rhabdomyolysis [created by Paul Young 20/12/07]

general

- The term rhabdomyolysis refers to disintegration of striated muscle, which results in the release of muscular cell constituents into the extracellular fluid and the circulation. One of the key compounds released is myoglobin, an 18,800-Dalton oxygen carrier.
- Normally, myoglobin is loosely bound to plasma globulins and only small amounts reach the urine. When massive amounts of myoglobin are released, the binding capacity of the plasma protein is exceeded. Myoglobin is then filtered by the glomeruli and reaches the tubules, where it may cause obstruction and renal dysfunction.
- The degree of rhabdomyolysis that can manifest ranges from a subclinical rise of creatine kinase (CK) to a medical emergency comprising interstitial and muscle cell oedema, contraction of intravascular volume, and pigment-induced acute renal failure.

compartment syndrome

- Most striated muscles are contained within rigid compartments formed by fasciae, bones, and other structures. If the energy-dependent transcellular pump systems fail in the traumatized tissue, the muscle cells swell.
- As a result, intracompartmental pressure rises and may occasionally reach excessive values. High intracompartmental pressure provokes additional damage and necrosis. Because such compartments are noncommunicating, closed systems, the only way to decrease the pressure is to decompress the fascial system surgically by fasciotomy.

- Prolonged pressure may provoke irreversible paralytic damage to the peripheral nerves. It is generally accepted that compartment pressures >30 mmHg produce clinically significant muscle ischemia. In hypotensive patients, even lower compartment pressures will cause perfusion problems.
- The measurement of intramuscular pressure provides an objective parameter for the decision to perform fasciotomy. In nonhypotensive patients, this should be done when the intramuscular pressure exceeds 50 mmHg or if pressure values between 30 and 50 mmHg show no tendency to decrease after a maximum of 6 h.

metabolic derangements during the course of rhabdomyolysis

- Release of constituents of necrotic muscle results in altered plasma concentrations of several anorganic and organic compounds, which are responsible for toxic and sometimes life threatening complications. The accumulation of these compounds is aggravated by the simultaneous development of renal failure.
- Necrosis of the muscles, together with inflammation, results in the accumulation of substantial amounts of fluid in the affected limbs (up to 10 L per limb). Unless large amounts of volume are administered, shock, hypernatremia, and deterioration of renal function will supervene.

- Release of organic acids from dying muscle cells provokes high anion gap acidosis. In particular, hypoxic muscles release lactic acid into the circulation.
- The lower urinary pH and intratubular acidosis will facilitate intratubular precipitation of myoglobin and uric acid.

- During the early stages of rhabdomyolysis, calcium accumulates in the muscles. Sometimes massive calcification of necrotic muscles or even heterotopic ossification is seen. In the presence of hyperkalemia, severe hypocalcemia may lead to cardiac arrhythmia, muscular contraction, or seizures.
- During later stages of the disease, the accumulated calcium is released from the storage sites. This is often associated with hyperparathyroidism and hypervitaminosis D, and overt hypercalcemia. However, the hyperparathyroidism and hypervitaminosis D are not seen in all cases

- In patients with massive breakdown of muscles, substantial amounts of potassium are released into the blood. Elimination via the kidneys fails if patients have ARF. Frequently, hyperkalemia in patients with rhabdomyolysis is life-threatening, requiring immediate treatment. In nontraumatic rhabdomyolysis, hyperkalemia is not consistently present at the time of admission.

- Nucleosides are released from disintegrating cell nuclei into the blood and metabolized in the liver to purines such as xanthine, hypoxanthine, and uric acid, among which the latter may contribute to tubular obstruction.

diagnosis

- Myoglobinuria does not occur without rhabdomyolysis, but rhabdomyolysis not necessarily results in visible myoglobinuria
- During rhabdomyolysis, extreme quantities of CKMM are released and peak concentrations of 100,000 IU/ml or more are not unusual. Because overall degradation and removal are slow, the concentration of CK remains elevated much longer and in a more consistent manner than that of myoglobin.
- Consequently, CK is more reliable than myoglobin in assessing the presence and intensity of damage to the muscles.

treatment

general
- The primary therapeutic goal is to prevent the factors that cause ARF, i.e. volume depletion, tubular obstruction, aciduria, and free radical release.
- Once overt renal failure has developed, the only reliable therapeutic modality is extracorporeal blood purification.

(i) iv fluids
- Hypovolemia may result from sequestration of water by muscles and must be prevented by the aggressive administration of intravenous fluids. To obtain volume equilibrium, the amount of fluid required is as high as 10 L or more per day.

(ii) sodium bicarbonate
- sodium bicarbonate helps to correct the acidosis induced by the release of protons from damaged muscles, to prevent precipitation of myoglobin in the tubules, and to reduce the risk of hyperkalemia.

(iii) mannitol
- mannitol may be added to the fluid regimen serves several potential purposes:

(1) mannitol increases renal blood flow and GFR;
(2) mannitol is an osmotic agent that attracts fluid from the interstitial compartment, thus counterbalancing hypovolemia and reducing muscular swelling and nerve compression;
(3) mannitol is an osmotic diuretic that increases urinary flow and prevents obstructive myoglobin casts; and
(4) mannitol scavenges free radicals.

(iv) Loop diuretics (furosemide and bumetanide)
- increase tubular flow and decrease the risk of precipitation of myoglobin, while simultaneously acidifying urine and increasing calcium losses.

(v) Allopurinol
- may be useful because it reduces the production of uric acid and also acts as a free radical scavenger

(vi) Hyperkalaemia
- An important therapeutic goal is control of hyperkalemia.

(vii) Renal replacement therapy
- Once acute renal failure has been established, or severe hyperkalemia and acidosis are present, the patient requires dialysis. Fluid overload is a rare indication to start dialysis,because patients tend to be dehydrated due to massive fluid accumulation in the damaged muscle.
- Removal of myoglobin by plasma exchange has no demonstrated benefit

aetiology

- Physical causes
  - trauma and compression
    - traffic or working accidents
    - disasters
    - torture
    - abuse
    - long-term confinement to the same position
  - occlusion or hypoperfusion of the muscular vessels
    - thrombosis
    - embolism
    - vessel clamping
    - shock
  - strainful exercise of muscles
    - exercise
    - epilepsy
    - psychiatric agitation
    - delirium tremens
    - tetanus
    - amphetamine overdose
    - ecstasy
    - status asthmaticus
  - electrical current
    - high-voltage electrical injury
    - lightning
    - cardioversion
  - hyperthermia
    - exercise
    - high ambient temperatures
    - sepsis
    - neuroleptic malignant syndrome
    - malignant hyperthermia
- Nonphysical causes
  - metabolic myopathies
    - McArdle disease
    - mitochondrial respiratory chain enzyme deficiencies
    - carnitine palmitoyl transferase deficiency
    - myoadenylate deaminase deficiency
    - phosphofructokinase deficiency
  - drugs and toxins
    - regular and illegal drugs (see Table 2)
    - toxins
      - snake and insect venoms
      - buffalo fish (United States), burbot (Northern Europe)—Haff disease
  - infections
    - local infection with muscular invasion (pyomyositis)
    - metastatic infection (sepsis)
    - systemic effects
      - toxic shock syndrome
      - *Legionella*
      - tularemia
      - *Salmonella*
      - falciparum malaria
      - influenza
      - HIV
      - herpes viruses
      - coxsakievirus
  - electrolyte abnormalities
    - hypokalemia
    - hypocalcemia
    - hypophosphatemia
    - hyponatremia
    - hypernatremia
    - hyperosmotic conditions
  - endocrine disorders
    - hypothyroidism
    - diabetic coma, related to electrolyte disturbances
  - polymyositis/dermatomyositis

differential diagnosis

causes of red discolouration of urine

- Myoglobinuria
  - rhabdomyolysis
    - traumatic
    - nontraumatic
  - Hemoglobinuria
    - hemolysis
      - mechanical damage
      - immunologic damage
      - structural fragility of erythrocytes
      - microangiopathy
  - Hematuria
    - renal causes
    - postrenal causes
  - External factors
    - red beets
    - drugs
      - vitamin B12
      - rifampicin
      - phenolphthalein
      - phenytoin
    - metabolites
      - bilirubin
      - porphyrin

pathophysiology of myolysis

changes in cellular metabolism
- Stretching or exhaustive work of muscle cells increases sarcoplasmic influx of sodium, chloride, and water, which results in cell swelling and autodestruction. Calcium entersthe cell, in exchange for intracellular sodium. Large quantities of free calcium ions trigger persistent contraction, resulting in energy depletion and cell death.

Reperfusion Injury
- In ischemic tissue injury (e.g., myocardial infarction, acute renal failure), most of the damage is not inflicted during the period of ischemia, but after the blood flow into the damaged tissue is restored (reperfusion injury).
- In the case of traumatic rhabdomyolysis, the muscles are initially compressed and ischemic, and muscle dysfunction starts to develop only when the patient is evacuated, i.e., when perfusion of the damaged muscles is restored.

pathophysiology of ARF

- The pathophysiology of myoglobinuric ARF has been studied extensively in the animal model of glycerol-induced ARF. The main pathophysiologic mechanisms are:
(i) renal vasoconstriction,
(ii) intraluminal cast formation, and
(iii) direct heme-protein induced cytotoxicity.