CrackCast Show Notes – Rhabdomyolysis – November 2017
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Chapter 119 – Rhabdomyolysis

Episode overview

1. List the pathophysiology of rhabdomyolysis
2. List 8 causes of Rhabdomyolysis
3. List 6 metabolic derangements associated with Rhabdomyolysis
4. List 5 causes of pigmenturia
5. List 4 treatments of Rhabdomyolysis

Wisecracks

1) What is the pathophysiology of pigment nephropathy?
2) How is pigment nephropathy in the setting of rhabdomyolysis managed?

Rosen's In Perspective:

Rhabdomyolysis is a potentially life-threatening condition characterized by the breakdown of skeletal muscle and the release into the circulatory system of intracellular contents, including creatine kinase, aspartate transaminase, lactate dehydrogenase, aldolase, the heme pigment myoglobin, and electrolytes. **- Rosen's 9th Edition, Chapter 119**

Core questions

1) List the pathophysiology of rhabdomyolysis

Muscle cells have delicate Na-K-Ca balances to work properly. ATP is the prime fuel to keep calcium - which is toxic to muscle cells - outside the cell.

Rhabdomyolysis occurs after a final common pathway—increased cytoplasmic calcium concentration, leading to myocyte destruction, with the release of muscle components into the circulation. There are two primary mechanisms whereby calcium pathologically accumulates in the cell, (1) direct cell membrane damage and (2) ATP depletion.

- **Membrane damage** from trauma and genetic or biochemical factors results in a massive influx of extracellular calcium into the cytoplasm driven by electrical and chemical gradients.
- **ATP depletion** results in failure of cellular transport and increased permeability to sodium ions.

Sequence of events:

Increased cytoplasmic Ca++ → mitochondria get overwhelmed with calcium causing:

1. Triggered apoptosis

2. Disruption of oxidative phosphorylation → further increasing intracellular Ca++ because of no ATP production
3. Escalating production of free radicals
4. Destruction of lipids, proteins, DNA, → DESTRUCTION OF MYOCYTES

Rhabdomyolysis results in muscle cell breakdown, with the **release of toxic contents into the extracellular space and damage to adjacent capillaries, resulting in local edema, increased compartmental pressures, and regional ischemia**, which further induces energy depletion and destroys more capillaries.

See Rosen's Fig 119.2 for a diagram of the pathophysiology.

2) List 8 causes of Rhabdomyolysis

Rhabdomyolysis is classified into four basic pathophysiologic processes:
*1. **Impairment of the muscle's production or use of ATP** at the cellular level. ATP concentrations within the cell fall; energy-dependent mechanisms falter, including Na+,K+, ATPase pumps, leading to disruption of chemical gradients, sarcolemma and cell membrane compromise, and cell destruction.*
*2. **Disruption** in the delivery of oxygen, glucose, and other nutrients to skeletal muscle*
*3. **Increases in metabolic demands** beyond the ability of the organism to deliver oxygen and nutrients*
*4. **Direct myocyte damage***

- Rosen's 9th Edition, Chapter 119

Causes of rhabdomyolysis:

- Prolonged immobilization
- Excessive muscle activity (can be high or low intensity!)
- Muscle ischemia (Rhabdo occurs after reperfusion!)
    - arterial occlusion, carbon monoxide poisoning, and external compression.
        - Muscle cell hypoxia leads to muscle damage in as little as 2 hours, with irreversible anatomic and functional changes within 4 hours and muscle necrosis in as little as 6 hours.
- Temperature extremes
    - A core body temperature of 42°C (107.6° F) for more than 45 to 60 minutes leads to cellular damage.
    - Heat stroke, neuroleptic malignant syndrome, and malignant hyperthermia
    - hypothermia causes sarcolemma membrane dysfunction - e.g. post-cardiac arrest cooling
- Electrical current
    - High-voltage electrical injury, including lighting, poses the highest risk.

    - Post-repeated cardioversion
- Electrolyte abnormalities
    - hypoK+
    - hypoPhos
    - HypoNa+ / HyperNa+
- Illicit drugs
    - opioids, antipsychotics, benzodiazepines, amphetamines, ecstasy, LSD, and synthetic cannabinoids
    - Due to: immobilization with muscle tissue hypoperfusion and hypoxia, psychomotor agitation, direct myotoxicity, and electrolyte abnormalities, particularly hypokalemia and hypophosphatemia.
- Medications
    - Statins
    - Antipsychotics
- Infections
    - Any infection
    - Most common: Sepsis (esp due to legionella), influenza A.
- Metabolic myopathies
    - Inborn errors of metabolism - appear in children
- Connective tissue disorders
    - polymyositis, dermatomyositis, and Sjögren's syndrome.
- Rheumatologic disorders - SLE
- Endocrine disorders - hypothyroidism
- Biologic toxins
    - Snakebite, Africanized bees, wasps and honey bee envenomations are known to release myotoxic agents causing rhabdomyolysis.
- Other + unknown
    - Post-succinylcholine, post caffeine overdose, and others!

Simpler mnemonic for causes of rhabdomyolysis: **"Dead MUSCLE"**

- Drug use
- Medications - Rx
- Unconscious - muscle compression
- Snake bites
- Convulsions - seizures, overexertion
- L
- Electrocution

3) List 6 metabolic derangements associated with Rhabdomyolysis

- **Hyperkalemia**
  - 98% of potassium is intracellular
  - Necrosis of 100g of muscle can lead to serum potassium increase of 1 mmol/L
- **Metabolic acidosis**
  - Dehydration, myoglobin induced kidney dysfunction
  - Metabolic acidosis is also induced by the release of organic acids (eg, lactic acid, uric acid, sulfur-containing proteins).
- **Hyperphosphatemia**
  - From muscle cell destruction
- **Early hypocalcemia** (calcium phosphate crystal deposition in the muscle cells)
  - → **late hypercalcemia** (as the cytoplasm of necrotic muscle cells gets extruded into the circulation)
- **Hyperuricemia**
- **Hypoalbuminemia**
- **Anemia**
- **Hypovolemia**
  - Fluid moves from intravascular compartments into damaged muscle, causing profound intravascular volume depletion. This shift may exceed 15 L.
- **Hepatic dysfunction:**
  - The cause of this finding is not fully understood, but proteases released by muscle cells have been implicated. However, aspartate transaminase level elevations may also be of skeletal muscle origin.

4) List 5 causes of pigmenturia

When serum myoglobin concentrations exceed 0.3 mg/L and the renal threshold of 1.0 mg/dL is met, this reabsorptive capacity is overwhelmed, and excess myoglobin appears in the urine. This myoglobin is detected by urine dipstick as positive for blood. **- Rosen's 9th Edition, Chapter 117** However, on urine microscopy - few if any red blood cells will appear

[See Rosen's Table 119.1 for full details]

Cause	Results for blood in urine	Sediment	Supernatant
Hematuria	+++	Red	Yellow
Myoglobinuria	+++	Normal	Red to brown
Hemoglobinuria	+++	Normal	Red to brown
Porphyria	-	Normal	Red
Bile pigments	-	Normal	Brown
Food and drugs	-	Normal	Red to brown

Foods and drugs that can cause red urine include beets, blackberries, rhubarb, food colouring, fava beans, phenolphthalein, nifampin, doxorubicin, deferoxamine, chloroquine, ibuprofen and methyldopa

Because it is only detectable early in the course of disease, the absence of plasma or urine myoglobin does not rule out rhabdomyolysis (peaks in the first 12 hrs).

Note that the differential diagnosis of blood positive urine dipstick excludes: porphyria, bile pigments, and food/drug causes.

5) List 4 treatments of Rhabdomyolysis

Management of rhabdomyolysis focuses on treatment of the cause, prevention of renal failure, and management of life- or limb-threatening complications.

Four treatments:

1. **Fluid replacement / resuscitation**
    a. If using normal saline - watch for hyperchloremic metabolic acidosis
    b. Lactated ringers may be more physiologic in large volumes
    c. IV fluid administration should be continued until the plasma CK concentration decreases to less than 1000 U/L. A total of 10 to 20 L of IV fluid is often administered in the first 24 hours, depending on the severity of illness and underlying comorbidities
    d. Goal is at least 300 ml/hr of urine output in the average adult
2. **Urinary alkalinization -** urine pH goal > 6.5 { NOT a proven therapy}
    a. alkalinization inhibits redox cycling of myoglobin and lipid peroxidation. However, the clinical benefits of alkalinization compared with simple saline volume repletion are not firmly established, and sodium bicarbonate therapy has not been proven necessary or superior to normal saline diuresis at increasing urine pH.
3. Mannitol: {NOT a proven therapy}
    a. Shown to be helpful in animal studies
    b. In human studies, the addition of mannitol has not been shown to be more beneficial than fluid expansion alone, and no randomized controlled trials have shown any beneficial effect.
    c. Do NOT use:
        i. Lasix
        ii. Acetazolamide
4. *Continuous renal replacement therapy*
    a. indications for emergent dialysis or filtration remain uncorrectable metabolic acidosis, life-threatening hyperkalemia and other electrolyte disturbances despite medical management, manifestations of uremia, and anuria or oliguria, despite volume expansion with complications related to fluid overload.

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Rhabdomyolysis, when recognized and treated early, carries an excellent prognosis. With the exception of hyperkalemia-related death or the rare complication of DIC, acute kidney injury is the most serious complication of rhabdomyolysis, regardless of cause. **- Rosen's 9th Edition, Chapter 119**

The definitive diagnosis of rhabdomyolysis is reliably made by serologic testing for creatine kinase (CK). This test can assist the clinician in assessing at-risk patients when historical and examination findings are lacking. **Elevated levels of CK are the hallmark of rhabdomyolysis.**

CK has a half-life of 1.5 days; its level elevated in the first 12 hours, peaks during the first 3 days, and normalizes at around 5 days after injury.

A CK level five times the upper limit of normal (≈1000 U/L), without apparent cardiac or brain injury, confirms the diagnosis.

Wisecracks

1) What is the pathophysiology of pigment nephropathy?

Myoglobin is a dark red protein composed of globin and a molecule of heme. Its normal function is to supply oxygen to skeletal and cardiac muscle in times of need (it stores oxygen in the muscle cells). The excretion of myoglobin occurs renally. **- Rosen's 9th Edition, Chapter 119**

The pathophysiologic process of myoglobinuric acute kidney injury are:

1. myoglobin cast formation in the **distal convoluted tubules** (in an acidic environment, myoglobin precipitates with uric acid to form obstructive casts)
2. Direct cytotoxic action of myoglobin on the **epithelial cells of the proximal convoluted tubules**
    a. *Myoglobin itself has been shown to exhibit peroxidase-like enzyme activity. Ferrihemate causes direct nephrotoxic effects along with the resultant increased oxidative stress within the tubular epithelial cell, leading to* ***acute tubular necrosis through lipid, protein, and DNA peroxidation.***
3. **intrarenal vasoconstriction and ischemia** (dehydration)
    a. Fluid shifts and renal dysfunction lead to activation of the renin-angiotensin-aldosterone system and sympathetic nervous system and production of vasoconstricting molecules such as endothelin 1 and vasopressin. There is also decreased production of vasodilatory prostaglandins.

2) How is pigment nephropathy in the setting of rhabdomyolysis managed?

The CK level *should be used as a* ***diagnostic marker for rhabdomyolysis*** *and not as a prognostic indicator of acute renal injury.*

Once the diagnosis is made, the eGFR can be used to predict renal injury and determine the need for admission;

Management of rhabdomyolysis focuses on treatment of the cause, prevention of renal failure, and management of life- or limb-threatening complications. **- Rosen's 9th Edition, Chapter 119**