Review Article

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Anaphylaxis and rhabdomyolysis. Any early relationship?

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Abstract

***Introduction*: Rhabdomyolysis (RML) had been identified in different traumatic and non-traumatic conditions; few reports described its association with anaphylaxis. We report two cases of anaphylaxis both complicated with RML.**

***Aim of the work*: To discus the possible casual relation between anaphylaxis and RML and so the value of early screening of creatine phosphokinase (CPK) in patients with anaphylaxis.**

***Setting*: Two patients were enrolled in a multidisciplinary intensive care unit.**

***Results*: Both patients survived, both developed RML shortly after admission, evidenced by 5-fold or greater increase in serum CPK. They had transient hypotension through the presentation, but none of them had persistent shock requiring vasopressors or complicated with acute renal failure.**

***Conclusion*: We observed rapid increase in serum CPK in our two cases suggesting the potential benefits of early assessment of CPK in such patients which may amplify early goal guided management and avoiding logistic organ dysfunction.**

Key words: Rhabdomyolysis, anaphylaxis.

Introduction

Background

Anaphylaxis is an acute, potentially lethal, multisystem syndrome resulting from the sudden release of mast cell and basophile-derived mediators into the circulation. (1) Rhabdomyolysis was first described in the victims of crush injury during the 1940-1941 London, England blitzkrieg bombing raids of World War II. (2) It has many etiologies. However few reports described association between rhabdomyolysis and anaphylaxis.

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Pathophysiology

Organ system involvement in anaphylaxis varies from species to species and determines the clinical manifestations observed. Factors that determine a specific "shock organ" include variations in the immune response, the location of smooth muscle, and the distribution, rate of degradation, and responsiveness to chemical mediators. (3,4) Human anaphylaxis was traditionally considered a form of distributive shock characterized by a profound reduction in venous tone, with similarities to septic shock and toxic shock syndrome. An emerging view, however, is that anaphylaxis has features of hypovolemic shock also, with fluid extravasation causing reduced venous return, as well as depressed myocardial function. (5)

Rhabdomyolysis is the breakdown of muscle fibers with leakage of potentially toxic cellular contents into the systemic circulation. The final common pathway of rhabdomyolysis may be a disturbance in myocyte calcium homeostasis. (6) Clinical sequelae of rhabdomyolysis include the following:

hypovolemia (sequestration of plasma water within injured myocytes), hyperkalemia (release of cellular potassium into the systemic circulation), metabolic acidosis (release of cellular phosphate and sulfate), acute renal failure (nephrotoxic effects of liberated myocyte components) and disseminated intravascular coagulation (DIC). (2,6)

Laboratory studies

Preliminary diagnosis of rhabdomyolysis requires a high index of suspicion. Definitive diagnosis is made by laboratory evaluation. Most authorities would agree that a 5-fold or greater increase in serum CK is consistent with the diagnosis, although levels 40 times greater than normal may often be seen. Early rhabdomyolysis should be suspected in at-risk patients with only a 2- to 3-fold increase in serum CK. Serial CK levels should be trended, but most authorities would agree that a 5-fold or greater increase in serum CK is consistent with the diagnosis, although levels 40 times greater than normal may often be seen. (7) Serum CK levels peak within 24 hours and should decrease by approximately 30-40% per day after the initial insult. (8) Persistent elevation suggests continuing muscle injury or development of a compartment syndrome. (9)

A urine dipstick test for blood has positive results in the presence of hemoglobin or myoglobin. Myoglobinuria may be sporadic or resolve early in the course of rhabdomyolysis. Urine dipstick findings are positive in only 50% of patients with rhabdomyolysis; therefore, a normal urine dipstick test result does not rule out this condition. Aldolase, lactate dehydrogenase (LDH), and serum glutamic-oxaloacetic transaminase (SGOT) are nonspecific enzyme markers that are elevated in patients with rhabdomyolysis. (9)

Patients and method

Two patients enrolled in this paper, both were subjected to routine laboratory investigations including CPK, the diagnosis of anaphylaxis was made according to the criteria of the multidisciplinary group of experts in 2005 and 2006. (2,10) Total CK elevation is a sensitive but nonspecific marker for rhabdomyolysis. Suspect early rhabdomyolysis in patients with serum CK levels in excess of 2-3 times the reference range and risk factors for rhabdomyolysis, and total CK levels should be drawn every 6-12 hours until a peak level is established.

Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any ONE of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
   A. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   B. Reduced BP* or associated symptoms of end-organ dysfunction (e.g., hypotonia, collapse, syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   A. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   B. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   C. Reduced BP* or associated symptoms (e.g., hypotonia, collapse, syncope, incontinence)
   D. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP* after exposure to a known allergen for that patient (minutes to several hours):
   A. Infants and children: low systolic BP (age specific)* or greater than 30 percent decrease in systolic BP
   B. Adults: systolic BP of less than 90 mmHg or greater than 30 percent decrease from that person's baseline

Legend: PEF=peak expiratory flow; BP=blood pressure; *=low systolic blood pressure for children is defined as less than 90 mmHg from 11 to 17 years. (Adapted from: Sampson, et al. 2006) (1)

Cases Report

Case 1

An 18 year-old man with anaphylactic reaction was seen in the emergency department (ED) with shortness of breath, generalized itching. After he woke up later he developed rash allover the body, the patient denied taking any medicine, eating something new for him. The patient was hypotensive on presentation 90/60 mmHg, tachycardia 120/m.

The patient had past medical history of allergic rhinitis since the age of 3 years but not asthma with family history of bronchial asthma. There was no history of allergy. There was no history of tobacco, alcohol or illicit drug use.

In the medical intensive care unit, the patient had temperature of 37.1 °C. His heart rate was 126 beats/minute and blood pressure was 110/65 mmHg. There were diffuse inspiratory and expiratory wheezes with expiratory phase prolongation. The cardiac examination was normal except for tachycardia. There was no pallor, cyanosis, or clubbing. The skin and extremities were normal.

The white blood cell count, electrolytes, minerals and liver and renal function tests were normal. Blood lactate was 1 mmol/L (normal: 0.2-2.5). Creatine phosphokinase (CPK) was 2,900 U/L (normal: 0-125). The first CPK level was performed in the emergency department (ED) as soon as the patient arrived, prior to administration of systemic steroids and epinephrine. The CPK MB was not elevated. Urine toxicology screen was negative. The chest radiograph was normal.

The patient received two liters of intravenous fluids with fair response in the blood pressure, then received one dose of epinephrine 1:1,000 dilution, 0.5 mL, followed by steroids, H1 and H2 antagonists. CPK 12 hours after admission increased to 6,800 U/L with a normal serum creatinine, potassium, and phosphate. Hydration and sodium bicarbonate were initiated for management of rhabdomyolysis. The peak CPK was 14,400 U/L at 36 hours. It dropped steadily thereafter to 400 U/L by the 5th hospital day (**Table 1**).

Case 2

A previously healthy 44-year-old woman was transferred from a clinic after having hypotension there. The patient was given one dose of epinephrine in the clinic, came to ED hypotensive, requiring 2nd dose of epinephrine followed by IV fluids. The patient gave a history of intake of mefenamic acid, and after that she had swelling on her face, arms and legs.

Her physical examination revealed a pulse rate of 116 beats/minute, blood pressure of 110/60 mmHg, temperature of 37.5 °C, and respiration of 22 breaths/minute. She was initially on a non-rebreather mask (FiO2 of 100%) with 100% oxygen saturation and was switched to 2 L/minute oxygen by nasal cannula maintaining oxygen saturation above 90%. Pertinent positive findings included periorbital edema, numerous erythematous maculopapular and vesicular lesions on the eyelids, forehead, both upper extremities, and over the chest and upper abdomen, diffuse wheezing throughout lung fields and hypoactive bowel sounds. Lips were swollen significantly. Other systems were normal.

The patient had no past medical history of any medical illness, no family history of allergy or bronchial asthma. There was no history of allergy. There was no sensitivity to aspirin. There was no history of tobacco, alcohol or illicit drug use. The patient stated that she took two tablets of mefenamic acid for her menstrual pain.

The white blood cell count, electrolytes, minerals and liver and renal function tests were normal. Blood lactate on admission was 4.6 mmol/L (normal: 0.2-2.5). Creatine phosphokinase (CPK) was 2,900 U/L (normal: 0-125). The first CPK level was performed in the ED as soon as the patient arrived, prior to administration of systemic steroids, and epinephrine. The CPK MB was not elevated. Urine toxicology screen was negative. The chest radiograph was normal. The patient received steroids, IV fluids, H1 and H2 antagonists.

CPK 12 hours after admission increased to 10,100 U/L with a normal serum creatinine, potassium, and phosphate. Hydration and sodium bicarbonate were initiated for management of rhabdomyolysis. CPK dropped steadily thereafter to 400 U/L by the 5th hospital day (**Table 2**). At day 7 after admission to ICU he was discharged to the medical ward.

Discussion

An elevated serum CPK and the presence of myoglobin in the urine characterize rhabdomyolysis. (11) It may result from

crash injury, tissue ischemia, prolonged immobilization, major trauma, illicit drugs and use of paralytic agents like succinylcholine. Myoglobinemia after severe exercise has also been reported. (12) Few reports addressing the association between rhabdomyolysis and anaphylaxis, most of them were in the sitting of envenomations. (13)

In our cases both patients had elevation of CPK, with peak levels 14,400 and 10,100 (IU/L) in the 1st and in the 2nd case respectively. Both patients developed rhabdomyolysis after anaphylaxis, and the cause of anaphylaxis was unknown in the 1st patient, and drug induced in the 2nd one.

Rhabdomyolysis in our patients could be explained by hypotension, use of sympathomimetic drugs, or steroid use. Blood flow to the periphery is decreased during shock, to preserve perfusion of central organs. Oxygen consumption by skeletal muscle is impaired, despite an increase of partial pressure of oxygen, leading to anaerobic metabolism. (14) Decreased perfusion leads rapidly to anaerobic metabolism. This may partly explain why end organ injury and irreversible shock can develop so quickly. (15)

Factors like extended use of high dose corticosteroids (16) may contribute to rhabdomyolysis. (17) Excessive use of beta sympathomimetic agents may cause agitation and tremors leading to rhabdomyolysis. (18)

In our cases there were no obvious consequences of CPK elevation such as overt neuromuscular weakness prolonging the need for assisted ventilation or acute renal failure. Hypotension was transient, small doses of sympathomimetics were used. This report adds to the literature confirming an association between anaphylaxis and the development of rhabdomyolysis.

Conclusions

We observed rapid increase in serum CPK in our two cases suggesting the potential benefits of early assessment of CPK in such patients which may amplify early goal guided management and avoiding logistic organ dysfunction. We recommend CPK determinations in all severely ill asthmatics and treatment of rhabdomyolysis using accepted measures such as vigorous hydration to avoid complications of acute renal failure.

Table 1. Laboratory and clinical findings of the first case

	Day 1	Day 2	Day 3	Day 4	Day 5
Serum Na (mmol/L) N: 136-145	145	140	131	135	137
Serum K (mmol/L) N: 3.6-5.1	3.9	4.5	4.6	3.8	4.2
Serum Cl (mmol/L) N: 101-111	110	106	96	106	103
Serum CO2 (mmol/L) N: 12-40	22	22	27	27	26
Creatinin (µmol/L) N: 58-96	84	77	91	58	60
Serum protein (g/L) N: 61-79	70	63	66	60	58
Albumin (g/L) N: 35-48	44	40	41	40	
Bilirubin total (µmol/L) N: 5-22	22	15	18	16	
Bilirubin direct (µmol/L) N: 0-7				7	
Alkaline phosphatase (IU/L) N: 38-126	78	75	81	68	
GGT (IU/L) N: 9-35	10		13	12	
AST (IU/L) N: 15-41	56	115	181	106	
ALT (IU/L) N: 14-54	39	55	73	47	
Total CK (IU/L) N: 38-234	2900/6800	12599/14400	8100/4100	1200	400
WBCs ($x10^9$/L) N: 4.5-11	13			23	
Hb (g/L) N: 117-155	14.4			12.9	
RBCs ($x10^{12}$/L) N: 4.0-5.2	4.5			4.1	
Platelets ($x10^9$/L) N: 140-450	478			410	
Lactate (mmol/L) N: 0.7-2.2	1			0.9	
CRP (mg/L) N: 0-10	31		19		19
SBP (mmHg)	90	120	110	108	115
HR (beats/min)	120	125	100	90	88
Temperature (°C)	37.5	37	36.8	37	36.7

Legend: N=normal values

Table 2. Laboratory and clinical findings of the second case

	Day 1	Day 2	Day 3	Day 4	Day 5
Serum Na (mmol/L) N: 136-145	136	140	141	144	
Serum K (mmol/L) N: 3.6-5.1	3.4	4.1	3.7	3.4	4.1
Serum Cl (mmol/L) N: 101-111	107	114	108	110	106
Serum CO2 (mmol/L) N: 12-40	15	17	24	21	23
Creatinin (µmol/L) N: 58-96	95	67	56	47	43
Serum protein (g/L) N: 61-79	56	52	66	66	61
Albumin (g/L) N: 35-48	29	34	32	31	34
Bilirubin total (µmol/L) N: 5-22	14	14	10	11	11
Bilirubin direct (µmol/L) N: 0-7					
Alkaline phosphatase (IU/L) N: 38-126	70	64	89	80	85
GGT (IU/L) N: 9-35	56	52	66	61	70
AST (IU/L) N: 15-41	381	189	133		38
ALT (IU/L) N: 14-54	286	201	191		111
Total CK (IU/L) N: 38-234	1800/3700	4900/10100	5100	2100	200
WBCs ($x10^9$/L) N: 4.5-11	4.1	4.3		7	
Hb (g/L) N: 117-155	108		98	115	
RBCs ($x10^{12}$/L) N: 4.0-5.2	3.6		3.2	4.2	
Platelets ($x10^9$/L) N: 140-450	224		193	310	
Lactate (mmol/L) N: 0.7-2.2	1.4		0.9		
CRP (mg/L) N: 0-10	31		80		
SBP (mmHg)	110	130	122	118	127
HR (beats/min)	116	100	80	85	77
Temperature (°C)	37.5	37	38	37	37.4

Legend: N=normal values

Figure 1 . CK changes throughout the course in the two cases

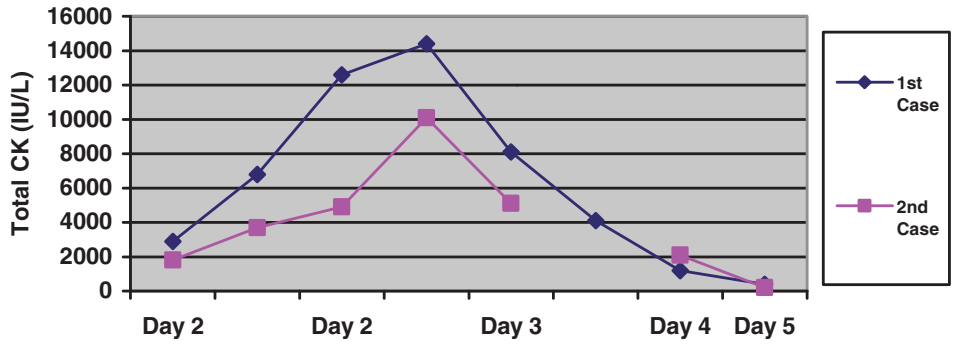
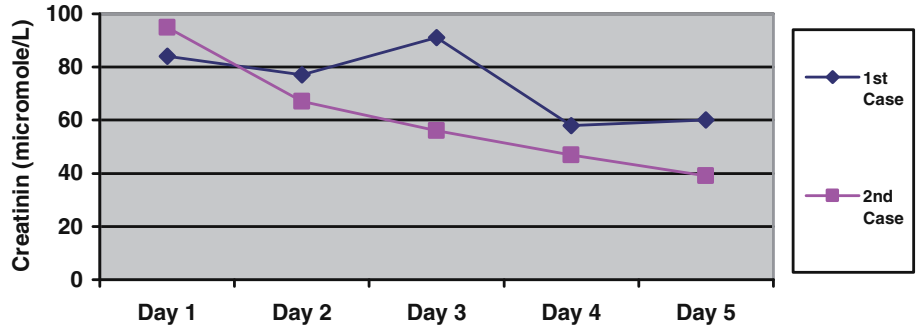


Figure 2 . Serum creatinin changes throughout the course in the two cases



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