RHABDOMYOLYSIS

The dissolution or disintegration of striated muscle causing a clinical/biochemical syndrome resulting from the release of intracellular contents into the extracellular fluid and circulation.

The diagnosis of rhabdomyolysis rests on measurement of these released substances in either plasma or urine. The classic presentation includes symptoms of myalgias, weakness, red to brown urine due to myoglobinuria, and elevated serum muscle enzymes, such as creatine kinase (CK). The spectrum of disease severity ranges from an asymptomatic elevation of muscle enzymes to life-threatening electrolyte imbalances, acute renal failure, multiorgan failure and death.

Acute renal failure (ARF) is one of the most serious complications of rhabdomyolysis & the presence of ARF is associated with multisystem organ failure and a higher mortality rate.

Principles of Disease.

Recall function & physiology of skeletal muscle (sarcolemma, sarcoplasmic reticulum, Na-K ATPase, calcium fluxing [calcium-induced Ca2+ release] etc).

Myoglobin is the major heme protein supplying oxygen to skeletal and cardiac muscle.

- Under normal circumstances, plasma myoglobin is bound to haptoglobin and the concentration is low.
- When >100g of skeletal muscle is damaged, serum haptoglobin-binding capacity is exceeded, and “free” myoglobin is filtered by the glomerulus, producing the classic dark-colored urine of rhabdomyolysis.
- When myoglobin precipitates in the glomerular filtrate, it causes renal tubular obstruction and ARF.

Pathophysiology.

The final common pathway involves damage to the sarcolemma resulting in;

- A rise in the intracellular calcium
- Liberation of intracellular contents [myoglobin, AST, LDH, CK, potassium, uric acid, and phosphorus].

Direct cellular membrane damage (e.g., crush injury) or ATP depletion results in loss of the ionic gradients created by the sodium-potassium pumps and the sodium-calcium channels.

- Membrane damage from direct trauma makes the sarcolemma more permeable to calcium, which follows the electrochemical gradient and travels into the cell.
- This causes extracellular hypocalcemia and intracellular hypercalacemia.

In atraumatic rhabdomyolysis, lack of adequate ATP causes membrane ion pump dysfunction, which also results in excess intracellular calcium accumulation.

- ATP depletion may result from an imbalance in energy (supply vs demand) [eg. prolonged or vigorous exercise]
- Defect in energy use [McArdle's Syndrome].

Once myocyte destruction begins, myoglobin is released and excess is filtered by the kidneys.

- Excess myoglobin, when coupled with hypovolemia and acidosis, can precipitate and block renal tubular flow.
- Tubular obstruction is part of the pathology;
    - Myoglobin may be toxic to tubules
    - There may be secondary toxic injury from dissociative by-products of the myoglobin itself.

Acute intrinsic renal failure (AIRF) is defined as a decrease in the glomerular filtration rate caused by a toxic or ischemic event that is not reversed on discontinuation of the insult.

BOX 125-1 DIAGNOSTIC PARAMETERS IN ACUTE RENAL FAILURE AND ACUTE INTRINSIC RENAL FAILURE

Odorless urine
Specific gravity <1.015
Urine sediment: "dirty" brown, granular casts
Urine osmolarity <350 mOsm/L
U/P osmolarity ratio <1.1
Urine sodium >20–40 mEq/L
U/P urea <4
U/P creatinine <20
Renal failure index: U_{Na} > 1–2
Fractional excretion of filtered sodium >1–20%
Free water clearance: rising to >15 mL/hr

Compartment syndrome may be a cause or a complication of rhabdomyolysis. Once established, compartment syndrome tends to be self-sustaining because;

1. Capillaries become occluded as a result of the increased pressure
2. venous pressure increases, further decreasing perfusion pressure
3. arteriolar vasospasm leads to tissue ischemia, swelling, and edema.

In 2-4 hours, ischemic skeletal muscle may develop functional deficits, which may become irreversible after 10 hours. Within 30 minutes of ischemia, nerve tissue exhibits reversible deficits that may become permanent after 12-24 hours of ischemia.

Aetiology.

BOX 125-2 GENERAL CAUSES OF RHABDOMYOLYSIS

Metabolic myopathies
Drugs and toxins
Trauma and compression
Infections
Exertion
Electrolyte abnormalities
Electrical current
Hypoxia
Hyperthermia
Idiopathic

In addition to trauma and compression, exercise, alcohol, drugs, infections, and seizures are the leading causes of rhabdomyolysis. Generally, the aetiology is multifactorial.

Metabolic Myopathies.

- Specific genetic disorders do not allow for appropriate use of CHO & lipids as energy substrate, resulting in ATP depletion.
- Can result in recurrent & reversible episodes of rhabdomyolysis or progressive weakness.
- Should be considered when no obvious precipitate can be found; or with significant muscle cramps or exercise intolerance.

Trauma & Compression.

- Most frequent cause of death following earthquakes (other than direct trauma itself).
- Direct mechanical trauma disrupts sarcolemma homeostasis.
    - Abrupt rise in intracellular calcium activates enzymes that are destructive to the cell and sarcolemma.
    - Water influx (following concentration gradient) contributes to intravascular volume depletion.

Exertion.

- Results from prolonged or strenuous exercise and is seen in both trained and untrained athletes.
- Hot conditions contribute to the incidence because of increased dehydration and increased activity of heat-sensitive degradative enzymes.
- Compounded by *hypokalaemia.* (limits vasodilatation)
- Associated with other conditions including status epilepticus, myoclonus, dystonia, chorea, tetanus, psychotic agitation, and mania.

Electrical Current.

- Occurs in ~10% of patients who initially survive a high-voltage electrical injury or lightning strike.
- Severity of rhabdomyolysis is not related to the size of the wound or the site of entry.
- A result of both the heat & current.

Heat & Cold Injury.

- Sarcolemma disruption as a result of elevated core body temperature.
- Occurs with NMS, malignant hyperthermia & classic/exertional heatstroke.
- Elevated cellular energy demands outstrip energy supply leading to membrane dysfunction and cellular injury.
- Hypothermia can cause rhabdomyolysis by cold-induced injury & direct trauma.

Drugs & Toxins.

- Almost any class of drug can result in rhabdomyolysis.
- Common offenders include ethanol, cocaine (& other illicit drugs), lipid-lowering agents, carbon monoxide and biologic toxins.
- *Ethanol:*
    - Directly toxic to skeletal muscle tissue.
    - Compounded by electrolyte disturbance & direct cell injury that occurs as a result of CNS depression/obtundation.
- *Cocaine:*
    - Several proposed mechanism including cocaine-induced vasospasm, excessive energy demands & direct toxic effects.

    - Generally, the severity of the rhabdomyolysis mirrors the severity of the intoxication.
    - IV is worse than inhalational route.
- *Other illicit drugs:*
    - Generally occurs due to agitation & delirium with associated excessive muscle contraction.
- *Lipid-lowering Agents.*
    - HMG-CoA reductase inhibitors are the main culprit. (the Statins)
    - Mechanism is unclear.
    - Patients with preexisting renal dysfunction, hypothyroidism & inflammatory myopathies may be at greater risk.
    - Again, compounded by dehydration and hypokalaemia.
- *Carbon Monoxide.*
    - Pathophysiology is unknown, but hypoxia, muscle compression from coma, and direct myocyte toxic effects may play a role.
- *Biological Toxins.*
    - Snake envenomation (myotoxins) cause rhabdomyolysis via direct myocyte injury (particularly the *brown* & *tiger* snakes of Australia)
    - Mushroom poisoning can result in rhabdomyolysis also.

Infections.

- Bacterial, viral, and parasitic infections have been associated with rhabdomyolysis.
    - Viruses associated include influenza, coxsackie, parainfluenza, adenovirus, HSV, EBV, CMV & HIV.
    - Typically there is a viral illness 1-2 weeks prior to myalgias & myoglobinuria.
    - Bacteria cause muscle damage via multiple mechanisms including direct muscle infection (pyomyositis), exotoxins and cytokines.
    - Of parasitic infections, falciparum malaria is the most notorious cause.

Electrolyte Abnormalities.

- A variety of electrolyte abnormalities particularly hypophosphataemia & hypokalaemia have been linked with rhabdomyolysis.
    - Low *phos* likely results in low ATP levels.
    - Potassium is a vasodilator and low K likely reduces flow in microcirculation.
- Other associated electrolyte disturbances include hypocalcaemia as well as hyper & hyponatraemia.

Hypoxia & Ischaemia.

- Intravascular injury or obstruction, hypotension & external compression of the blood supply to a muscle may all cause tissue hypoxia and subsequent rhabdomyolysis.
- When reperfusion occurs extruded intracellular contents are released into circulation (this includes myoglobin).
- Vascular thrombosis can also occur with *sickle cell disease.*

Clinical Features.

Classic presentation involves muscles pain, weakness & tea-colored urine.

- Myalgias can be focal or generalized.

History.

- Can be incredibly unhelpful.
- Thorough exposure/environmental/toxicology and medication Hx are all required.

Physical Examination.

- Muscles weakness & tenderness on palpation.
    - Sensory & motor deficits will not follow a peripheral nerve distribution.
- Respiratory failure can occur with diaphragmatic involvement.
- Assess for volume status & degree of dehydration
- Assess for possible compartment syndromes.

Diagnostic Strategies.

- **Myoglobin;**
    - Serum myoglobin is an insensitive marker for rhabdomyolysis
        - Can be completely cleared from plasma in 6 hours following injury.
    - Urinary myoglobin is very similar and is also insensitive.
        - Can be absent in late presentations.
    - Urinalysis will demonstrate dark urine which is positive for blood.
        - Few to no RBCs on microscopy however.
- **Creatinine Kinase.**
    - Much more sensitive than myoglobin.
        - Easily measured
        - Levels climb quickly after muscle injury
        - Half life of 1.5 days ensures few false negatives.
    - Whilst no actual CK level is deemed *diagnostic* of rhabdomyolysis
        - Levels 5x normal suggest the pathology
        - > 16,000 are predictive of ARF.
    - Patients can still have severe pathology with only modest CK levels.
- **Other tests;**
    - Full electrolyte screen:
        - Potassium, phosphate, calcium & uric acid.
        - Most common electrolyte abnormality is hypocalcemia
            - occurs early
            - exacerbated by hyperphosphatemia.
    - Coagulation profile:
        - DIC is common.
        - Thrombocytopenia, prolonged PT, hypofibrinogenemia and elevated D-dimer.
    - Elevated AST, ALT & LDH are also associated (from skeletal muscle & not liver injury)

BOX 125-3 DIFFERENTIAL DIAGNOSIS OF PIGMENTURIA

Hemoglobinuria
Hemolysis
Hematuria
Renal causes
Trauma
Acute Intermittent Porphyria
Bilirubinuria
Food
Beets
Drugs
Vitamin B_{12}
Rifampin
Phenytoin
Laxatives

Differential Diagnoses.

Complications.

Early (within 24 hours)

- Electrolyte disturbances
- Hepatic dysfunction (occurs in 25%)

Later (24-48 hours)

- DIC
- Renal failure

Compartment syndrome can occur early (usually from traumatic injury itself) or late (example after copious IV fluids).

Management.

- Resuscitation and stabilization.
- Identify & treat underlying cause
- Avoidance and management of complications.

Saline infusion.

- The mainstay of therapy often requiring large volumes.
  - Delays in fluid administration is associated with development of ARF and oliguria.
- Fluid is sequestered in necrotic muscle and contributes to intravascular hypovolemia and prerenal renal failure.
- Target a urine output of 200-300mL/hour.

Mannitol.

- Though to have benefit as a volume expander and osmotic diuretic.
- Controversial with little supportive evidence.

Urine Alkalinisation.

- Myoglobin precipitation is enhanced in acidic conditions
- Urine alkalinization theoretically facilitates renal myoglobin clearance by increasing its solubility
- Goal is to keep urine pH > 6.5
  - Typically be adding bicarbonate to IV fluids
  - Bicarbonate can result in hypernatraemia & can precipitate fluid overload.
- Evidence is not supportive of its use.

General Measures.

Hyperkalemia

- potentially life-threatening complication of rhabdomyolysis and must be treated
- intravenous calcium may be ineffective as a treatment for hyperkalemia if given to the patient with hyperphosphataemia.
- Hyperkalaemia can be treated with alternate means; insulin/dex, resins, bicarbonate

Correction of the initial hypocalcaemia can exacerbate the delayed hypercalcaemic response.

- Better to withhold calcium in the asymptomatic hypocalcaemic patient

Symptomatic hypercalcaemia can be usually treated with volume expansion & diuresis.

DIC.

- Treat precipitant
- Targeted reversal of coagulopathy (platelets, FFP, fibrinogen)

Compartment Syndrome.

- Fasciotomy should be strongly considered if compartment pressure exceed 30-35 mmHg.

Disposition.

There is no good data on standardizing the approach to rhabdomyolysis.
Most patients require admission to hospital and monitoring for complications.