Multifactorial Pathogenesis of Rhabdomyolysis in Alcoholic Leading to Acute Renal Failure - Case Report with a Review of Etiologic Factors

Tomaz Rott

Institute of Pathology, Medical Faculty, University of Ljubljana, Slovenia

Abstract

Numerous sometimes interrelated conditions are leading to rhabdomyolysis with consequent acute renal failure and even death: exertional states, muscle injuries, infections, systemic diseases, circulation disorders, inherited and acquired metabolic, toxic disorders and various drugs. The author present 34-years old male chronic alcoholic, who went through epileptic seizures, delirium tremens, hypotension and febrile condition and developed crush-syndrome like clinical state with myoglobinuria, acute renal failure and died. Autopsy revealed acute tubular necrosis with interstitial edema and numerous immunohistologically proven myoglobin casts in the tubules. Skeletal muscles disclosed patchy muscle fibres necroses.

The author suggest multifactorial pathogenesis of rhabdomyolysis in the patient induced by: exertional states during epileptic seizures and delirium tremens, febrile state, direct toxic influence of alcohol, and influence of hypotension with hypoxia.

Key words: rhabdomyolysis - etiology, acute renal failure, alcoholism, myoglobinuria, immunohistology.

BAM 2 (4): 271-276, 1992

Rhabdomyolysis is caused by numerous sometimes interrelated conditions, divided in several groups as reported in some previous excellent comprehensive reviews [13, 29]. The aim of this report is to summarize known factors leading to the destruction of skeletal muscles with its consequences, and to present a patient who died from such disease caused by multifactorial pathogenesis.

Presentation of the patient

34 - years old male patient, already unsuccessfully treated for chronic alcoholism, was admitted to the psychiatric clinic because of malaise, sweating, vomiting, restlessness, and collapse. The day before the admission to the hospital he also underwent through two attacks of presumed epileptic seizures.

During the first day of hospitalization he had epileptic attack of grand mal type. He was treated symptomatically. The third day, he became even more agitated, delirious with hallucinations, refusing food and therapy. The fourth day, lowering of blood pressure was registered with systolic pressure 90 mm Hg, and even disturbances of consciousness appeared. He became anuric. The patient was transferred to intensive care department to be monitored every two hours for blood pressure, pulse, respiration, body temperature, diuresis, and central venous pressure. He was found to be somnolent, trembling, dehydrated, with body temperature up to 40.2°C, tachypnoic (40/minute) and tachycardic (160/minute) with systolic blood pressure up to 90 mm Hg, without any signs of traumatic lesions.

During the next four days, patient was febrile all the time, azotemia was increasing (the fifth day of hospitalization serum creatinin reached 1030 µmol/L - normal value 44 - 97; urea 36.6 mmol/L - normal 2.8 - 7.5) and in spite of intensive hydration and therapy with dopamine and mannitol, the diuresis was not restored. Therefore, the patient was treated with hemodialysis. The highest values of serum enzymes : lactate dehydrogenase 76 µkat/L (normal 2.33 - 4.83), aspartate aminotransferase 41.3 µkat/L (normal 0.60), alanine aminotransferase 4.3 µkat/L (normal 0.70), and the fifth day of hospitalization, creatine phosphokinase reached the value 3090 µkat/L (normal 0.17 - 2). Some other laboratory findings: sedimentation rate 43 mm/h, leukocyte count 12.5 x 10^9/L (neutrophil granulocytes 79%), total serum bilirubine 54 µmol/L (normal 17),

direct bilirubine 23 μmol/L (normal 5), serum phosphate in the range 0.81 - 1.8 mmol/L (normal 0.8 - 1.4).

Electrocardiogram showed sinus tachycardia. Central venous pressure gradually increased up to 20 mm H_2O. The eighth day of hospitalization (the fourth day after admission to the intensive unit), bradycardia with respiratory arrest appeared and the patient died in spite of resuscitation. It was concluded that rhabdomyolysis, leading to acute renal failure and patient's death, was most probably caused by exertional states during epileptic convulsions and delirium tremens, combined with circulatory disturbances and septic state (suggested by protracted febrile state, leukocytosis, shift to the left in the differential white blood cell count), although the latter was not proved with repeated hemocultures.

Autopsy findings

There were signs of acute heart failure with secondary pulmonary edema and pleural effusion. The weight of the heart with dilated chambers was 430 g. There was not any coronary sclerosis. Histologically, focal mononuclear infiltrations were disclosed in the heart muscle of the left ventricle. The lungs weighing over 700 g each, were moderately emphysematous with marked congestion and edema and congested airways' mucosa. There were 400 ccm and 300 ccm pleural effusions on the left and on the right side respectively. Autopsy revealed also much heavier kidneys (right 340 g, left 320 g) with widened pale cortex and purple-dark pyramids. Light microscopy disclosed acute tubular necrosis with interstitial edema, dilated tubules with flattened and necrotic epithelium and numerous immunohistologically proven myoglobin casts in distal canaliculi (Figure 1). Glomeruli showed only some myoglobin casts between the parietal and visceral wall of Bowman capsule. Biceps and especially quadriceps muscles showed disseminated focal muscle fiber necroses (Figure 2). There were moderate fatty change and focal alcoholic hepatitis (with Mallory hyalin and associated inflammatory infiltrates) in the enlarged liver (3220 g), but no other inflammatory focus explaining febrile state.

Discussion

Patient died from acute renal failure combined with acute heart failure and consequent pulmonary edema and bilateral pleural effusion. The histological changes in the heart could not be designated as chronic focal interstitial myocarditis, because they do not entirely correspond to the Dallas criteria. Morphologically, the heart changes could be evaluated as congestive dilatative presumably alcoholic cardiomyopathy [37].

Febrile state with leukocytosis, in the absence of any other inflammatory focus, could be explained and attributed to liver changes, to alcoholic hepatitis, supported by biochemical parameters and postmortem histology. On the other hand febrile state with leukocytosis is a very common finding in patients with tremens.

Rhabdomyolysis of different etiology shares in many cases some common denominators: various noxious agents interfere with microcirculation and with usually increased metabolic demands of the muscles. In general, from the functional point of view, we may be dealing with increased energy consumption, decreased energy production - inherited or acquired, impaired oxygenation of the muscles, caused by different deleterious physical or chemical agents, and various microorganisms.

From the clinical point of view and based on autopsy findings we can conclude that, in our patient, rhabdomyolysis was caused by various etiopathogenetic factors, cited among many others in the table 1. The most important

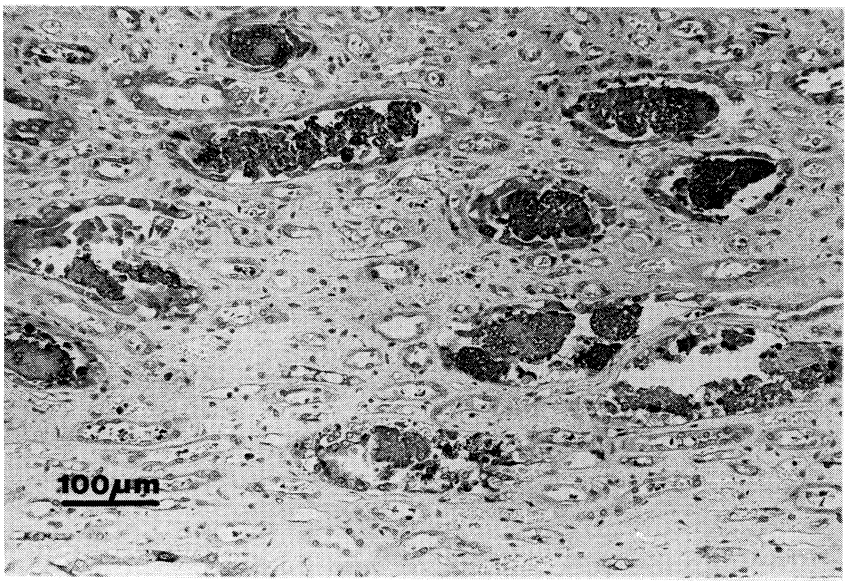

Figure 1. Focal necroses of muscular fibers in m.quadriceps. Masson's trichrome staining, orig. magnif. x 40.

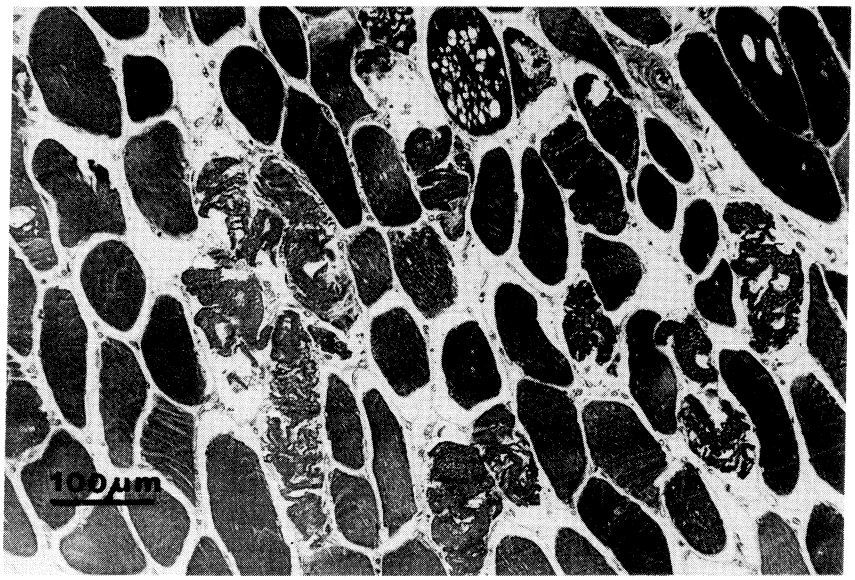

Figure 2. Numerous myoglobin casts in distal tubules and collecting ducts in the kidney. Immunoperoxidase method for demonstration of myoglobin, orig. magnif. x 40.

Table 1. The causes of rhabdomyolysis (modifications of 13,29).

1. EXERTIONAL STATES (alcoholic delirium tremens[3,11,27]; convulsive disorders - heat stroke, brain injuries, epilepsy; physical: contact sports; marathon runners, rectus-abdominis syndrome[25], untrained soldiers; electrical injury - high voltage shock, reanimation[16])

2. MUSCLE INJURIES (burns, compartment-crush syndrome[24] - earth quakes, wars; Conga drums, contact and other sports - firearm recoil, ice skating, jackhammer, karate, rugby; pressure necrosis in coma, reanimation - physical injury[16], toe-walking)

3. INFECTIONS (bacterial - Haemolytic streptococcus, Aeromonas hydrophila[32], Clostridium tetani, Clostridia causing gas gangrene, Herbicola lathyri, Legionella[31], Leptospira, Pseudomonas, Shigella, Salmonella; Rickettsia; viral - Influenza, Coxsackie, hepatitis C virus; parasitic - Trichinosis, Falciparum malaria[35] etc)

4. SYSTEMIC DISEASES (vasculitis, polymyositis)

5. CIRCULATION DISORDERS (ischaemia - arterial occlusion: thromboses and emboli, traumatic presssure, inferior vena cava ligation[21])

6. INHERITED AND ACQUIRED METABOLIC DISORDERS AFFECTING CARBOHYDRATE,

LIPID METABOLISM ETC (calciphylaxis, diabetic acidosis, hypernatremia, hypokaliemia[34], hypophosphatemia[33], hypothyroidism[15], nonketotic hyperosmolar coma; adenine diaminose deficiency, deficiencies of carnitine and carnitine palmytil transferase, glucosidase, amylo-L, 6-glucosidase, phosphohexoisomerase, familial paroxysmal rhabdomyolysis[26], lipid metabolism disorder, phosphorylase deficiency - Mc Ardle's syndrome, phosphofructokinase deficiency - Taruis syndrome,)

7. TOXIC DISORDERS (pollution of water - quail-eaters disease, toxins in fish - "Haff"disease, venoms of Malay sea-snake, household brown spider, hornet and africanized bee[1]).

8. CHEMICALS & DRUGS (alcohol, amphetamine[9], amphotericin B, arachidonic acid, barbiturates, bezafibrate[12], CO[8,39], heroin[22], caffeine[17], carbenoxolone, chemotherapy[23], cholestyramine[5], cocaine [19,28], codeine, corticosteroids[38], diazepam, 2, 4-dichlorophenoxy - acetic acid, epsilon aminocaproic acid, fenoverine[10], glutethemide, isopropil alcohol, ethylene glycol, liquorice - glycyrrhizate, lovastatine[6,36], LSD, methadone, ethylenedioxymetamphetamine (MDMA,"ecstasy")[7,30], propoxyphene, strychnine[40], succinyl choline, theophylline[14], etc).

9. MISCELLANEOUS (fever, hypothermia, malignant hyperpyrexia of not established cause, Reye's syndrome, sickle-cell trait)

The numbers represent references.

causes were exertional states during epileptic muscular convulsions and delirium tremens, combined with circulatory disorders - long-lasting hypotension with ischemia . We can also presume that alcohol played considerable role, partly with its direct toxic effect on muscular tissue [37], partly indirectly, provoking delirious status with muscular trembling which increased metabolic demands in muscles already rendered susceptible to damage by ischemia, toxic effect of alcohol, and malnutrition [3, 11, 27].

Rhabdomyolysis was demonstrated indirectly by increased serum levels of creatine phosphokinase and directly by standard light microscopy of skeletal muscle demonstrating necroses of muscle fibers without any inflammation. The renal failure was explained by light microscopic and immunohistological evidence of myoglobin casts in the tubules accompanied by degenerative changes of tubular epithelium [4].

In alcoholics there may appear also traumatic lesions of the muscles leading to "compartment syndrome" [24], but in our patient there were no obvious signs of any trauma, found neither by clinical examination, nor at autopsy.

The causes of above mentioned "compartment syndrome" are reduction of compartment volume (tight plaster or bandage, compression in accidents, elementary disasters etc), enlargement of compartment volume (haemorrhage in the muscles, venous stasis etc), high energy trauma (extensive contusions of muscles, lesions of major vessels etc). Microcirculation is disturbed in affected muscles with elevation of interstitial pressure exceeding normal level of 10 mm Hg . The difference between interstitial pressure and diastolic blood pressure becomes less than 30 mm Hg. Lowered arterio-venous gradient results in tissue hypoxia [24]. Muscles are namely very sensitive to pressure - stretch forces arising from external mechanical pressure or internally from muscle swelling within non-compliant fibrous sheaths.

Stretch activation of calcium channels and increased intracellular osmolality because of break-down of large molecules into smaller ones, favours the leak of interstitial fluid into muscle cells.

The end result is an increase in intramuscular interstitial pressure. The increase in cytosolic ionized calcium concentration and release of calcium from cellular organelle stores activate autolytic enzymes and interfere with mitochondrial function and energy production and the end result may be rhabdomyolysis [2].

We can briefly look at some other causes of rhabdomyolysis with possible subsequent renal failure. In many times there are combinations of various causes: exertional states, circulatory disturbances, infections, muscle injuries and toxic disorders as it has been also assummed to be in our case.

In the case of inferior vena cava ligation there is reduction of the venous return, cardiac filling and output with consecutive hypotension and renal hypoperfusion, but on the other hand, it also increases interstitial pressure because of elevated hydrostatic venous pressure. Therefore, arterial blood flow is compromised leading to ischemic rhabdomyolysis and myoglobinuria [21].

Rectus abdominis syndrome was described in athletes during banal infections, when sport exercise exertionally involved abdominal muscle and could lead to rhabdomyolysis [25].

Familial paroxysmal rhabdomyolysis is a rare disease of young children. Attacks not related to exercise are usually triggered by intercurrent infections. Fasting is also precipitating factor [26].

Rhabdomyolysis appears also in some other inherited diseases such as phosphorylase deficiency (type V glycogenosis) and phosphofructokinase deficiency (type VII glycogenosis) [29].

Elevation of serum creatine phosphokinase after cardiopulmonary resuscitation is related to rhabdomyolysis caused by traumatic physical as well as exertional electrical injury during reanimation [16].

Hypothyroidism as a cause of rhabdomyolysis should be eliminated in all patients with increased serum muscle enzymes [15].

Biochemical evidence of rhabdomyolysis was also found in 36% of 129 patients with hypophosphatemia [33]. Chronic alcoholics become acutely hypophosphatemic during the course of alcohol withdrawal. Severe hypophosphatemia triggers acute rhabdomyolysis.

Since the occurence of rhabdomyolysis may elevate the serum concentration of potassium, hypokaliemia is unrecognized in many cases of rhabdomyolysis. In hypokalemic patients, subclinical rhabdomyolysis commonly occurs and its severity is not connected with serum concentration of potassium but with higher serum osmolality [34].

Carbon monoxide poisoning was also described as the cause of rhabdomyolysis complicated by acute renal failure. A direct toxic effect of carbon monoxide is one of mechanisms contributing to the muscle necrosis besides local ischemia leading to the development of "compartment syndrome" [8, 39].

Besides amphetamine intoxication [9], acute renal failure secondary to ingestion of methylenedioxymethamphetamine (MDMA, "ecstasy ") is also attributed to multifactorial pathogenesis: induced disseminated intravascular coagulation, rhabdomyolysis and possibly a direct effect of the drug itself. There may be additional factors such as are alcohol abuse, vigorous dancing in hot environment of night clubs leading together with MDMA to hyperpyrexia and finally to rhabdomyolysis. This syndrome may resemble heat stroke [7, 30].

Among other drugs, leading to rhabdomyolysis, there are reports about spasmolitic drug fenoverine [10], antilipemic drugs such as lovastatine [6, 36], simvastatine, fibrates etc [11], caffeine after suicidal ingestion [17], strychnine [40] and theophylline poisoning.[14] etc.

The disease occurs even after long-lasting therapy with corticosteroids in status asthmaticus [38] and chemotherapy using doxorubicin, cytarabine, thioguanine and vincristine [23].

We should be acquainted with the documented data that after hard exercise with consequent rhabdomyolysis, the muscle proteins do not increase in the serum significantly until 48 hours, and reach peak values the third or fifth day. There is either delay in muscle protein release from the damaged muscle fibers, or the proteins are unable to leave interstitial area for the 24 to 48 hour period after exercise [20]. Based on these data, the early appearance of anuria in our patient suggest the muscular injury already before hospitalization because of presumed alcoholic delirium and epileptic seizures already at home.

The data about muscle protein release could be also important in determination of the appropriate time for the therapy of the disease in populations with high risk for rhabdomyolysis.

Namely, also recent experimental work in rats proved successful therapeutic measures : it was ascertained that the induction of the heme-degradating enzyme, heme oxygenase, and the increased synthesis of ferritin drastically reduce mortality [18]. It was also proved in rats that mannitol and deferoxamine can each protect against myohemoglobinuric acute renal failure [41]. In connection with above mentioned data, taking in consideration very probable muscular damage already at home and thinking over the unsuccessful treatment of our patient, the question arises, if the adequate therapy against anuria should be introduced earlier.

Acknowledgments

The author is obliged to the staff of the Centre for intensive care in the Clinical Centre Ljubljana, for providing him with necessary clinical data about the patient, illustrating this report.

Address correspondence to:

Assist. prof. Tomaz Rott, MD, PhD, Institute of Pathology, Medical Faculty, University of Ljubljana, Korytkova 2, 61105 Ljubljana, Slovenia.

References

[1] AzevedoMarques MM, Ferreira DB, Costa RS: Rhabdomyonecrosis experimentally induced in Wistar rats by Africanized bee venom. *Toxicon* 1992; 3: 344-348.

[2] Better OS: Post-traumatic acute renal failure: pathogenesis and prophylaxis (Clinical presentation from the Mario Negri Institute, Bergamo. *Nephrol Dial Transplant* 1992; 7: 260-264.

[3] Bleich HL, Moore MJ: Alcoholic myopathy in heart and skeletal muscle. *N Engl J Med* 1979; 301: 28-33.

[4] Cooper PN, Tapson J, Morley AR: Immunoperoxidase techniques and histology in the diagnosis of rhabdomyolysis related acute renal failure. *J Clin Pathol* 1992; 45: 825-827.

[5] Chrysanthopoulos C, Kounis N: Rhabdomyolysis due to combined treatment with lovastatin and cholestyramine. *B M J* 1992; 304: 1225.

[6] East C, Alivizatos PA, Grundy SM, Jones PH, Farmer JA: Rhabdomyolysis in patients receiving lovastatin after cardiac transplantation. *N Engl J Med* 1988; 318: 47-48.

[7] Fahal IH, Sallomi DF, Yaqoob M, Bell GM: Acute renal failure after ecstasy. *B M J* 1992; 305: 29.

[8] Florkowski CM, Rossi ML, Carey MP, Poulton K, Dickson GR, Ferner RRE: Rhabdomyolysis and acute renal failure following carbon monoxide poisoning - two case reports with muscle histopathology and enzyme activities. *J Toxicol Clin Toxicol* 1992; 30: 443-454.

[9] Ginsberg MD, Hertzman M, Schmidt-Nwara WW: Amphetamine intoxication with coagulopathy, hyperthermia and reversible renal failure. *Ann Intern Med* 1970; 73: 81-85.

[10] Hébuterne X, Chichmanian RM, Cohen HL, Rampal P: Rhabdomyolyse aiguë medicamenteuse imputable à la fénovérine. *Gastroenterol Clin Biol* 1991; 15: 861-862.

[11] Kahn LB, Meyer JS: Acute myopathy in chronic alcoholism. *Am J Clin Pathol*; 1970; 53: 516-530.

[12] Kanterewicz E, Sanmarti R, Riba J, Trias I, Autonell J, Brugues J: Bezafibrate induced rhabdomyolysis. *Ann Rheum Dis* 1992; 51: 536-538.

[13] Knochel JP: Rhabdomyolysis and myoglobinuria. *Semin Nephrol* 1981; 1: 75-86.

[14] Laurence AS, Wight J, Forrest ARW: Fatal theophylline poisoning with rhabdomyolysis. *Anaesthesia* 1992; 47: 82.

[15] Leonetti F, Dussol B, Berland Y: Rhabdomyolyse et insuffisance rénale au cours d'une hypothyroïdie. *Presse Méd* 1992; 21: 31-32.

[16] Mattana J, Singhal PC: Determinants of elevated creatine kinase activity and creatine kinase MB-fraction following cardiopulmonary resuscitation. *Chest* 1992; 101: 1386-1392.

[17] Michaelis HC, Sharii S, Schol G: Rhabdomyolysis after suicidal ingestion of an overdose of caffeine, acetaminophen and phenazone as a fixed-dose combination (Spalt-N). *J Toxicol Clin* Toxicol 1991; 29: 521-526.

[18] Nath KA, Balla G, Vercellotti GM, Balla J, Jacob HS, Levitt MD, Rosenberg ME: Induction of heme oxygenase is a rapid, protective response in rhabdomyolysis in the rat. *J Clin Invest* 1992; 90: 267-270.

[19] Nolte KB: Rhabdomyolysis associated with cocaine abuse. *Hum Pathol* 1991; 22: 1141- 1145.

[20] Nosaka K, Clarkson PM, Apple FS: Time course of serum protein changes after strenuous exercise of the forearm flexors. *J Lab Clin Med* 1992; 119: 183-188.

[21] Olivero J, Ayus JC: Rhabdomyolysis and acute myoglobinuric renal failure. Complications of inferior vena cava ligation. *Arch Intern Med* 1978; 138: 1548-1549.

[22] Otero A, Esteban J, Martinez J, Cejudo C: Rhabdomyolysis and acute renal failure as a consequence of heroin inhalation. *Nephron* 1992; 62: 245.

[23] Papakonstantinou C, Papanastasiou K, Kotsopoulou M, Mouratidou M, Sotiropoulos D, Kyrtsoni MC, Pouli A, Stamatelou M, Maniatis A: Chemotherapy - related acute rhabdomyolysis. *J Natl Cancer Inst* 1992; 84: 536-537.

[24] Princic J: Compartment syndrome. *Med Razgl* 1992; 31: 85-93.

[25] Reimers CD, Haider M, Mehltretter G, Kaab S, Wunderer B, Pongratz: Rectus - Abdominis Syndrome. *Dtsch Med Wochenschr* 1992;117: 1474-1478.

[26] Ramesh V, Gardner-Medwin D: Familial paroxysmal rhabdomyolysis - management of two cases of the non-exertional type. *Dev Med Child Neurol* 1992; 34: 73-79.

[27] Rott T: Rhabdomyolysis with acute renal failure following alcoholic delirium (Abstract) *Zdrav Vestn* 1992; 61: 523-524.

[28] Rubin RB, Neugarten : Medical complications of cocaine - changes in pattern of use and spectrum of complications. *J Toxicol Clin Toxicol* 1992; 30: 1-12.

[29] Schiff HB, MacSearraigh ETM, Kallmeyer JC: Myoglobinuria, rhabdomyolysis and marathon running. *Q J Med* 1978; 188: 463-472.

[30] Screaton GR, Cairns HS, Sarner M, Singer M, Thrasher A, Cohen SL: Hyperpyrexia and rhabdomyolysis after MDMA (ecstasy) abuse. *Lancet* 1992; 339: 677-678.

[31] Shah A, Check F, Baskin S, Reyman T, Menard R: Legionnaires· disease and acute renal failure - case report and review. *Clin Infect Dis* 1992; 14: 204-207.

[32] Siddiqui MN, Ahmed I, Farooqui BJ, Ahmed M: Myonecrosis due to Aeromonas - Hydrophila following insertion of an intravenous cannula - case report and review. *Clin Infect Dis* 1992; 14: 619-620.

[33] Singhal PC, Kumar A, Desroches L, Gibbons N, Mattana J: Prevalence and predictors of rhabdomyolysis in patients with hypophosphatemia. *Am J Med* 1992; 92: 458-464.

[34] Singhal PC, Abramovici M, Venkatesan J, Mattana J: Hypokalemia and rhabdomyolysis. *Miner Electrolyte Metab* 1991; 17: 335-339.

[35] Taylor WRJ, Prosser DI: Acute renal failure, acute rhabdomyolysis and Falciparum malaria. *Trans R Soc Trop Med Hyg* 1992; 86: 361.

[36] Thompson PD, Gadaleta PA, Yurgalevitch S, Cullinane E, Herbert PN: Effects of exercise and lovastatin on serum creatine kinase activity. *Metabolism* 1991; 40: 1333-1336.

[37] Urbano - Marquez A, Estruch R, Navarro - Lopez F, Grau JM, Mont L, Rubin E: The effects of alcoholism on skeletal and cardiac muscle. *N Engl J Med* 1989; 320: 409-15.

[38] Vasquez JL, Roux L, Salame M, Maindivide J: Myopathie aiguë compliquant une curarisation et une corticothérapie prolongées pour état de mal asthmatique. *Presse Méd* 1992; 21: 1433.

[39] Voncina D, Dekleva A, Rode P, Varl J: Mišicna nekroza pri akutni zastrupitvi z ogljikovim monoksidom. *Zdrav Vestn* 1979; 48: Suppl II: II 43-II 46.

[40] Yamarick W, Walson P, Ditraglia J: Strychnine poisoning in an adolescent. *J Toxicol Clin Toxicol* 1992; 30: 141 -148.

[41] Zager RA: Combined mannitol and deferoxamine therapy for myohemoglobinuric renal injury and oxidant tubular stress - mechanistic and therapeutic implications. *J Clin Invest* 1992; 90: 711-719.