UDK :61 ISSN 1857-5587

PHYSIOACTA

Journal of Macedonian Association of Physiologists and Anthropologists

Vol 14 No 1
2020

CONTENTS

UDK: 616.74-002.2:615.9

RHABDOMYOLYSIS AND COMPLICATIONS IN ACUTE DRUG POISONING – CASE REPORT AND LITERATURE REVIEW

Babulovska A. Caparoska D. Simonovska N, Pereska Z, Kostadinoski K, Naumoski K.

University Clinic of Toxicology, Medical Faculty, University "St. Cyril and Methodius", Republic of North Macedonia

Abstract

Introduction: Rhabdomyolysis is a syndrome of skeletal muscle cell damage, which results in releasing a large amount of toxic components from the muscle cells into the plasma. The aimof this study wasto present a case ofa massive rhabdomyolysis and complications in acute drug poisoning.Case report: A 38-year-old male patient was admitted in a somnolent condition with skin changes on both knees and erythematosus changes on the right foot and left tight.Upon admission with elevated CPK, myoglobin, AST, ALT, LDH, degradation products and electrolyte imbalances. Due to acute rhabdomyolysis, elevated levels of degradation products and electrolyte imbalance, the appropriate treatment has started immediately. The patient was with preserved diuresis and progressive growth of degradation products for which hemodialysis was indicated and performed. As a result of a verification of a deep vein thrombosis during the hospitalization, he was put on anticoagulant therapy protocol.Conclusion: Acutekidney injury as the most common complication of rhabdomyolysis in acutely intoxicated patients is a life-threatening condition. In patients with rhabdomyolysis, as a result of the ischemic tissue injury, changes in the skin color and bullae can appear, and as a result of immobilization deep vein thrombosis can develop. Timely diagnosis and adequate treatment of rhabdomyolysis and its complications in acutely intoxicated patients play a key role in the outcome of this condition.

РАБДОМИОЛИЗА И КОМПЛИКАЦИИ КАЈ АКУТНО МЕДИКАМЕНТОЗНО ТРУЕЊЕ-ПРИКАЗ НА СЛУЧАЈ И ПРЕГЛЕД ВО ЛИТЕРАТУРА

Апстракт

Вовед: Рабдомиолиза е синдром на дезинтеграција во скелетните мускули, што резултира со ослободување на големи количини на токсични компоненти од мускулната клетка во плазмата. Цел на овој труд беше анализа на случај на масивна рабдомиолиза и компликации кај акутно медикаментозно труење.

Приказ на случај: Пациент од машки пол на возраст од 38 години беше донесен во сомнолентна состојба со промени на кожата -були на двете колена и еритематозни промени на десно стапало и лева натколеница. При прием со покачени вредности на CPK, миоглобин, AST, ALT, LDH, деградациони продукти и електролитен дисбаланс. Поради акутната рабдомиолиза, покачените вредности на деградациони продукти и електролитниот дисбаланс веднаш е започнат соодветен третман. Пациентот со сочувана диуреза и прогресивен пораст на деградациони продукти за што беше индицирана и изведена хемодијализа. Во тек на хоспитализацијата беше верифицирана длабока венска тромбоза, за што беше поставен на антикоагулантна терапија.

Заклучок: Акутно бубрежно оштетување како најчеста компликација на рабдомиолиза кај акутно интоксицирани пациенти преставува животно загрозувачка состојба. Кај пациентите со рабдомиолиза, како резултат на повреда на исхемичко ткиво, може да се настанат промени на бојата на кожата и були, а како резултат на имобилизација се јавува длабока венска тромбоза. Навремената дијагноза и соодветниот третман на рабдомиолизата и на нејзините компликации кај акутно интоксицирани пациенти се клучни за исходот на оваа состојба.
Клучни зборови: Рабдомиолиза, Акутно Бубрежно Оштетување, Медикаментозна Интоксикација, Длабока Венска Тромбоза

Introduction

Rhabdomyolysis is a syndrome of skeletal muscle cell damage, which results in releasing a large amount of toxic components from the muscle cells into the plasma. The etiology of the skeletal muscle injuries is very diverse: enormous stress and ischemia, genetic defects, as well as toxic and physical injury [1]. Muscle cells are directly affected by rupture of the cell membrane or by energy reduction [2]. Free ionized calcium enters the intracellular space and activates proteases and apoptosis pathways [3]. Production of reactive oxygen species leads to mitochondrial dysfunction and muscle cell death [4].

Clinical signs of rhabdomyolysis are muscle weakness and fulminant acute kidney injury. Classical triad of symptoms includes skeletal muscle injury, pigmented urine and some aspects of renal failure [5].

The aim of this study was to present a case of massive rhabdomyolysis and complications in acute drug poisoning.

Case report

A 38-year-old male patient was admitted to our Clinic from GH Ohrid with an ambulance car. He was somnolent, having pains in the legs, inability to walk, redness and bullae on both knees, both groins, left thigh and under left rib. He was found unconscious by his family, lying in an unnatural/constrained position. Heteroanamnestic data revealed intended use of a larger number of tablets of risperidone, biperiden and diazepam, which were in fact his regular therapy. The family transferred him to the GH Ohrid in unconscious, tachycardiac condition. There he was treated with supportive therapy (infusion solutions, amp. Amiodarone NII, tbl. Atenolol of 50 mg, amp.

Methylprednisolone of 40 mg), and was monitored by a surgeon for several hours. Over the last two years, his change in the mood and behavior was noticed, and he was observed by a psychiatrist; he was also hospitalized in the Psychiatric Hospital Demir Hisar and discharged with the diagnosis F22 (delusional disorders).

On admission Glasgow Coma Scale Score 14, SaO2 95%, body temperature 36.2C, blood pressure 95/60 mmHg, heart frequency 140/min, respirations 18/min. ECG finding on admission in sinus rhythm 140/min with normal morphology and conduction of S-T segment and T wave. All other clinical examination was normal.

Table 1 Biochemical findings during hospitalization

	On admission	2 day	3 day	4 day	5 day	6day	7 day	8 day	9day	10day
CPK U/L	>42670	>42670	/	/	/	/	/	7582	3500	/
CK-MB U/L	2401/2663	2520	1217	358	380	219	/	216	117	
LDH U/L	3375	3520	2963	1542	1807	1138	/	/	/	/
AST U/L	756	/	524	/	187	/	/	/	/	/
ALT U/L	376	/	283	/	134	/	/	/	/	/
AP U/l	81	/	/	/	/	/	/	/	/	/
GGTU/l	26	/	/	/	/	/	/	/	/	/
Urea mmo/L	12,6/15,8	26,4/29,6	32,4/32,3	33,8	36,7	23,2	14,3	13,5	12,5	10,9
Kreatinin mmol/L	248/290	398/453	633/595	759	772	524	291	260	241	218
Myoglobin ng/ml	>500	>5000	/	1000	/	/	/	135,5	/	/
Nammol/L	131/132	129/127	127/125	126	132	135	136	138	139	141
Ca mmol/L	2,2/2,1	2,0/1,9	2,0	1,9	2,0	2,0		2,1	2,1	2,3
Kmmol/L	5,9/6,6	6,9/5,6	5,4/5,4	5,1	5,2	4,8	4,4	4,0	4,5	5,1
Jon Ca mmol/L	/	1,02	/	/	/	/	/	/	/	/
Glikemijammo/l	10,1	5,3	5,0	/	/	/	/	/	/	/
Troponin ng/L	19,9/4,6	5,5	/	/	/	/	/	/	/	/
Le 10na9/uL	24,4/26,6	26,4	14,2	11,7	12,3	/	13,2	11,0	11,7	11,9/13,3
Er 10na 12/uL	6,9/6,1	5,3	4,0	3,7	3,3	/	3,2	3,0	3,3	3,0/3,4
Hb gr/L	191/166	149	122	113	103	/	90	87	95/94	/
Hct r/v	0,57/0,51	0,43	0,34	0,31	0,27	/	0,27	0,26	0,51	0,43
Tr 10na 3/uL	316/313	267	184	190	249			331		308/378
CRP	88,7	/	/	/	/	/	/	/	/	/
Vk prot/alb/glob g/L	66/40/26	/	/	/	/	/	/	/	/	/
Urina naod so sediment	PH 5,0 Le 8-10 . Prot-, Er-, aceton -	/	PH5,0 Prot trag Er 3-5 Bakterii++ Amorfni soli I Kristali 1	/	/	/	/	/	/	/
diureza	400ml	300ml	2400ml	6200ml	6100	6800	7400	6200	5200	5800

Skin changes (bullae) on both knees and erythematous changes of the right foot and left thigh were accompanied by:

1. X-ray of both hips: pelvic skeleton was without x-ray signs of acute trauma. Skeletal structure and morphology were normal.
2. X-ray of the left knee: no signs of acute traumatic injury were seen. Normal bony structure as well as preserved articular space.
3. X-ray of the spine: reduced discus space at level L4/L5 with subchondral sclerosis of the cartilage surface of vertebral bodies, speaking in favor of

discopathy with degeneration of the IV disc. The vertebrae along the lumbar spinal segment were with preserved morphology.

4. Dermatological examination: Dg. Erythema et haemoraghia reg. inguinalis. Bulla reg. inguinalis. Erythema and bullae on the site of pressure, for which therapy was recommended.

Table 2 Gas analyses with ABS during the hospitalization

Gas analyses with ABS	1 day of hospitalization	3 day of hospitalization
pH	7,275	7,357
pCO_2 (kPa)	4,24	3,80
pO_2 (kPa)	7,56	12,73
sO_2	86,7%	98,6%
HCO_3 mmol/L	14,9	17,7
BE	-12,1	-7,3

On admission, gas analyses went in favor of decompensated metabolic acidosis, and on the third day after hospitalization it changed to compensated metabolic acidosis. The patient was with preserved diuresis, but due to increased degradation products, electrolyte imbalance and rhabdomyolysis a specialist in nephrology was consulted and hemodialysis was realized on two occasions.

Echo of abdomen and UGT: the liver was slightly enlarged, edematous with 16 cm under right rib; parenchyma was with normal echogenicity, without focal changes. The bile was with thickened wall of 5 mm, with signs of multiple lithiasis, predominantly organic. The spleen was with normal form and borderline size without defects. Kidneys enlarged with dimensions 14.60 x 6.38 and parenchyma 3.18. The left kidney with dimensions 12.27 x 7.10 and parenchyma 3 cm, without signs of stasis and macrocalculi. Paraaortic region - unremarkable. Urovesica with normal wall and placed urinary catheter. No liquid in the abdominal cavity.

Pain present in the left low extremity that was enlarged. Echo of the lower extremities was made and showed non-compressive vena femoralis to the left in absence of murmur. Occlusal thrombosis in VFC. Considering femoral phlebothrombosis, control hemostasis was made and anemia with markedly activated fibrinolysis was registered.

D-dimmers (6745 ng/ml) and the patient was given anticoagulant therapy.

Psychiatrist was consulted by protocol for attempted suicide.

After all examinations and treatment were completed at the Clinic, the patient was discharged on the thirteenth day in improved general condition for further treatment of femoral phlebothrombosis and was referred to the GH Ohrid.

Discussion

In the past, the most common causes of acute rhabdomyolysis were crush injuries during war and crush injuries during natural catastrophes [6]. Nowadays, common agents that cause up to 81% of cases with rhabdomyolysis are due to abuse of drugs

and alcohol [7]. Rhabdomyolysis caused by drugs can be divided primary and secondary myotoxic effects. Primary toxically-induced rhabdomyolysis is caused by direct damage of myocytic function and integrity. Secondary effects of the toxins are due to predisposing risk factors such as local compression of the muscles during coma, prolonged attacks, trauma and metabolic abnormalities [7].

Table 3 The most common causes that lead to rhabdomyolysis (8)

Muscle injury	**Medications/illicit drugs**	**Increased muscular activity**
Trauma	Alcohol	Sports
Burns	Cocain	Seizures/status epilepticus
Electrocution	Amphetamines and its derivatives	Status asthmaticus
Prolonged immobilization	PCP	
	Stains	Infections
Metabolic disorders	Nevroleptics	
DKA	Amfotericin B	Inflammatory myopathies
Hyponatraemia		
Hypokalemia	Toxins	Hereditary metabolic myopathies
Hypophosphataemia	Isopropyl alcohol	
	Ethlyene glycol	Others
Ischaemia	Tetanus toxins	Hypo-/hyperthermia
Compression	Venom (Various)	Idiopathic
Vascular injury	Quail	
Sickle cell disease		

Acute kidney injury/failure associated with rhabdomyolysis can be caused by several mechanisms, including hypovolemia, myoglobinuria and metabolic acidosis [9]. During muscle destruction, intracellular components are released into the extracellular fluid. The reduced intravascular volume activates the renin-angiotensin system, vasopressin and sympathetic innervation and leads to renal vasoconstriction. Other inflammatory factors such as endothelin-1, tromboxan A2 and TNF-α, as well as decrease of nitric oxide also contribute to renal vasoconstriction [10]. The released myoglobin in the systemic circulation has cytotoxic effects on the nephron directly and by its compounds. The free Fe in the kidney released from the degraded myoglobin reacts with hydrogen peroxide compounds (Fenton reaction), thus reactive oxygen species (ROS) are created that damage renal tubular integrity [11]. The second mechanism of kidney injury is lipid peroxidation: components of lipid membrane in the kidney react with ferryl myoglobin (process called redox cycling) [11].

It is estimated that 10-40% of patients with rhabdomyolysis develop acute kidney injury (AKI), and up to 15% of all patients with AKI are due to rhabdomyolysis [12,13].

Diagnosis of rhabdomyolysis is based on clinical characteristics and laboratory findings, such as myoglobinuria and the level of serum creatinine kinase increased by five times more than normal level; high levels of lactate dehydrogenase, aspartate and alanine aminotransferase, phosphates and potassium; initial low concentration of calcium in the serum [14].

Our presented patient had increased levels of myoglobin, CPK, AST, ALT, LDH, degradation products and electrolyte imbalance. The cause of rhabdomyolysis in our patient was mixed drug poisoning with neuroleptic drug, anticholinergic drug and benzodiazepine, after which the patient lost his conscience and was found by his family in a unnatural position. A diagnosis of acute rhabdomyolysis was established as a result of mixed poisoning and acute kidney injury.

The patient underwent hemodialysis on two occasions due to increased levels of degradation products and electrolyte imbalance in spite of the preserved diuresis.

Risperidone is an atypical antipsychotic drug with a strong anti-serotonin (5-HT2) en-antidopamine (D2) activity. It is also an agonist for alpha 1, alpha 2 and histamine receptors. In more than 10% of patients who are treated with risperidone adverse effects appear including parkinsonism, sleep disorders, headache or altered mental status. The mechanism by which risperidone causes rhabdomyolysis has still not been completely elucidated. Necrosis and enormously increased serum CPK can appear by a blockage of 5-HT2A increasing the permeability of sarcolemma into skeletal muscles. It is believed that Ca influx occurs because of the reduced function of Na-K-ATPase pump in the muscle cell membrane. This activates intracellular proteases, which on the other hand, degrades myofibrils and as a result the muscle enzymes and other proteins such as creatine kinase and myoglobin enter the circulation. This hypothesis emphasizes the role of risperidone in the rhabdomyolysis process [15].

The use of quetiapine, risperidone or olanzapine can help in developing acute kidney failure that appears as a result of neuroleptic malignant syndrome and/or rhabdomyolysis [16,17,18,19]. The anamnesis revealed information that our patient had taken unknown dose of the anticholinergic drug biperiden. Biperiden is used in the clinical practice for prophylaxis and treatment of extrapyramidal adverse effects caused by neuroleptic drugs as well as for tremor in Parkinson disease [20]. It acts as a muscarinic receptor antagonist with high affinity for muscarinic (M1) receptor [21]. M1 receptors are primarily located in the central nervous system and are included in perception, attention and cognitive function. Delirium is associated only with the antagonism of post-synaptic M1 receptors and until today other subtypes of receptors are not included [22]. Peripheral muscarinic receptors are part of the autonomous nervous system innervated by postganglionic cholinergic nerves. M2 receptors are found in the brain and heart; M3 receptors are found in salivary glands and M4 receptors in the brain and lungs [23]. Acute overdose with antimuscarinic compounds cause anticholinergic syndrome that is manifested with peripheral and central nervous symptoms [24,25].

As a result of overdose with tbl. biperiden the initial symptoms that appear are: dry mouth, lethargy, agitation and pupillary dilatation. Consequently, red dry skin, tachycardia, hypertension, hyperthermia, urinary retention, ileus, disorientation, confusion, dysarthria, delirium, convulsions and coma can appear. Many

complications can develop, mainly associated with prolonged coma, excessive muscle activity and hyperthermia. The complications might lead to metabolic acidosis, rhabdomyolysis and acute kidney injury [26,27,28,29,30]. Benzodiazepines cause rhabdomyolysis by the secondary mechanism, mainly due to local compression of muscles and ischemia during prolonged immobilization in the state of prolonged conscience disorder.

In less than 10% of patients with rhabdomyolysis as a result of the ischemic tissue injury changes in the skin color and bullae can be noticed. These changes were registered in our patient, too [31,32].

Due to persistent pain and enlarged left lower extremity in our patient, Doppler of the lower extremities was made, as well as control hemostasis and D-dimers for deep vein thrombosis (DVT). The cause of DVT is patient immobilization. Risk factors that can cause DVT by the three mechanisms described as Virchow triad are: slowing of blood flow, damage of the blood vessel wall and hypercoagulation [33].

CONCLUSION

Acute kidney injury as the most common complication of rhabdomyolysis in acutely intoxicated patients is a life-threatening condition. In patients with rhabdomyolysis, as a result of the ischemic tissue injury, changes in the skin color and bullae can appear, and as a result of immobilization deep vein thrombosis can develop. Timely diagnosis and adequate treatment of rhabdomyolysis and its complications in acutely intoxicated patients play a key role in the outcome of this condition.

References

1. Ellenhorn MJ: Ellenhorn's Medical Toxicology, Diagnosis and Treatment of Human Poisoning. 2nd ed. Baltimore: Williams & Wilkins; 1997.
2. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. N Engl J Med. 2009;361(1):62–72.
3. Giannoglou GD, Chatzizisis YS, Misirli G. The syndrome of rhabdomyolysis: nathophysiology and diagnosis. Eur J Intern Med.2007;19(2):90–100.
4. Torres PA, Helmestetter JA, Kaye AM, Kaye AD. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J. 2014;15(1):58–69.
5. Emadian SM, Caravati EM, Herr RD: Rhabdomyolysis: A rare adverse effect of diphenhydramine overdose. Am J Emerg Med 1996, 14:574–576.
6. Vanderholder R, Sever MS, Erek E, et al.: Disease of the month: Rhabdomyolysis.J Am Soc Nephrol 2000, 11:1553–1561.
7. Prendergast BD, George CF: Drug- induced rhabdomyolysis: Mechanisms and management. Postgrad Med J 1993, 69:333–336.
8. Bagley WH, et al. Rhabdomyolysis. Intern Emer Med. 2007;2:210-218.
9. Petejova N, Martinek A. Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review. Crit Care. 2014;18(3):224. doi: 10.1186/cc13897.
10. Plotnikov EY, Chupyrkina AA, Pevzner IB, Isaev NK, Zorov DB. Myoglobin causes oxidative stress, increase of NO production and dysfunction of kidney's mitochondria. Biochim Biophys Acta. 2009;1792(8):796–803

11. Boutaud O, Roberts LJ., 2nd Mechanism-based therapeutic approaches to rhabdomyolysis-induced renal failure. Free Radic Biol Med.2011;51(5):1062–1067. doi: 10.1016/j.freeradbiomed.2010.10.704.
12. Efstratiadis G, et al. Rhabdomyolysis updated. Hippokratia. 2007;11:129-137.
13. Malinoski DJ, et al. Crush injury and rhabdomyolysis. Crit Care Clin. 2004;20:171–192.
14. Mallinson RH, Goldsmith DJ, Higgins RM, Venning MC, Ackrill P. Acute swollen legs due to rhabdomyolysis: initial management as deep vein thrombosis may lead to acute renal failure. BMJ. 1994;309(6965):1361-2.
15. Jullian-Desayes I, Roselli A, Lamy C, Alberto-Gondouin M, Janvier N, et al. Rhabdomyolysis with Acute Renal Failure and Deep Vein Thrombosis Induced by Antipsychotic Drugs: A Case Report. Pharmacopsychiatry 2015;48: 265-267.
16. Raitasuo V, Vataja R, Elomaa E. Risperidone-induced neuroleptic malignant syndrome in young patient. *Lancet.* 1994;344(8938):1705.
17. Ahuja N, Palanichamy N, Mackin P, Lloyd A. Olanzapine-induced hyperglycaemic coma and neuroleptic malignant syndrome: case report and review of literature. *J Psychopharmacol.* 2010;24(1):125–130.
18. Duggal HS, Singh I. Neuroleptic malignant syndrome presenting with acute renal failure. *Prog Neuropsychopharmacol Biol Psychiatry.* 2008;32(4):1074–1075.
19. Khan I, Vasudevan V, Arjomand F, Ali R, Shahzad S. Quetiapine induced fatal neuroleptic malignant syndrome (NMS) and hyperosmolar hyperglycemic nonketotic coma (HHNC). *Chest.* 2011;140(4_MeetingAbstracts):113A–113A.
20. M. Dose and H. D. Tempel, "Abuse potential of anticholinergics,"*Pharmacopsychiatry*, vol. 33, no. 1, pp. 43–46, 2000.
21. E. Wezenberg, R. J. Verkes, B. G. C. Sabbe, G. S. F. Ruigt, and W.Hulstijn, "Modulation ofmemory and visuospatial processesby biperiden and rivastigmine in elderly healthy subjects,"*Psychopharmacology*, vol. 181, no. 3, pp. 582–594, 2005.
22. Pratico C, Quattrone D, Lucanto T, Amato A, Penna O,Roscitano C, Fodale V. Drugs of anesthesia acting on central cholinergic system may cause post-operative cognitive dysfunction and delirium. Med Hypotheses 2005; 65: 972–82.
23. Brann MR, Jørgensen HB, Burstein ES, Spalding TA, Ellis J, JonsS SVP, Hill-Eubanks D. Studies of the pharmacology, localization, and structure of muscarinic acetylcholine receptorsa. Ann N Y Acad Sci 1993; 707: 225–36.
24. Danze LK, Langdorf MI. Reversal of orphenadrine-induced ventricular tachycardia with physostigmine. J Emerg Med 1991 Nov-Dec; 9 (6): 453-7.
25. Coremans P, Lambrecht G, Schepens P, Vanwelden J, Verhaegen H. Anticholinergic intoxication with commercially available thorn apple tea. J Toxicol Clin Toxicol 1994; 32 (5): 589-92.
26. Caksen H, Odabas D, Akbayram S, Cesur Y, Arslan S, Uner A, Oner AF. Deadly nightshade (Atropa belladonna) intoxication: an analysis of 49 children. Hum Exp Toxicol 2003 Dec; 22 (12): 665-8.
Stella L, Vitelli MR, Palazzo E, Oliva P, De Novellis V, Capuano A, Scafuro MA, Berrino L, Rossi F, Maione S. Datura stramonium intake: a report on three cases. J Psychoactive Drugs 2010 Dec; 42 (4): 507-12.

28. Hsu CK, Leo P, Shastry D, Meggs W, Weisman R, Hoffman RS. Anticholinergic poisoning associated with herbal tea. Arch Intern Med 1995 Nov 13; 155 (20): 2245-8.
29. Ertekin V, Selimoglu MA, Altinkaynak S. A combination of unusual presentations of Datura stramonium intoxication in a child: rhabdomyolysis and fulminant hepatitius. [Letter] J Emerg Med 2005 Feb; 28 (2): 227-8.
30. Jeong TO, Lee JB, Jin YH, Yoon JC. Anticholinergic syndrome following ingestion of Lamprocapnos spectabilis (Bleeding Heart). [Letter] Clin Toxicol (Phila) 2015; 53 (8): 842-3.
31. Huerta-Alardín AL, Varon J, Marik PE. Bench-to-bedside review: Rhabdomyolysis -- an overview for clinicians. Crit Care 2005; 9:158.
32. Khan FY. Rhabdomyolysis: a review of the literature. Neth J Med 2009; 67:272.
33. Lowe GD. Virchow's triad revisited: abnormal flow. Pathophysiol Haemost Thromb 2003; 33: 455-457.