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DIRECT AND INDIRECT MECHANISMS PRODUCING RHABDOMYOLYSIS IN ACUTE POISONINGS

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Abstract. Rhabdomyolysis is a clinical and biochemical syndrome with potentially fatal result of an aggression that destroys the integrity of the sarcolemma of skeletal muscle cells, leading to release of toxic cellular components in the extracellular space and movement. In acute poisoning several proposed direct and indirect mechanisms have been observed. . The study of these mechanisms leads to a correct diagnosis and rapid toxic rhabdomyolysis, preventing major complications. We present six clinical cases of acute poisoning with ethylene glycol, buformin, carbon monoxide, doxylamine, venlafaxine and of exotic fish sting. Due to the early identification and maintainance of a high index of suspicion, most patients with rhabdomyolysis in acute intoxication have an excellent prognosis if they are rapidly and correctly treated.
Key words: rhabdomyolysis toxic, myoglobin, treatment

General considerations

Rhabdomyolysis is a clinical and biochemical syndrome with potentially fatal result, of an aggression that destroys the integrity of the sarcolemma of skeletal muscle cells, leading to release of toxic cellular components in the extracellular space and in circulation [1, 2, 3]. The etiology of skeletal muscle injury is quite diverse and includes: excessive muscular effort, ischemia, genetic defects and physical aggression or direct toxicity [4].

In acute poisoning several mechanisms have been observed, related to direct producion: inhibition by sarcoplasmic reticulum calcium metabolism, impaired production of adenosine triphosphate resulting in disintegration of the cell membrane, alterations in carbohydrate metabolism. Indirect production mechanisms include prolonged immobilization or muscle compression in toxic induced coma, seizures, myoclonus, altered mental status due to trauma, agitation or delirium. Clinical manifestations range from asymptomatic disorder evidenced only by increased creatinine kinase, to potentially fatal forms associated with extreme elevations in creatinine kinase levels, electrolyte disturbances, renal failure and disseminated intravascular coagulation [5]. Between 10 - 50% of patients with rhabdomyolysis develop acute renal failure [6]; reported mortality in these patients is approximately 20% [7], being higher in the presence of multiple organ failure and systems. In general, in acute poisonings, toxicity affects various organs involving kidney, liver, gastrointestinal tract, central nervous system, while skeletal muscles are less affected. Although rhabdomyolysis acute poisoning was rarely described in the past, its incidence has increased mainly through the introduction of more potent substances in medical practice, but also by increasing information in the medical world about this syndrome. The exact incidence of rhabdomyolysis in acute poisonings in unknown because this syndrome is often unreported. Similarly, the mortality rate is not specified. Regardless of the mechanism of production, a favorable prognosis will be determined only by maintaining a high index of suspicion, early identification and appropriate therapy syndrome.

Studying the mechanismsthat cause acute poisoning syndrome will lead to a fast and accurate diagnosis of rhabdomyolysis and will prevent major complications by establishing the appropriate treatment.

Clinical cases

1. Rhabdomyolysis in a severe delayed ethylene glycol poisoning

Acute ethylene glycol intoxication is a life-

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threatening emergency which, if not diagnosed correctly and treated aggressively, has a high risk of persistent end-organ damage. The toxicity is due to a combination of severe metabolic acidosis caused by glycolic acid and precipitation of calcium oxalate crystals resulting in impaired organ function, especially in the kidneys. Rhabdomyolisis is characterized by the breakdown of skeletal muscle resulting in the subsequent release of intracellular contents into the circulatory system, resulting in myoglobinuria and acute renal failure.

Case report 1

A 24 years old male was admitted 24 hours after ingesting 200 mL ethylene glycol in a suicidal attempt. The patient was a former athlete, 110 kg body weight and 1.90 m tall, with a large muscular mass. On presentation: dizziness, restlessness, agitation, hyperventilation, tachycardia, emesis, present diuresis; soon after he became comatose and was intubated and put on ventilator support; he presented hemodynamic instability and was initiated with vasopressor support.

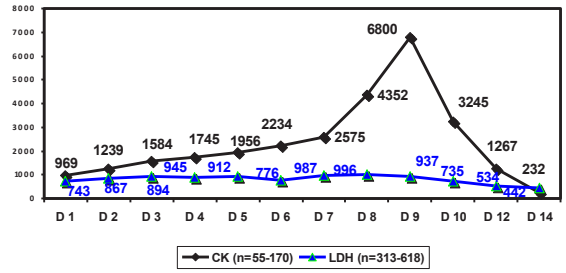

Fig. 1. Evolution of CK and LDH

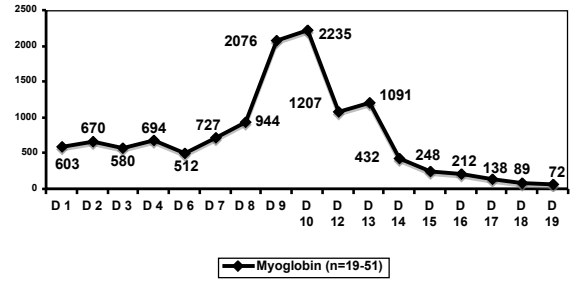

Fig. 2. Evolution of myoglobin

Laboratory tests revealed severe metabolic acidosis with increased anion and osmolarity gap. In addition, we found elevated CK 969 U/L and myoglobinemia of 603 µg/L; BUN 48.5 mg/dL, creatinine 2.75 mg/L. We rapidly started continuous-venovenous haemodiafiltration in an attempt to reverse the toxicity damage, along ethanol infusion, volemic repletion, alcalinization and supportive measures. We maintained the patient on ventilator and renal support. On day 2 the patient became oliguric, but hemodinamically stable; the acidosis corrected after 24 hours; CK, myoglobinemia, BUN and creatinine increased. The increase of CK peaked in day 9 (6800 U/L) (Fig.1.) myoglobinemia in day 10 (2235 micrograms/L) (Fig.2.), BUN (257 mg/dL) and creatinine (5.40 mg/dL) in day 14 - 15. The MRI highlighted diffuse edematous and haemoragic modifications at the level of the gluteal and adductor mus¬cles. The patient was extubated in day 11 and entered in polyuric state in day 12 with the constant regression of altered parameters; that was the moment we stopped renal support. In day 22 the renal function parameters returned to normal and diuresis was in normal range. The patient was discharged in day 24 with normal renal function, no other sequelae.

Conclusion. In this case, acute renal failure was due to direct ethylene glycol toxicity and concomitant myoglobinuric state. Rhabdomyolisis developed in an agitated and then comatose patient, with large muscular mass and prolonged immobilization, with acidosis and decreased blood flow; direct myotoxic effect of ethylene glycol may be involved.

2. Rhabdomyolysis in a Buformin Poisoning case

Buformin is an oral antihyperglycemic drug of the biguanide class, chemically related to metformin and phenformin. Biguanides decreases gluconeogenesis in alanine, pyruvate, and lactate, causing accumulation of lactic acid and development of lactic acidosis. It is a type of high anion gap metabolic acidosis and is associated with various pathological processes: disturbances of consciousness, Kussmaul's respiration, shock, hypothermia, hypoglycemia.

Case report 2

We present the case of a 19 year old previously healthy patient admitted in our department for suicidal ingestion of 30 tablets (1 tablet = 100 mg, total dose = 3 g) of Silubin retard (mother's medication) ten hours from hospital presentation. On admission: altered general status, conscious but confuse, spontaneous and normal breathing, BP=140/70 mmHg, 70 beats/min., diffuse abdominal pain, diarrhea. Arterial blood gas test: pH = 7.36, lactate = 5.5 mmol/L, HCO3 = 21 mmol/L, BE = 4.5 mmol/L. The patient started treatment with fluids, bicarbonate, analgesics. The patient status did not improved, he became more agitated, with severe abdominal pain, high breathing rate and increasing lactic acidosis; 12 hours after admission he became hemodynamically unstable and was initiated vasopressor support. The laboratory tests show increasing elevated values for CK, CK-Mb, LDH (Fig.3.), liver and pancreatic enzymes, with significant variations of glycemia (Fig.4.).

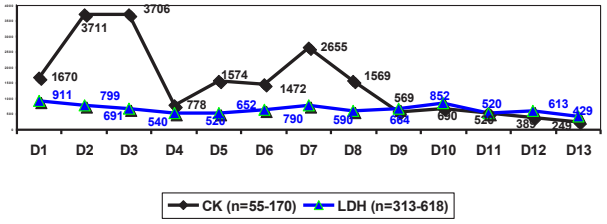

Fig. 3. Evolution of CK and LDH

Continuous venovenous haemodialysis (CVVHD) and ventilator support was initiated. The haemodialysis was performed over 4 days until complete correction of metabolic acidosis (Fig. 5.) and decrease of muscular enzymes. The patient was weaned from ventilator support after 6 days; the laboratory tests normalized. Psychiatric examination revealed only a reactive depression (an argument with the girlfriend). He was discharged after 14 days with normal mental status and no other sequelae

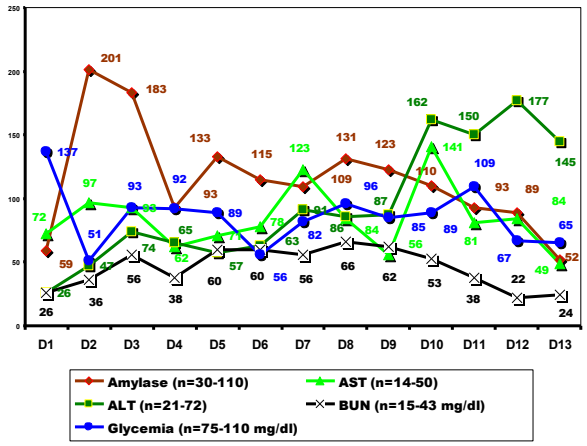

Fig. 4. Other laboratory tests evolution

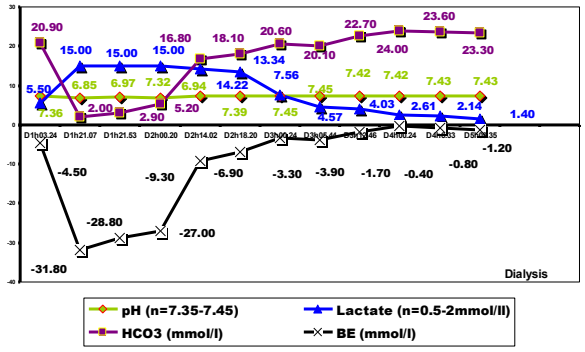

Fig. 5. ABG in dynamics

Conclusion. Buformin poisoning induced lactic acidosis is a life-threatening event and should be suspected in patients presenting with high-anion gap metabolic acidosis and high blood lactate concentration. Clinical presentations are non-specific, but it may show severe complications like severe hypotension, rhabdomyolysis and respiratory failure. Therapeutic approach for buformin-associated lactic acidosis includes adequate supportive care, correction of acidemia, acceleration of lactate metabolism and elimination of the offending drug by renal excretion or dialysis. Dialysis techniques are the recommended treatment of lactic acidosis since it rapidly corrects the acid-base disorders and assures myoglobin epuration.

3. Rhabdomyolysis and Acute Renal Failure in a Carbon Monoxide Poisoning

Carbon monoxide (CO) is the leading cause of accidental poisoning in our country and worldwide. CO causes tissue hypoxia and produces various systemic and neurological complications. Rhabdomyolysis is one of the major complications of acute carbon monoxide poisoning. Myoglobin has a constant CO affinity ,approximately eight times lower than that of hemoglobin. The combination of this affinity and the lower constant dissociation for CO favors retention of CO in muscular tissue, and thus a considerable amount of CO can be potentially stored in the skeletal muscle. Rhabdomyolysis can also occur due to prolonged coma status or seizures.

Case report 3

We present the case of a young patient transferred to our department 18 hours after accidental CO exposure. Initial treatment was carried out in another hospital where the medical record described a patient with GCS8, with dyspnoea, tachypnoea and oligoanuria. The status improved under oxygen administration, the patient became conscious, but amnesic.

	CK (U/l)	CKMB (U/l)	BUN (mg/dl)	Creatinine (mg/dl)	LDH (U/l)	AST (U/l)	ALT (U/l)
Day 1	> 16000	1669	86	3.07			
Day 2	> 16000	1382	85.1	3.68	7859	850	346
Day 3	9637	949	151	6.40	7285	1049	332
Day 4	> 16000	1035	176	7.30	1529	1013	322
Day 5	> 20000	396	216	8.20	1247	528	244
Day 6	10819		173	6.60		316	201
Day 7	3407	59	163	6.30	889	162	148
Day 8	2000	41	148	5.50	862	184	152
Day 9			138	4.50	731	197	200
Day 10	660		115	3.40	683	183	217
Day 11			95	2.60		126	195
Day 12			66	2.00		81	162
Day 13	150		63	1.80		74	166
Day 14	113		52	1.50	395		
Day 15	91		40	1.30	381	53	128
Day 16			93	1.10	330	43	118
Day 17					323	37	104
Day 20					215	31	91

Table I. Main laboratory parameters in dynamics

The oligoanuria persisted, the tests of azotate retention raised and the patient was transferred to our department. On admittance: severe general status, conscious but confused, bradylalia, spontaneous and normal breathing, normal lung auscultation, BP 120/90 mmHg, 110 beats/min, sinus rhythm, oligoanuria. Neurological examination diagnosed hypoxic encephalopathy and proximal myopathy. Laboratory tests lead to a diagnosis of acute renal failure with anuria, hepatic and pancreatic dysfunction, and secondary anemia. These show elevated values for CK, CK-Mb, LDH, liver and pancreatic enzymes, BUN and creatinine (Table I.).

The patient received supportive care and haemodialysis. Haemodialysis was performed

over 5 days and afetr which the patient became polyuric while BUN and creatinine began todecrease. All system and organ dysfunction improved (Fig. 6.). He was discharged after 20 days with normal mental status, without neurological sequelae, with normal renal, liver and pancreas function.

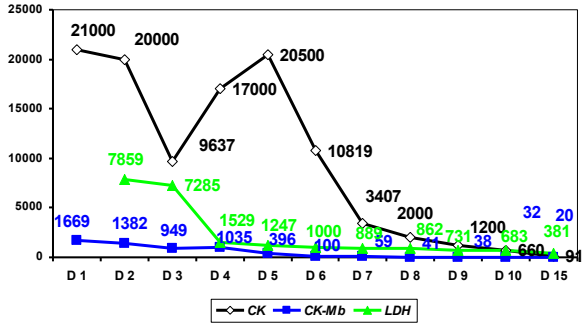

Fig. 6. CK, CK-Mb and LDH in evolution

Conclusion. In this case, rhabdomyolysis and consequent acute renal failure were due to the direct myotoxic effect of CO. The patient was not in a deep coma and his neurological status improved shortly after he began the oxygen therapy. There was no history of seizures. No evidence of muscle swelling was found. The muscle enzymes rose soon after the exposure. Renal failure due to myoglobin effects developed rapidly. In CO poisoning it is important to monitor the muscle enzyme levels in order to prevent myoglobinuric acute renal failure. Most cases of CO poisoning may be associated with rhabdomyolysis. Its recognition and diagnosis, therefore, depend on a high index of clinical suspicion.

4. Seizures and Rhabdomyolysis in a Doxylamine Poisoning case

Doxylamine succinate, an over-the-counter ethanolamine-based antihistamine, used as a night-time sleep aid, can cause severe anticholinergic effects at toxic doses, including seizures, rhabdomyolysis and death. We present a case of severe doxylamine overdose in which instead of high plasma concentration, we limited the toxic effects with adequate therapy.

Case report 4

A 29 year old woman, with aplastic anemia was admitted following suicidal ingestion of 90 tablets (1 tablet = 25 mg, total dose = 2.25 g, BW = 55 kg) of a doxylamine over-the-counter medication bought from the Internet (not approved in our country). The emergency physicians found her at home confused and agitated, 2 hours after ingestion; soon after she developed seizures with coma. On admission: sedated and intubated patient, fixed equal mydriasis, flushed and dry skin, normal pulmonary sounds, hypertension, non-invasive BP = 140/80 mmHg, tachycardia 136 b/min., hyperthermia 38°C, dark coloured urine. Initial abnormal findings: myoglobin 482.3 µg/L, creatine kinase (CK) 3500 U/L, lactate dehydrogenase (LDH) 842 U/L. Toxicology analysis by GS/MS was positive for doxylamine in urine. The first GS/ MS urine test (SIS method) at 4 hours from ingestion showed doxylamine 8.58 mg/L with 2 metabolites (M1 – carbinol-doxylamine = 0.77 mg/L and M2 – nor-doxylamine = 0.05 mg/L); the second test at 16 hours from ingestion: doxylamine 84.6 mg/L with 2 metabolites (M1 = 14.5 mg/L, M2 = 3.78 mg/L). The plasma concentrations of doxylamine were 2.08 mg/L at 16 hours, 1.875 mg/L at 24 hours, 0.904 mg/L at 32 hours. The therapy initiated was ventilatory support, sedation with benzodiazepines, aggressive intravenous fluid replacement and forced alkaline diuresis. Gastric lavage was performed and a 50 g dose of activated charcoal was administered. The outcome was favorable. Myoglobin, CK, LDH decreased (Table 2., Fig. 7., Fig. 8.), renal function remained normal. The patient was weaned from ventilator support after 3 days and discharged to a psychiatric institution after 7 days, with normal laboratory tests.

	CK (n =55-170 U/l)	LDH (n=313-618 U/l)	AST (n=14-50 U/l)	ALT (n=21-72 U/l)	BUN (n=15-43 mg/dl)
Day 1	3500	842	59	45	24.8
Day 2	6700	1875	123	89	32
Day 3	5378	1546	189	102	32.7
Day 4	3523	1214	112	93	23.7
Day 5	1976	986	95	67	22.4
Day 6	645	732	52	57	23.5
Day 7	165	456	43	34	21.4

Table II. Main laboratory parameters in dynamics

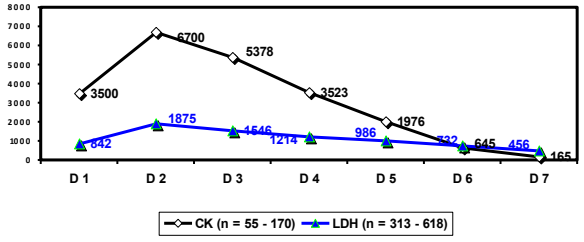

Fig. 7. CK and LDH in evolution

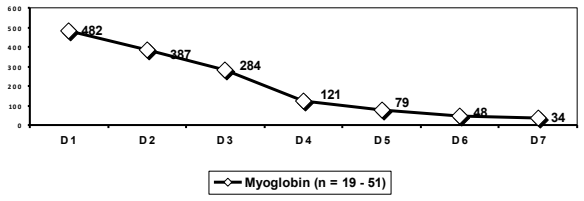

Fig. 8. Myoglobin in dynamics

Conclusion. Antihistamine overdose is a life-threatening situation and needs immediate treatment in order to avoid complications. The patient can be managed successfully, even if the ingested dose is higher than 20 mg/kg because the physicians are aware of the multiple receptor and organ effects.

5. Venlafaxine-Induced Rhabdomyolysis

Venlafaxine, an antidepressant drug, inhibits CNS serotonin and norepinephrine neuronal uptake. In overdose, venlafaxine has been reported to cause rhabdomyolysis.

Case report 5

A 46 year old man with a history of bipolar depression was admitted following suicidal ingestion of 100 tablets (1 tb. = 75 mg; total dose = 7.5 g) of venlafaxine twelve hours before hospital presentation.

	CK (n =55-170 U/l)	Amylase (n=30-110 U/l)	BUN (n=15-43 mg/dl)	LDH (n=313-618 U/l)	AST (n=14-50 U/l)	ALT (n=21-72 U/l)
Day 1	6452	235	33.8	645	57	24
Day 2	> 20000	370	31	2976	539	72
Day 3	> 20000	412	27.9	3136	738	106
Day 4	12859	383	24.5	1555	680	103
Day 5	7851	197	25.3	1234	331	86
Day 6	5284	180	23.5	980	192	80
Day 7	2960	150	33.4	750	144	89
Day 8	1540	124	43.4	534	100	97
Day 9	527	98	38.5	445	69	102
Day 10	516	82	35.5	330	55	86
Day 11	290	70	25.6	320	45	66

Table III. Main laboratory tests in dynamics

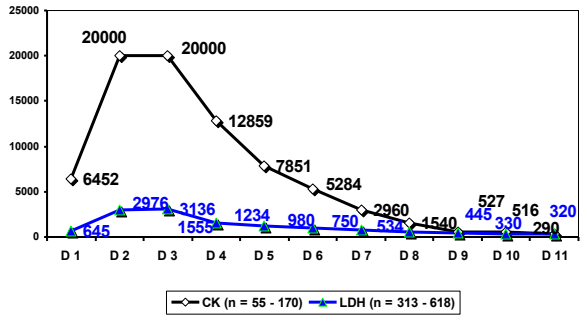

Fig. 9. CK and LDH in evolution

There was no history of seizures. Findings on admission included Reed II coma, fixed equal mydriasis, muscular hypertonia, bradypnoea, hypoventilation, hypertension (BP = 140/80 mmHg), tachycardia (130 b/min.), fever (39°C) and dark coloured urine. Pulmonary radiography revealed aspiration pneumonia. Initial abnormal laboratory findings were myoglobin > 1000 ng/mL, CK 6452 U/L (normal range 55 – 170 U/L), and LDH 645 U/L (normal range 313 – 618 U/L).

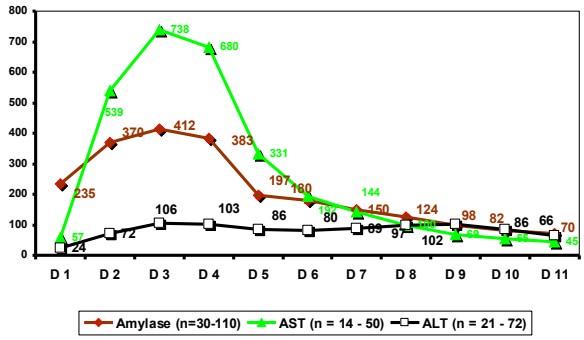

Fig. 10. Other parameters in dynamics

The therapy initiated was ventilatory support, sedation with benzodiazepines, intravenous fluid repletion and alkaline diuresis, and broad spectrum antibiotics. Gastric lavage was performed and a 50 g dose of activated charcoal was administered. Toxicology analysis by GS/MS was positive for venlafaxine in urine. Twenty-four hours post-admission, CK elevated to > 20.000 U/L along with LDH, hepatic enzymes and amylase, but after 48 hours began to decrease (Table III., Fig. 9., Fig. 10.).

Renal function remained normal throughout treatment procedures. The outcome was favourable. The patient was weaned from ventilator support after 5 days, regained consciousness at 7 days, and correction of hepatocytolysis and rhabdomyolysis syndromes occurred at 11 days. Pulmonary healing and discharge occurred after 16 days.

Conclusion. Rhabdomyolysis, resulting from serotonin toxicity and acute muscle injury, complicates venlafaxine poisoning and prolongs the hospital stay.

6. Rhabdomyolysis after a Heteropneustes fossilis Sting

In recent years the number of exotic fish in private aquarium settings increased. Heteropneustes fossilis (Stinging catfish) – Fig. 11., belongs to the Heteropneustidae family and is found in Asian waters [8].

Fig. 11. Heteropneustes fossilis

The spines (containing a heat unstable toxin) cause a sting which produces an initial intense pain, followed by an intense inflammatory reaction that can include erythema, swelling, local hemorrhage, tissue necrosis. Systemic reactions are rare but can include nausea, vomiting, weakness, hypotension, syncope, and respiratory.

Case report 6

We report the case of 27 year old patient admitted 40 minutes after he was stung by a Heteropneustes

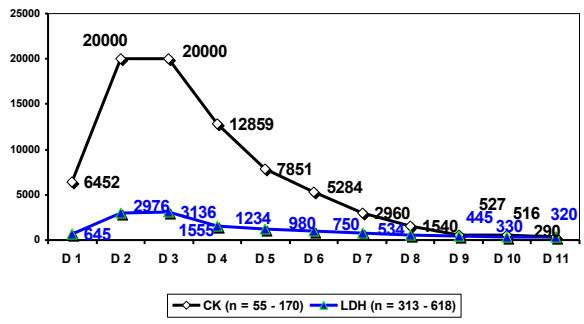

Fig. 12. CK and LDH evolution

fossilis fish spine when he tried moving it into another aquarium. Shortly after the sting, he presented with excruciating pain, shortness of breathing, nausea and vomiting, fainting sensation, dizziness.

On admission: altered general status, conscious but confused, bradylalia, somnolence, intense pain in the right hand, spontaneous breathing, some sibilant rales on lung auscultation, BP = 80/30 mmHg, 112 beats/min. Local examination: puncture wound radial border of finger 5 right hand, with perilesional pallor 0.8/1 cm, erythema of dorsal area, lymphangitis and swelling to the right elbow. The laboratory tests showed elevated values for CK, CKMb, LDH and liver enzymes, positive urine myoglobin (Fig. 12., Fig. 13.)

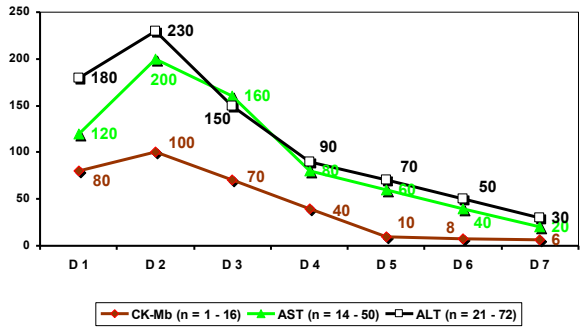

Fig. 13. Other laboratory tests in dynamics

The patient received intensive care therapy: aggressive volume replacement, corticosteroids, urine alkalinisation, osmotic diuretics, potent analgesics, antibiotics and tetanus antitoxin. After stabilization mental status improved, BP normalized, no rales on lung auscultation. The patient underwent a plastic surgery intervention with excision of necrotic tissue, large debridement, drainage. The laboratory parameters showed an increase of muscular enzymes in the next 2 days, normalization in day 7. No signs of renal dysfunction or infection appeared. The wound healed in 10 days.

Conclusion: In this case, systemic and local symptoms were due to a fish toxin, with neurotoxic and anaphylactoid effects. The rapid swelling of the hand and probably a myotoxic effect of the venom produced rhabdomyolysis. Because of the aggressive action of fish venom it is important to educate the general public about poisonous fish or other animals.

Conclusions

The etiology of rhabdomyolysis production is extremely diverse and multifactorial.

Rhabdomyolysis is a syndrome of acute poisoning often life-threatening, which is often not identified.

This type of rhabdomyolysis is complicated by the fact that the mechanisms of cell injury are produced directly and indirectly.

There are many compounds that can cause rhabdomyolysis. Symptoms can be diverse and misleading, hnce acute poisoning requiring thorough case history, clinical examination and laboratory of properly.

Treatment should be set up quickly in order to avoid severe complications, such as acute renal failure.

Due to the early identification and maintainance of a high index of suspicion, most patients with rhabdomyolysis in acute intoxication have an excellent prognosis if they are rapidly and correct treated.

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