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Review

Non-traumatic rhabdomyolysis: Background, laboratory features, and acute clinical management

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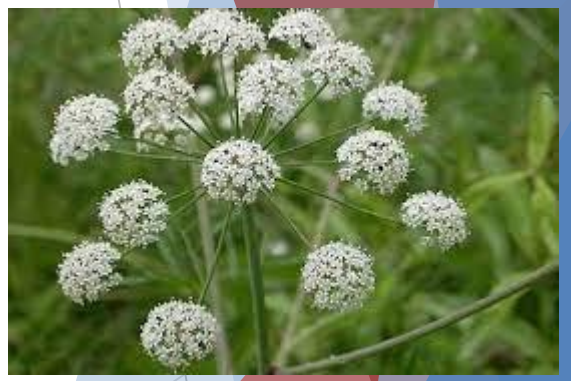
Contents

Historical background

- The first “reference” on rhabdomyolysis → the Pentateuch, the first five books of the Bible→ episode of mass poisoning afflicting the Jews soon after the ingestion of quails caught during their staying in the Sinai desert
- (“And while the flesh was yet between their teeth, ere it was chewed, the wrath of the Lord was kindled against the people, and the Lord smote the people with a very great plague”; Numbers 11.33)



- The second “reference” on rhabdomyolysis is probably associatedwith the description of the execution of Socrates by the Athenian state in 399 BCE.

- The third “reference”,which actually represents the first medical description of the syndrome, is dated back to the early 1900s, describing the clinical pictures of survivors of the tremendous earthquake followed by a tsunamiwhich destroyedMessina and Reggio Calabria in Southern Italy and caused N100.000 victims, on December 28, 1908

Historical background

- The pathophysiological mechanisms, however, were first identified by Bywaters et al. in 1941, when the traumatic form of rhabdomyolysis was accurately described in the victims of the bombing of London .

- Non-traumatic rhabdomyolysis represent a rapidly growing →number of publications on this topic: N= 350 new articles have been published in 2016

Definition and epidemiology

- rhabdomyolysis describes the rapid breakdown of striated, or skeletal, muscle
- rupture and necrosis of muscle fibers → release into the bloodstream and extracellular space of cell products

- Since skeletal muscles comprises ~40% of body weight→ the destruction of just 100 g of muscle tissue is capable to induce the clinical syndrome of rhabdomyolysis → it is easy to understand that this "breakpoint" can be reached quite easily

Definition and epidemiology

- Rhabdomyolysis occurs with a wide spectrum of signs and symptoms

ranging from a completely asymptomatic increase of plasma creatine kinase (CK)→ AKI , electrolyte imbalance and DIC.

- AKI secondary to rhabdomyolysis varies from 13% to over 50%, mainly depending on the clinical and organizational setting where it is diagnosed

Definition and epidemiology

- Rhabdomyolysis → damage to striated muscle cells or fibers
- crush injury→ injuries occurring as consequence of crushing of bodily parts (usually a limb)
- compartment syndrome →the complications developing for increased pressure inside one or more muscular compartments → interruption in the regional circulation and ischemic injury to nerves and muscles
- crush syndrome → the complex pathophysiological consequences caused by massive rhabdomyolysis, mainly involving both kidneys and coagulation system.

Etiology

- Direct muscle injury remains the most common cause of rhabdomyolysis,

	intrinsic	extrinsic
Hypoxic	✓ compartment syndrome ✓ compression ✓ immobilization ✓ vascular occlusion due to thrombosis or vasculitis	✓ Carbon monoxide ✓ cyanide poisoning
Physical	➢ Exertion ➢ Seizures ➢ status asthmaticus ➢ Agitation ➢ malignant hyperthermia	➢ Trauma ➢ Burns ➢ Electrocution ➢ hypo/hyperthermia
Chemical	❑ Electrolyte disorders (hypokalemia; hypophosphatemia; hypocalcemia; hypo/hypernatremia).	❑ Environmental toxins ❑ Alcohol ❑ drugs or substances of abuse
Biological	▪ dermatomyositis/polymyositis ▪ Endocrinopathies → mainly thyroid dysfunction	▪ Infections from bacteria, viruses, parasite;

Etiology

- A frequent mechanism causing rhabdomyolysis is prolonged compression during immobility.
- This is usually due to
  - stroke in elderly patients,
  - time consuming surgery without adequate periodic patient mobilization
  - self-induced intoxication (with the concomitant effects of immobilization and toxicity from substances).

- In general, 1 h of compression might be sufficient, but cases of rhabdomyolysis have also been described when compression lasted ~20 min

Etiology

- Excessive muscular activity can also cause rhabdomyolysis
  - strenuous sports activities (typically in marathon runners)
  - Epilepsy
  - Delirium tremens
  - Tetanus

- Electrical injuries are a frequent cause of rhabdomyolysis
  - tetanic contraction of the muscles
  - Direct effects of electricity on muscle fibers

Etiology

- Among medical causes, drugs and toxic substances play a pivotal role, with opioids [24], alcohol [25], cocaine and other substances of abuse [26–29], among the most frequent
  - toxic effect on muscle fibers
  - indirectly, through immobilization-compression or muscular hyperactivity

Etiology

- Alcohol can induce rhabdomyolysis →
  - Direct:

a) inhibiting calcium accumulation into the sarcoplasmic reticulum

b) disrupting muscle cell membranes

c) inhibiting the sodium- potassium ATPase pump which helps maintaining cellular integrity

  - Indirect :

a) Delirium tremens and/or alcohol withdrawal seizures

b) muscle hypoxia due to prolonged immobilization and limb compression

c) hypoperfusion following volume depletion

d) hypokalemia

e) Hypophosphatemia (poorly nourished alcoholic patients)

Etiology

- cocaine-induced rhabdomyolysis→ the severity of muscle injury seemingly parallel the severity of cocaine intoxication.
- 5–24% incidence of increased CK activity.
  - causes: seizures, excessive muscle activity, hyperthermia, tissue hypoxia from limb compression following loss of consciousness, and hypovolemia.
  - Myocardial infarction (MI)

- Recently, synthetic cannabinoids have been added to the list of substances capable to induce rhabdomyolysis

Etiology

- Statins: → best known.
  - ✓ can induce muscle injury are not well established, and are probably multifactorial.
  - ✓ reduce both selenoprotein and ubiquinone levels.
  - ✓ some genetic polymorphisms
  - ✓ range : myopathy ranges from asymptomatic elevations of serum CK → elevated serum levels of CK, and renal damage
  - ✓ The risk of rhabdomyolysis is significantly increased when statins are used in association with fibrates
  - ✓ Because fibrates are excreted by the kidney, the risk of myopathy increases exponentially in patients with impaired renal function

Table 1
Phenotypes classification of statin-induced myotoxicity (SIM). Adapted from [43]

Classification SIM	Phenotype	Incidence
SIM 0	CK>4x upper threshold of normality	1.5–26%
SIM 1	Tolerable myalgia	190/100.000 patients/year; 0.3–33%
SIM 2	Intolerable myalgia	0.2–2/1000
SIM 3	Myopathy	5/100.000
SIM 4	Severe myopathy	0.11%
SIM 5	Rhabdomyolysis	0.1–8.4/100.000 patients/year
SIM 6	Necrotizing myositis	~2/million patients/year

Table 2
Selected drugs that have been associated with rhabdomyolysis.

Antipsychotics and antidepressants	Abuse substances	Other medicines: miscellaneous
Amitriptyline	Alcohol	Amphotericin B
Amoxapine	Amphetamine/metamphetamine (MDMA, ecstasy)	Azathioprine
Chloropromazine	Caffeine	Corticosteroids
Doxepin	Cocaine	Colchicine
Fluphenazine	Heroin	Epsilon-aminocaprioc acid
Fluoxetine	Lysergic acid diethylamide (LSD)	Fluorochinolones
Fluphenazine	Mephedrone	Halothane
Haloperidol	Methadone	Macrolides
Lithium	Methanol	Moxalactam
Olanzapine	Phencyclidine	Oxprenolol
Protriptyline	Sintetic cannabinoids	Paracetamol
Perphenazine	Toluene ("glue sniffing")	Penicillamine
Promethazine	Alcohol	Pentamidine
Risperidone		Phenylpropanolamine
Trifluoperazine		Quinidine
		Salicylates
		Succinylcholine
		Theophylline
		Terbutaline
		Thiazides
		Trimethoprim-sulfamethoxazole
		Vasopressin
Hypnotics and sedatives	Antihistamines	Anti-hyperlipidemic agents
Diazepam	Diphenhydramine	Lovastatin
Nitrazepam	Doxylamine	Pravastatin
Flunitrazepam		Simvastatin
Lorazepam		Fluvastatin
Propofol		Atorvastatin
Triazolam		Rosuvastatin
Barbiturates		Cerivastatin (withdrawn)
		Clofibrate
		Bezafibrate
		Fenofibrate
		Gemfibrozil

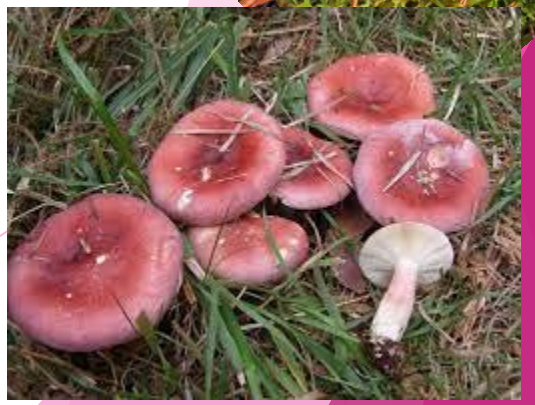
Etiology

- The most recent warning regard the widely-used proton pump inhibitors [46], levofloxacin [47], caffeine [48,49], mefloquine [50], pregabalin [51], and sildenafil [52], among others.

- Other important medical causes of rhabdomyolysis include
  - Malignant hyperthermia
  - Neuroleptic malignant syndrome
  - Heatstroke and hypothermia
  - Severe electrolytes alterations (e.G., Severe hypokalemia, hypophosphatemia and hyponatremia)
  - Diabetic ketoacidosis and non-ketotic hyperosmolar coma,
  - Severe hypo- or hyperthyroidism
  - hyperemesis gravidarum →by hypokalemia and hypophosphatemia .

Etiology

- Various natural substances can also trigger rhabdomyolysis.
- The best known is cicutoxin, a mixture of at least eight different alkaloids present at varying concentrations in different species of hemlock (poison hemlock – Conium maculatum – but also lesser hemlock – Aethusa cynapium– andwater hemlock – Cicuta virosa).
- In the Mediterranean region, cases of rhabdomyolysis are still observed in patients who have eaten quail
- In 2001, 12 cases of rhabdomyolysis, three of which fatal, were described in France after consumption of large amounts of Tricholoma equestre, a mushroom generally considered as edible.
- At least one species of Russula mushroom (i.e., Russula subnigricans) has been reported to provoke rhabdomyolysis and causing at least two deaths

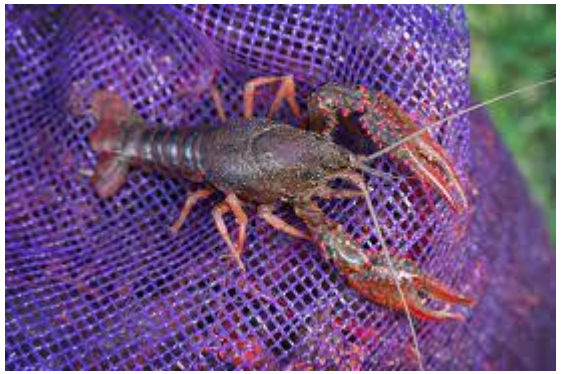


Etiology

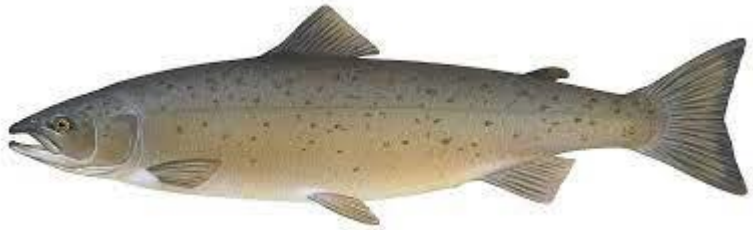
- Viper venom frequently causes rhabdomyolysis and compartment syndrome.
- Eating fish has been recognized as a potential cause of rhabdomyolysis, and the so called Haff disease (from the German word “Haff”, meaning “Lagoon”), has been described nearly a century ago in the Baltic region

- Buffalo fish

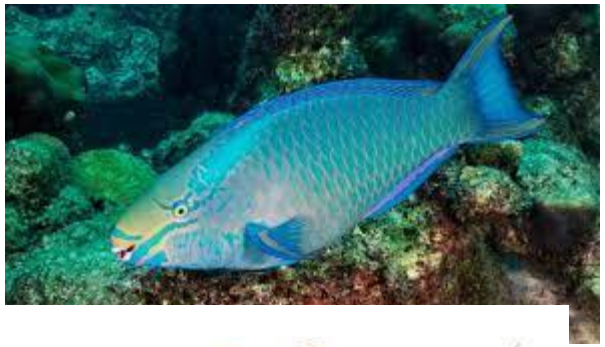
- crawfish,



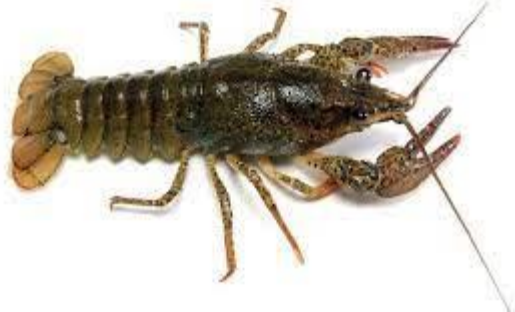
➢Salmon



➢Parrotfish



➢Crayfish



Etiology

- Multiple bee stings

- Carbon monoxide (CO) poisoning → hypoxic muscular damage & compression

Pathophysiology

- All the aforementioned mechanisms capable to produce muscle damage converge in a final common pathway that triggers a cascade of events leading to a rapid influx of calcium ions into muscle cells. → pathological interaction between actin and myosin → activation of cell protease → necrosis of muscle fibers→ release of intracellular metabolites (potassium, phosphates, and urates) and intracellular proteins (myoglobin, creatine kinase, aldolase, lactate dehydrogenase, among others) in the extracellular space and bloodstream.

- In normal conditions, myoglobin is bound to plasma globulins.
- The destruction of just **100 g of muscle** tissue is capable to overwhelm this binding capacity, and myoglobin → glomerular filtrate→ tubular occlusion and severe kidney damage

- Additional mechanisms causing renal damage include

I. a direct cytotoxic effect of myoglobin on renal cells
II. urate precipitation, leading to intraluminal casts, increased intratubular pressure and subsequent decreased glomerular filtration rate
III. renal vasoconstriction and ischemia due to the heme group of myoglobin causing activation of the cytokine cascade
IV. oxidant injury through heme-induced reactive oxygen species such as superoxide anion, hydrogen peroxide, or hydroxyl radicals causing

Pathophysiology

- Pigmented myoglobin casts, characteristic of rhabdomyolysis syndrome, are the result of the interaction between **myoglobin** and **Tamm-Horsfall protein** in an acid environment

- There is an **inverse relationship between urine pH** and the percentage of precipitated myoglobin, at any protein concentration.
- For example,when the urine pH is <5 73% of myoglobin precipitates, whereas at a pH of 6.5 only 4% of myoglobin precipitates

- In the case of **traumatic rhabdomyolysis**, other key aspect is the hypovolemia and/or shock that frequently accompanies this condition,

Clinics

- The classic triad of symptoms of rhabdomyolysis includes: muscle pain, weakness and dark urine.
- Muscle weakness and muscle pain can occur in any body region, but the muscle groups mostly involved are those of **the proximal leg**, **calf** and **lumbar region**
- These muscles may appear tense and swollen, sometimes associated with bed sores
- this classic triad is observed in <10% of patients only, and up to 50% of the patients do not complain of muscle pain or weakness, only complaining for non-specific symptoms
- In these cases, the first sign may be the appearance of dark urine

Clinics

- Systemic manifestations include : fever, general malaise, tachycardia, nausea and vomiting.
- The clinical manifestations of AKI, DIC and multiorgan failure may appear **later**

- Regardless of the underlying causes, the overall mortality rate due to rhabdomyolysis is still as high as 8% .

LABORATORY DIAGNOSTICS

- The laboratory diagnosis of rhabdomyolysis is still essentially based on the measurement of serum or plasma CK,
- a concentration **five to ten** times the URL (i.e., ~1000 U/L) is commonly used.
- In the case of a single event (i.e., mostly trauma), CK levels tend to **rise in the first 12** h, peak on the second or third day and return to baseline 3– 5 days later.

- CK values are generally considered to **predict** the likelihood of developing AKI with a **concentration >5000 U/L** thought to be closely associated with development of kidney damage.

- myoglobin is the crucial player in the pathogenesis of myoglobinuric AKI, has a **more rapid kinetics than** CK, so that its monitoring over time may allow to **mirror disease activity** and define therapeutic efficiency better than using CK

LABORATORY DIAGNOSTICS

- More specifically, CK has a half-life of 1.5 days.
- As a consequence, blood levels remain increased longer than for myoglobin, **which has a half-life of 2–4 h.**
- **Myoglobin values tend to normalize within 6–8 h following the event**

- Strong evidence has emerged that peak values of myoglobin in serum or plasma could be **better predictors** of AKI than CK values

- These data have been recently supported by a meta-analysis of 18 studies, concluding that AKI occurrence was significantly predicted by **CK** value in patients with **crush-induced rhabdomyolysis**, but not in those with other causes of rhabdomyolysis

LABORATORY DIAGNOSTICS

- Unlike serum or plasma myoglobin assessment, **there is inconclusive** data supporting the use of urine myoglobin measurement as a **predictor** of AKI in patients with suspected rhabdomyolysis

- Since the presence of **hematuria** is very frequent in patients with rhabdomyolysis, this might be a serious limitation, so potentially causing false **positive results and** leading to inappropriate therapeutic management.
- **Falsely low or false negative** results can especially occur in the presence of **ascorbic acid**, **high nitrite** concentrations, or *high specific gravity*.

- Cardiac troponins might also be occasionally increased in patients with rhabdomyolysis (up to 17% of cases)

LABORATORY DIAGNOSTICS

- It may hence be concluded that **CK** should still be considered the **biochemical "gold standard"** for **diagnosing** rhabdomyolysis,
- where as **myoglobin** should be considered the **"gold standard"** in prognostication, especially in patients with non-traumatic rhabdomyolysis

- The assessment of **severity** and **progression** of the syndrome should entail serial monitoring of renal function and electrolytes, as well as coagulation testing in order to promptly reveal the presence of early coagulopathy or DIC.

- Unfortunately, **blood creatinine and blood urea nitrogen** values are **late** markers of kidney damage.
- Other than renal damage, they often reflect the gradual deterioration of renal function

LABORATORY DIAGNOSTICS

- Recent focus has been placed on innovative biomarkers of kidney injury,
- N-GAL (neutrophil gelatinase associated lipocalin), a 178 AA polypeptidewhich is rapidly released from the kidney after an ischemic and/or nephrotoxic event
- **Urine and serum NGAL** concentrations increase **2 h after** an ischemic renal event (e.g., coronaryartery by-pass surgery), **displaying 95% sensitivity and 99% specificity** for identifying patients who later develop AKI.

- This protein, which measurement is also available on the market as **"point-of-care"** testing, may be useful for rapid identification of patients requiring more aggressive monitoring and treatment.

Emergency department treatment and management

- After establishing a definitive diagnosis of rhabdomyolysis, or even when is strongly suspected it (e.g., in case of crush syndrome), **fluid infusion should be promptly initiated**,
- with the goal of maintaining a urinary flow **of 200–300 mL/h**.
- In order to avoid volume overload, it is highly recommended to alternate **500 mL of sterile saline solution +** 500 mL of 5% glucose solution+ adding 50 mmol of sodium bicarbonate for each subsequent 2–3 L of solution (usually 200–300 mmol on the first day) and maintaining the urine pH above 6.5 and plasma pH below 7.50

- The speed of infusion should **be ~500 mL/h**, while hemodynamic parameters and urine output should be monitored closely.

Emergency department treatment and management

- The role of osmotic agents (i.e.,mannitol) or loop diuretics (i.e., furosemide) was **never proven** to be useful and should hence be **discouraged**
- Especially in **traumatic** forms, up to 12 L of fluid can be sequestered in the damaged tissue in the **first 48 h**
- In elderly patients, or in those with pre-existent heart disease, intravenous fluid therapy must be personalized and carefully monitored due to the risk of fluid overload and pulmonary edema

Emergency department treatment and management

- Alkalinization add **little to the beneficial** effect of hydration
- Considered that sodium bicarbonate, targeting urine alkalinization around a pH of 6.5, prevent myoglobin precipitation into the renal tubuli, but may also help managing of one of the most frequent complications, i.e., hyperkalemia associated or not with metabolic acidosis
- Forced hydration should be continued **until disappearance of myoglobinuria**, which typically occurs in the third day.

Emergency department treatment and management

- Hyperkalemia must be managed using the usual techniques
- considering that treatment with **glucose and insulin** may be ineffective in this setting due to inability of damaged muscle tissues to capture potassium from the extracellular liquid,
- so enhancing the importance of administering sodium bicarbonate.
- It is often necessary to treat **severe hyperkalemia** with **hemodialysis**.

Emergency department treatment and management

- **Hypocalcemia**, secondary to sequestration of calcium into damaged muscle cells ,must not be uncritically treated.
- The administration of intravenous calcium (both chloride and gluconate) should be used only to treat life threatening ECG alterations, secondary **to hyperkalemia or extreme hypocalcemia**

نقد مقاله

- نقاط قوت

1) متن خوب وروان

2) تقسیم بندی مطلب

- بیان خوب علل

نقد مقاله

نقاط ضعف

1) باوجود بیان رابدومیولیز غیر ترومایی خیلی از مطالب آن مربوط به رابدومیولیز ترمایی بود
2) ضعف در بخش درمان
3) ضعف در موردشاخص هاو بیومارکر های جدید رابدومیولیز و نارسایی کلیه
4) عدم بیان عوامل پیش بینی کننده نارسایی کلیه
5) عدم بیان واشاره به آمفتامینها به عنوان یک علت مهم در رابدو میولیز

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A Risk Prediction Score for Kidney Failure or Mortality in Rhabdomyolysis

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Abstract

Table 1 McMahon Score

Variable	Score
Age, years	
>50 to ≤70	1.5
>70 to ≤80	2.5
>80	3
Female	1
Initial creatinine, mg/dL	
1.4–2.2	1.5
>2.2	3
Initial calcium <7.5 mg/dL	2
Initial CPK (Creatine Phosphokinase) >40 000 U/L	2
Origin not seizure, syncope, exercise, statins, or myositis	3
Initial phosphate, mg/dL	
4.0–5.4	1.5
>5.4	3
Initial bicarbonate <19 mEq/L	2

When calculated at admission from demographic and blood chemistry data, a score ≥6 is 86% sensitive and 68% specific for patients who will require RRT.

The patient above would have a McMahon score of 11, demonstrating a high risk of needing renal replacement therapy.


THANK YOU!