticus. Clin Exp Neurol 1993; 30: 72–81.
8. Goh AY, Chan PW: Acute myopathy after status asthmaticus: steroids, myorelaxants or carbon dioxide? Respirology 1999; 4: 97–9.

9. Douglass JA, Tuxen DV, Horne M, et al: Myopathy in severe asthma. Am Rev Respir Dis 1992; 146: 517–9.
10. Williams TJ, O'Heir RE, Czarny D, Horne M, Bowes G: Acute myopathy in severe acute asthma treated with intravenously administered corticosteroids. Am Rev Respir Dis 1988; 137: 460–3.
11. Del-Rio-Navaro BE, Sienra-Monge JJ, Alvarez-Amador M, Reyes-Ruiz N, Arvelo-Salas A, Berber A: Serum potassium levels, CPK-MB, and ECG in children suffering asthma treated with beclomethasone or beclomethasone-salmeterol. Allergol Immunopathol (Madr) 2001; 29: 16–21.
12. Craig VL, Bigos D, Brilli RJ: Efficacy and safety of continuous albuterol nebulization in children with severe status asthmaticus. Pediatr Emerg Med 1996; 12: 1–5.
13. Lovis C, Mach F, Unger PF, Bouillie M, Chevrolet JC: Elevation of creatine kinase in acute severe asthma in not of cardiac origin. Intensive Care Med 2001; 27: 528–33.
14. Craig TJ, Smits W, Soontornniyomkiu V: Elevation of creatine kinase from skeletal muscle associated with inhaled albuterol. Ann Allergy Asthma Immunol 1996; 77: 488–90.
15. Sykes AP, Lawson N, Finnegan JA, Ayres JG: Creatine kinase activity in patients with brittle asthma treated with long term subcutaneous terbutaline. Thorax 1991; 46: 580–3.
16. Cepero M, Perez-Pertejo Y, Cubria JC, et al: Muscle and serum changes with salbutamol administration in aerobically exercised rats. Comp Biochem Physiol C Toxicol Pharmacol 2000; 126: 45–51.
17. Li AM, Li CC, Chik KW, Shing MM, Fok TF: Rhabdomyolysis following status asthmaticus. J Paediatr Child Health 2001; 37: 409–10.
18. Bando T, Fujimura M, Noda Y, Ohta G, Matsuda T: Rhabdomyolysis following status asthmaticus. Respiration 1996; 63: 309–11.
19. Chugh KS, Singhal PC, Khatri GK: Rhabdomyolysis and renal failure following status asthmaticus. Chest 1978; 73: 879–80.
20. Burki NK, Diamond L: Serum creatine phosphokinase activity in asthma. Am Rev Respir Dis 1977; 116: 327–31.