Rhabdomyolysis and Acute Kidnez Injury

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Abstract

Rhabdomyolysis (Rh.) and myoglobinuria as a cause of acute intrinsic renal injury (AKI) are a well desribed, but uncommon (about 5% from the cases with AKI) conditions in the last thirty five years. The complexity of variant etiologic moments involved in the production of high myoglobinemia, together with the insufficient basic and clinical knowledge-makes difficult the precise and early diagnosis of this syndrome. We expose our experiences with this type of AKI, presenting the cases with Rh. associated acute tubular necrosis (ATN) in the 26 years period. The critical laboratory finding included in the diagnosis of Rh. in cases with AKI, was an augmented plasma ceatinin kinase activity (CK, values more than six times above the upper normal limit),with presence of myoglobinuria.In the 346 patients (out of 438) the presence of entity associated with Rh. appearance, have been observed (79.0%). In the rest of investigated group (n=92, 21%) the Rh. was not detected (the cases with urinary tract obstruction, tubulotoxic injury, hemolysis, acute pancreatitis, acute nephrotic, nephritic, interstial syndrome and aminoglicozides-related tubulopathy). AKI due to Rh. was noted in 84 patients (out of 346), that is one quart of our group or more precisely-24.3%.The association between Rh. and ARF was the most prominent in cases with polytrauma and crush syndrome (75-100%). The non-traumatic myonecrosis complicated with ARF was in strong relation to heroin abuse (66.7%), chronic alcoholism with nutritional hypophosphatemia (60%), eclamptic and barbituric In conclusion we may say that the association between Rh. and AKI series is about 20%, non underestimating the other factors included in the etiology of this syndrome.

Key words:myonecrosis, acute kidney injury

1 Introduction

Rhabdomyolysis (Rh.) and myoglobinuria as causes of acute intrinsic kidney injury (azotemia or uremia) and acute tubular necrosis (ATN) developed in this setting, are a consequence of myoglobin induced kidney lesions, emmited from traumatically or non-traumatically injured muscles [1,2].

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The etiology of Rh. is very different, unpredictable and in many cases,non satisfactory elucidated. The most common factors associated with Rh. and AKI are as following: mechanical muscle trauma,electric shock, hypo and hyperthermia, various infections, immunologic diseases.metabolic disorders and an inherited muscles dysfunctions.

The pathophysiologic pathways of AKI due to Rh. are also very complex and non-completely understood (from intratubular obstruction by myoglobin casts to tubulocpithelial kidney lesions related to ferrihematc production and OH-emission). The specific data strictly related to Rh. associated ATN, may be very difficult selected from the complex clinical picture ordinary present in the context of acute kidney injury, beside the symptoms related to muscle damage (weakness, swelling, tenderness, hypotonia, localized or diffuse pain, muscle cramps or stiffness...) and pigment induced tubular injury (myoglobinuria, oliguria).

The critical laboratory finding included in the diagnosis of Rh. is an augmented plasma creatinin kinase activity (CK). This parameter may demonstrates a very different level of enzyme activity from six times above the upper normal limit of enzyme action-to several millions units. The persistence of high CK activity is non necessarily related to ATN. But, inversely in the case of AKI, the high CK plasma level with or without myoglobinuria may orientate to Rh. associated kidney injury [3].

The aim of the present study is to summarize the actual medical knowledge concerning “myoglobiriuric AKI" and to demonstrate our experience with the Rh. associated AKI (frequency, outcome, mortality) through the "one center practice" overview.

2 Material and Method

We have analyzed all the patients with AKI treated in the Department of Nephrology (Faculty of Medicine,Skopje) in the last 26 years (1989-2015).There are 438 patients in total or 3.1% of all the hospitalized patients in intensive care nephrologic unit.Less than one quarter of the AKI patients (97/438, 22.2%) were in the relation with obstetrical complications in the first (septic abortion), in the last three months of the pregnancy (gestosis), or immidiately before/or after delivery (placental abruption, missed abortion, eclamptic coma and puerperal sepsis).

The table 1, presents the initial diseases complicating AKI, the frequency of Rh. in each group and lethality rate. Because of an ubiquitarius presence of urinary oxalates in the AKI patients, the search for an urine oxalate crystals (ethylene glycol intoxication) is not so specific feature.

Table 1: Basic organ disturbances, acute kidney injury, presence of Rhabdomyolysis, and mortality (N=438,1989-2015)

DISEASE	FREQUENCY OF CASES (N, %)			
(**"Rh** positive entities")	AKI (N'438.%)	Rhabdomyolysis (N/%) N/basic disease	Lethality N/BD,%	N Rh.,S
trauma				
crush syndrome	2 (0.46)	2(100)	-	-
polytrauma	4(0.91)	3(75)	-	-
non traumatic myonecrosis				
infections				
septic abortion	52 (11.87)	12 (23.08)	20 (38.5)	5 (41.7)
puerperal sepsis	3 (0.68)	1 (33.33)	-	-
urosepsis	11 (2.51)	2 (18.18)	-	-
non-urologic sepsis	37 (8.45)	9 (24.32)	8 (21.62)	2 (22.2)
Hantaan fever	20 (4.57)	1 1 (55.00)	4 (20.00)	-
Influenza R	1 (0.23)	1. (100)		-
Others				
Snake bite	1 (0.23)	1.(100)	-	-
Food poisoning	9(2.05)	1 (11.11)	-	-
(Salmonela enteritidis)				
Acute arterial oclusion	2 (0.46)	1(50)	-	-
Polymiositis	2 (0.46)	1 (50)	-	-
Acute hypokalemia	7 (1.60)	2 (28.57)	-	-
Eclamptic coma	12(2.74)	4 (33.33)	7 (58.33)	4(100)
Postoperative anuria	31 (7.08)	3 (9.68)	-	-
Dehidratation with renal ischemia				
(hypovolemiaand acidosis)	119(27.17)	14 (11.76)	-	-
Malignant neuroleptic syndrome	1 (0.23)	1 (100)	-	-
Cardiogenic shock	10(2.28)	3 (30.00)	3 (30.00)	2 (66.67)
Barbituric coma	9 (2.05)	4 (44.40)		-
Heroin abuse	3 (0.68)	2 (66.67)	-	-
Hypophosphatcmic alcoholism	10 (2.28)	6 (60.00)	-	-
Total	346 (78.99)	84 (24.28)	42(12.14)	13(15.50)

3 RESULTS

The analysis of the precedent Table 1, notices a trauma-induced Rh. in 5 out of 6 patients, or 5/438 (1.1%) from all analyzed cases.The non-traumatic myonecrosis is associated mainly with bacterial (Clostridium, Staphylococcus, Pseudomonas strains) and viral infections (Hantaan, Influenza B). Thirty six out (36) of 124 cases from the "Rh. positive entities", developed a myonecrosis, that is seven fold more in comparison with the traumatic muscle injury. The other remnant reasons for clinically manifested Rh. (43 out of 216 from the same group, or about 10%) are very different (from the snake bite to malignant neuroleptic syndrome), with decreasing frequency as follows:

-heroin abuse (100%)

-chronic alcoholism in hospital conditions (66%)

-acute arterial oclusions/polymyositis (50%)

-barbituric/eclamptic coma (40%, 35%)

-cardiogenic shock (acute infarction excluded, 30%), and

-acute hypokalemia (29%)

Taking in account only the entities where the Rh. was noted (group of 346 patients), it is possible to calculate the percent of AKI associated with Rh. in our material (84/346;

24.3% or 19.2% from the 438 analyzed cases in 26 years period).

The lethality rate in the AKI related to Rh. group, varies from 22% to 100% with the mean value of 15.5% (13/84) in comparison with the 12.1% (42/346) in the selected group of “Rh. positive entities”, or 14.4% (63 out of 438) in the all patients group.It is interesting that the mortality rate in the “Rh. negative group” (N=92 patients) is higher (22.8%), and the presence of Rh. may not be taken anymore for a reason in the AKI related lethality.In the last three years (2012-2015) we have analyzed 18 out of 86 patients (20.9%) with AKI associated Rh. The extreme physical exercise (hard work or sport activity), ordinary in non-trained young man, is very often encountered phenomenon in addition to viral infection, before the onset of Rh, febrile state and ARF. The following table 2, attempts to present the frequency of clinical findings encountered in this period.

Table 2. Frequency of clinical symptoms and signs (N = 18/86,20.9%,2012-2015)

Clinical findings	***Frequency***
Febrile state (3 – 5 days)	14 (77.8%)
Myalgia (legs,arms)	14 (77.8%)
Black urine emission (myoglobinuria)	14 (77.8%)
Haemorrhagic complications: - skin/conjunctival bleeding - melaena - haematuria - haemathemesis	13 (72.2%) 6 (33.3%) 4 (22.2%) 2 (11.1%) 1 (5.6%)
Abdominal pain (epigastric,periumbilical,hypo-Gastric,suprapubic localization)	10 (55.6%)
Adynamia (with or without dyskalemia)	9 (50.0%)
GI symptoms (vopmitus,diarrhea,sub/ileus)	9 (50.0%)
Cardiovascular signs (hypotension,bradycardia, right bundle branch block,RBBB)	8 (44.4%)
Liver injury (icterus,pain)	7 (38.9%)
CNS findings (pseudoepileptic state, meningismus)	2 (11.1)

The more prominent reason for Rh. in our recent experience was a viral infection (Hantaan and Influenza B, 11/18=61.1%) followed by a three cases (16.7%) of ischemic myonecrosis, two hypo-phosphatemic alcoholic patients (11.1%) and respectively one patient with heroin abuse (5.6%) and another with polymyositis (5.6%).

The myolysis, haemorrhagic complications, gas-trointestinal symptoms, cardiovascular signs, liver injury and CNS findings-may be explained by viral induced, non-specific (arteriolocapillar) endothelial lesions with blood platelets activation and consecutive ischemia (heart, kidney, liver, muscles, stomach and intestine) beside the potential direct effect of viruses over the named parenchymas.The CNS symptomatology (especially the complete reversible pseudoepileptic state) may be partially explained by an excessive accumulation of myoglobin in the ganglionic brain cells after massive myolysis and possible perturbation of the sc. hematoencephalic "barrière" (theory of idio-genic osmols, Kennedy at al. 1962). This sophisticated view may formerly contraindicates the therapeutic use of aminoacids solution in these patients. The further investigations are necessary before the conclusion is made.The kidney biopsy revealed a globin tubular deposits and non-specific C3 precipitation (glomerular flocculus and distal tubule) in the context of the histological findings for acute tubulointerstitial nephritis. The serum levels of CK activity were taken in consid-eration, if the enzyme activity was six fold or more over the upper limit of the normal value (Rh. is defined as an increase of at least six times or more over the upper limit, that is 90 U/L). In all cases with elevated serum CK activity (especially CK3 MM isoenzyme), the hemolysis, myocar-dial infarction and cerebral vascular accident, have been excluded. Moreover, in addition to the specific epidemio-logical consideration (traumatic or non-traumatic Rh), the crucial diagnosis value was attributed to muscle cytosolic enzyme activity (AST, ALT, LDH) and especially CK, in relation to possible myonecrosis (red color urine after centrifugation readily without or with RBC and RBC casts), but strictly without presence of haemolysis.

Table 3: Relevant parameters related to myolysis in ARF patients (N=84/346= 24.3%, X±SEM)

	CK (U/L)	**LDH** (U/L)	**AST** (U/L)	**ALT** (U/L)	**uric acid** (μmol/L)	**Pi** (mmol/L)	**K** (mmol/L)	**Ca** (mmol/L)
traumatic muscle injury(N=5, 1.5%)	**24x10^4**± 22x10^4	**682**±l83	854±432	66±16	710±139	3.0±0.32	6.9±0.39	**1.8**±0.07
non-traumatic myonecrosis (N=79, 22.8%)								
infections (N=36,45.6%)	**4260±**5890	242±65	**306**±139	24±7	354±62	2.1±0.43	5.3±0.29	2.1±0.1
Hypovolemia and acidosis (N = 14, 17.7%)	580±310	254±62	41±12	37±10	310±30	1.7±0.45	6.1±0.52	2.2±0.30
hypophosphatemia and alcoholism (N-6, 7.6%)	640±336	160±112	92±11	16±4	270±58	**1.0**±0.2	4.1±0.35	2.2±0.1
eclamptic coma (N- 4, 5.1%)	**17.2x10^4**:11.2x10^4	270±81	**643**±238	19±9	680±116	2.7±0.34	5.7±0.37	**1.9**±0.2
barbituric coma (N 4, 5.1%)	990±552	190±28	82±19	25±7	340±45	2.2±0.48	4.7±0.20	2.4±0.1
others (N=15, 19.0%)	784±380	220±52	85±22	28±6	311±74	1.9±0.3	5.2±0.3	**1.9**±0.2

The Table 3, demonstrates the relevant parameters related to myolysis at the admission of the patients to the hospital, in comparison with the rest of the analyzed group ("Rh. negative patients"). The table presents the frequency of cytolytic parameters in relation to conditions where the Rh. was noted. The activity of CK is evidently higher (see Table 3) in the cases with mechanical muscle trauma, eclamptic coma and infection induced AKI (4000 to 240000 U/L). The activity of other enzymes (like LDH, AST, ALT) usually follows the CK enzyme levels, but without sufficient specificity.

The mean serum concentration of uric acid is higher in the eclamptic coma patients and traumatic muscle injury (680-710 μmol/L). The blood inorganic phosphorus level is near the lower limit of normal in alcoholics with Rh. and AKI (1.0 mmol/L) and moderate hyperkalemia (6.1-6.9 mmol/L) in patients suffering from crush and/or "hypovolemia-acidosis" syndrome.

The left etiologic conditions non-associated with Rh. (92/438, 21%) in our series were: urinary tract obstruction, tubulotoxic injury, acute pancreatitis, acute nephritic/nephritic and tubulo-intcrstitial syndrome, complicated advanced pregnancy (without eclamptic coma) and - aminozide related nephropathy.

4 Discussion

Any disorder which causes release of body pigment (especially myoglobin and hemoglobin) into circulation can lead to AKI. Myoglobin is released into blood stream following disruption of striated muscles related to impaired muscle cells metabolism. Acute Rh. and AKI (about 20% in this setting) probably occur more commonly than reported. They may be associated with very different etiologic factors divided mainly in two groups following the presence or absence of evident muscle tauma. The traumatic muscle injury is related to mechanic (crush syndrome), ischemic (arterial occlusion),electric or thermal trauma (heat injury,burns,congelating lesions)- or may be a result of ext-reme muscular exertion (delirium tremens, convulsions or exaggerated physical exercise).

The mehanisms of traumatic myopathy and acute compartment syndrome, may be explained by increase in intramuscular interstitial pressure, myooedema,stretch activation of calcium channels with increase of cytosol ionized calcium and increased energy requirements with depletion of ATP stores. The breakdown of large. molecules into smaller ones, increases the intracellular osmolality, interstitial pressure and muscle swelling.The fasciotomy decompress a muscles and to prevent a compression lesions, may be indicated when conservative mannitol therapy fails, or in the case of gross vascular disturbance to the limb, because the risk of uncontrollable infection and potentiation of muscle swelling [4].

Mechanism of muscle injury in non-traumatic Rh. (mainly drug induced muscles injury) consists in prolonged pressure (26 to 240 mmHg) on dependent muscles by the patients own body on a hard surface. That, compromises the regional arterial blood supply with consecutive ischemic injury and myonecrosis during period of diminished consciousness and immobilization.The degree and duration of stupor determine the extent of Rh, myoglobinuria and the presence of ATN.To the occurrence

of non-traumatic Rh. and ATN,contribute the frequent concomitants of drug overdose like hypoxia, volume depiction, hypotension, hyponutrition,disturbances in temperature regulation and acute acidosis. However, induction of an imbalance between the oxygen supply to the muscle cells and their oxygen consumption, may lead to lack of ATP in myocytes and Rh (probable mechanism in certain drug overdose [5,6].

For instance, we have described one patient with nerve entrapment syndrome ("brachial plexitis"), Rh.and ATN following an abuse of heroin [7], Additionally Rh.in this setting may be attributed to a direct toxic effect, an allergic reaction, tetanus or self injection of water with generalized muscle swelling in all extremities [8,9].

The non-traumatic Rh. accounting for one third of medical AKI in a few series from the western countries [10], and complicates the course of several diseases and pathologic states. The following Table 4, presents the most characteristic conditions associated with Rh., sometimes without striking muscle symptoms and signs.

Table 4: Characteristic pathologic conditions associated with rhabdomyolysis

Metabolic disorders	Hypokalemia (potassium loosing nephropathy) Hypophosphatemia (total parenteral nutrition in previously malnourished patient) Hypo/hypernatremia Hypermagnesemia,hypocalcemia,diabetic ketoacidosis Hyperosmolar coma (nephrogenic and pituitary diabetes insipidus) [18] Deep dehydratuion,prolonged immobilization with insufficient local muscle perfusion
Toxins	Strychnine,Phenylpropranolamine,Ethylene glycol,Toluene,Ethanol,Carbon monoxide,Snake and insect bites,Hemlock poisoning (2-propylpi-peridine,cicutoxin,cynaprine) [19],pareneteral heroin
Drugs	Amphetamines,Neuroleptics,EACA-prolonged exposition,Hypolipemics (fibrates,statins, gemfibrozyl,cave:preexisting chronic renal disease) [20,21],Theophyllines, Barbiturates, Phencyclidine,Methadone, Amoxepine, Temaze-pam [22]
Drugs interaction	Fluconazol+CsA+statins;Amoxepine+MAOI+Fluoxetine (crisis convulsive!)
Infections - viral and bacterila	Influenza A/B,Infectious mononucleosis,Coxsackie virosis,Legionnaire disease,Tetanus,polymycrobial sepsis
Immunologic diseases	Polymyositis (allergic reaction)
Myositis and inherioted myopathies	Deficiency of: myophosphorylase (McArdles'syndro-me),phosphofructokinase,myoadenilate deaminase and carnitine palmyltransferase (recurrent myoglobinuria with exercise induced cramps)

The precise mechanisms by which Rh. impairs GFR are still unclear, but intrarenal arterio-loconstriction, intratubular obstruction and direct tubule injury have been well documented as pathophysiologic characteristic factors.

Myoglobin promotes vasoconstriction probably by scavenging the vasodilator NO and thereby disrupting the critical balance between renal vasoconstrictors and dilators with consecutive kidney hypoperfusion and ATN. The fractional excretion of sodium is less than 1% during the oliguric phase of AKI, that suggests a diminished renal perfusion as a likely to the most important mec-hanism of lesion [11,12]. These facts developed the idea for prophy-lactic use of s.c "scavengers" for other vasoconstrictors to promote both-better vasodilators function and renal perfu-sion. At acid pH < 5.6, myoglobin, as ferrous iron com-pound , dissociates into globin moietie and ferrihemate which penetrates into tubular cells, inhibits the active tubule transport by local production of OH iones, and predisposes to pigment induced ATN [13].

The difference between hemoglobin and myoglobin induced ATN is simple in clinical practice. In the first one, the urine is strongly positive for hemoglobin, but contains few disrupted red blood cells and the plasma is usually pink {as free hemoglobin (mw=65 kD) is a larger molecule than myoglobin, (mw=17 kD), that is heavily protein bound (mainly to haptoglobin), and filtered slowly by the kidney}. Myoglobin is lightly bound to an alfa-2 globulin with a binding capacity of 23 mg% (for 50% of plasma myoglobin). The renal threshold for myoglobin is 0.5-1.5 mg% and so between mvoglobinemia of 1.5-23 mg%, about 50% of plasma myoglobin will be eliminated in the urine. In the case of pure myoglobinuria, the serum is not colored, but the urine is ordinary darker without RBC and negative for presence of bilirubin.

From the clinical point of view, evidence of muscle injury, such as muscle stiffness, swelling, tenderness, malaise, weakness, muscle hypotonia and localized pain (50% of the cases) especially in the legs' region, in addition to characteristic laboratory findings and marked reduction of urine output, are crucial in the diagnosis of Rh. Most of the patients with ATN in this setting have more than one

potential cause of Rh. In the 60% of the cases ATN (as a histologic finding) was not associated with AKI Based on an analysis of blood parameters, the following formula is proposed, as a predictor for the development of Rh. induced AKI.

*Risk = 0.7*K (mmol/L) + 1.1* Creatinine (mg%)+ 0.6* Albumin (g%) - 6.6*

If the risk is more than 0.1, the possibility of AKI appears high [14]. It should be noted that the pink serum and dark urine are indicative of haemolysis, whereas clear serum and dark urine suggests Rh. The severe myoglobinuric ATN may occur in the absence of visible pigmenturia (myoglobin and actin) and biochemical examination of the urine may be necessary [15], Because the myoglobin has a plasma half-life of 1 to 3 hours and disappears from the serum within 6 hours, the diagnosis of Rh. may be missed if muscle demage was transient and if the patient is not seen until in established AKI. The AKI due to Rh. is associated with severe *hypocalcemia* in oliguric phase (dystrophic calcification of injured muscles!), depressed production of 1.25 $(OH)_2D_3$ because the high phosphorous content in the proximal tubule cells, and with *hypercalcemia* in about 30% of patients in the recovery phase (probably because a raised level of calcitriol). Over the role of parathyroid hormone in Rh. associated dyscalcemia, remains a considerably controversy [16]. The muscle biopsy revealed non specific abnormalities related to myonecrosis or vasculitis.

The plasma myoglobin and creatinine increase dramatically in the presence of muscle damage [more than 25μmol/L/day for creatinine, and more than 40 ng/mL (or 27 nmol/L for myoglobin)] especially in young people,together with potassium, phosphorus, uric acid, serum muscle enzymes like CK, aldolase, AST, ALT and LDH. All together, the severity of the muscle injury linearly correlates with the myoglobinemia, myoglobinuria and should confirm the Rh. associated AKI and also prompt urgent treatment (forced alkaline diuresis) [17].

5 CONCLUSION

In conclusion we may say that the association between Rh. and AKI series is about 20%, non underestimating the other factors included in the etiology of this syndrome.

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Table 2: Frequency of Clinical Symptoms and signs (N=18/86, 20.9%, 1993-1996)

Clinical Findings	Frequency
Febrile state (3-5 days)	14(77.8%)
Myalgia (legs, arms)	14 (77.8%)
Black urine emission (myoglobinuria)	14(77.8%)
Haeemorrhagic complications:	13 (72.2%)
- skin/conjunctival bleeding	6 (33.3%)
- melaena	4 (22.2%)
- hematuria	2(11.1%)
- hematemesis	1 (5.6%)
Abdominal pain (Epigastric, periumbilical,hypogastric,suprapubic loalization	10 (55.6%)
Adynamia (with or without dyskalemia)	9 (50.0%)
GI symptoms (vomitus, diarrhea, sub/ileus)	9 (50%)
Cardiovascular signs (hypotension bradycardia, right bundle branch block)	8 (44.4%)
Fiver injury (ictenis, pain)	7 (3 8.9%)
CNS findings (Epileptic state, meningismus)	2(11,1%)

Table 3: Relevant parameters related to myolysis in ARF patients (N=84/346= 24.3%, X±SEM)

	CK (U/1)	LDH (U/1)	AST *cat* i)	ALT *cat* i)	uric acid (Umol/ 1)	Pi (mmol/ 1)	K (mmol/ 1)	Ca (mmol/1)
traumatic muscle injury (N=5, 1.5%)	24x10'! 22-104	682tl83	854±43 2	66±16	710±13 9	3.0±0.3 2	6.9±0. 39	1.8*0.07
non-traumatic myonecrosis (N=79, 22.8%)								
infections (N=36,45.6%)	4260i5890	242±65	306'139	24-J7	354.62	2.1±0.4 3	5.3*0.2 9	2.1*0.1
hypovolemia and acidosis (N = 14, 17.7%)	580±310	254±62	41±12	37*10	310±30	1.7±0.4 5	6.1±0. 52	2.2*0.30
hypophosphatemia and alcoholism (N--6, 7.6%)	640±336	160±11 2	92±11	16±4	270±58	1.0±0.2	4.U0.3 5	2.2±0.1
eclamptic coma (N-4, 5.1%)	17.2x194:11.2x 104	270±81	643±23 8	19±9	680±11 6	2.7±0.3 4	5.7±0. 37	1.9±0.2
barbituric coma (N 4. 5.1%)	990±552	190±28	82±19	25±7	340±45	2.2±0.4 8	4.7±0. 20	2.4*0.1

others (N=15, 19.0%)	784±380	220*52	85±22	28±6	311±74	1.9*0.3	5.2*0.3	1.9*0.2

Tabic 4: Characteristic pathologic conditions associated with Rhabdomyolysis

Metabolic Disorders	-Hypokalemia (potassium loosing nephropathy) -Hypophosphatemia (total parenteral nutrition in previously malnourished patients) -Hypo/Hypernatremia -Hypermagnesemia, hypocalcemia, diabetic ketoacedosis -Hyperosmolar coma (nephrogenic and pituitary diabetes insipidus [18] -Deep dehydration, prolonged immobilization with insufficient local muscle perfusion
Toxins	Strychnine, phenylpropranolamine, ethylene glycol, toluene, cthanol, carbon monoxide, snake and insect bites, Hemlock poisoning (2-propy-lpiperidine. cicutoxin. cynaprine) [19] parenteral heroin
Drugs	amphetamines, neuroleptics, EACA-prolonged exposition, hypolipemics (fibrates, statins, gemfibrozil, cave: preexisting chronic renal insufficiency) [20,21],theophyllines, barbiturates, phencyclidine, methadone, amoxepine, temazepam [22]
Drugs interaction	fluconazol + cylosporin A + statins amoxepine + MAOI + fluoxetine (crises convulsive!)
Infections	Influence A/B. infectious mononucleo sis, Coxsackie virosis.
Viral and Bacterial	Legionnaire disease, tetanus, polymy crobial sepsis
Immunologic diseases	Polymyositis (allergic reaction), deficiency of myophosphorylase
myositis and inherited myopathies	(McArdles' syndrome), phosphofructokinase, myoadenilate deaminase and carnitine palmyltransferase (recurr ent myoglobinuria with exercise induced cramps)