Rhabdomyolysis and Other Causes of Myoglobinuria

Rhabdomyolysis can be defined as a clinical syndrome associated with the breakdown of skeletal muscle fibres and myocyte cell membranes, leading to release of muscle contents into the circulation, resulting in multiple complications, including hyperkalaemia. It is a medical emergency and can lead to cardiac arrest if not promptly treated. Myoglobinuria is an early feature of rhabdomyolysis, but it may be cleared within a few hours despite other sequelae continuing.

Pathophysiology

Myocyte function under normal circumstances is maintained by adenosine triphosphate-dependent channels which ensure effective cell ion levels and play a role in calcium efflux from myocytes.[1] Damage to the myocyte membrane (eg, due to trauma or lack of energy for the cell membrane channels) causes an increase in the amount of calcium in the cell, which leads to apoptosis through various proteolytic enzymes.[1, 2] This leads to the muscle necrosis and the release of various substances into the circulation - eg, myoglobin, potassium, phosphate, creatine kinase (CK) and urate.[3]

The process is self-perpetuating in that damage to muscle cells releases further calcium which can then be taken up by the surrounding myocytes, causing further muscle necrosis and further leakage of ions and proteins into the circulation.[4]

Myoglobin is a skeletal muscle protein involved in metabolism and myoglobinemia usually occurs before a rise in CK in rhabdomyolysis. Any myoglobin that reaches the circulation will be filtered by the kidneys and can lead to acute kidney injury through either direct toxicity or precipitation, or both.[5] This process is facilitated by an acidic environment and hypovolaemia.[1, 2] Myoglobin can appear in the urine (myoglobinuria) causing 'tea-coloured' urine with a positive urine dipstick for blood. The latter can cause confusion with haematuria and haemoglobinuria.

Epidemiology

The exact incidence of rhabdomyolysis varies with the underlying cause, but levels increase with natural disasters - eg, earthquakes and in war zones.[3] Rhabdomyolysis is estimated to account for ~7-8% of all new cases of acute kidney injury.[1]

Aetiology

Any process which leads to muscle necrosis can lead to myoglobinuria and therefore an increased risk of rhabdomyolysis.[2] For example:

- Alcohol abuse.
- Status epilepticus.
- Over-exertion.
- Trauma, burns and compartment syndromes (including major disasters (eg, earthquakes) where a significant amount of muscle injury is likely to occur).
- Drugs.[5] For example: statins, erythromycin, corticosteroids, ecstasy,[6] heroin, cocaine, atropine,[7] ingestion of ethylene glycol and amphetamines (likely to cause muscle necrosis through a number of mechanisms such as, vasospasm).[1]
- Heat stroke.
- Neuroleptic malignant syndrome.
- Myositis and myocarditis.
- Infections, such as influenza virus, Epstein-Barr virus (EBV), streptococcus, legionella and malaria.[8]
- Snake bites - eg, a bite from the sea snake.[9]
- Acute tumour lysis - massive tumour lysis which occurs after starting chemotherapy.
- Hypothyroidism and hyperthyroidism.
- Diabetic ketoacidosis.
- Meyer-Betz disease - muscle pain, weakness and myoglobinuria following strenuous exercise.
- Genetic disorders - eg, abnormalities of lipid metabolism (eg, carnitine deficiency) or abnormalities of carbohydrate metabolism (eg, phosphofructokinase deficiency).

Presentation\(^1\)

Many features are nonspecific and therefore a high index of clinical suspicion is required - eg, elderly patients, history of trauma, history of a fall followed by long duration of lying on the floor.

- There may be features relating to the underlying cause - eg, swollen and painful muscles, paraesthesia of limbs in compartment syndrome or muscle tenderness.
- Nonspecific symptoms - eg, fever, malaise, anorexia, nausea and vomiting.
- Elderly patients may present with confusion, agitation and delirium.
- Patients may be anuric and clinically dehydrated.
- Myalgia and muscle weakness.
- 'Tea-coloured' urine may be present.
- Presenting features may also relate to the release of the intracellular electrolytes, which may be fatal:
  - Increased potassium ions - heart block, ventricular tachycardia, asystole.
  - Decreased calcium ions - may also be associated with arrhythmias and tetany.

- Disseminated intravascular coagulation.

Diagnosis

- This is based on clinical grounds - eg, the supportive case history.
- Urine - ‘tea-coloured’ and positive for blood on dipstick testing. Haemoglobinuria will look similar macroscopically and both will change the common urinalysis dipstick reagent even when there are no RBCs on the microscopy. They can be distinguished by using electrophoresis, spectrophotometry, or other techniques. There are also direct tests for myoglobinuria, such as immunoassays, but as the time course suggests myoglobinuria is present very early, their usefulness may be limited.
- CK - will be raised and may be up to several 10,000s; some argue that for the diagnosis a 5 x baseline or greater increase is needed.\(^2\)
- Electrolytes - high potassium, low calcium, high phosphate.
- Investigations to delineate the underlying cause may be indicated - eg, muscle biopsy and genetic testing in recurrent cases.

Complications

The complications of rhabdomyolysis are the cause of mortality and morbidity in these patients. These include:

- Hyperkalaemia causing arrhythmias and cardiac arrest.
- Hypocalcaemia (worsened by hyperphosphataemia).
- Hepatic abnormalities - but AST may be high representing muscle AST.
- Metabolic acidosis.
- Acute kidney injury from precipitation and obstruction of renal tubules by myoglobinuria and hypovolaemia.
- Disseminated intravascular coagulation.
- Pooling of fluid in the damaged muscle which adds to hypovolaemia and can lead to a compartment syndrome.

There may also be complications resulting from the original insult - eg, burns associated with sepsis. The presence of hyperkalaemia, metabolic acidosis and acute kidney injury are most likely to be associated with higher morbidity and mortality.

Treatment

- Fluid rehydration - needs to be prompt; this is the most important aspect of treatment, as it will lead to less precipitation and toxicity of myoglobin at the kidneys and dilute nephrotoxins.\(^1\)
- Treat hyperkalaemia - calcium gluconate (if indicated) and dextrose-insulin infusions.
- Diuretics - mannitol has been used but its use is contentious. Other diuretics have not been shown to improve renal impairment. Diuretics should not be used until hypovolaemia is corrected.\(^4\)
Alkaline diuresis - alkalinisation of the urine with bicarbonate can reduce the risk of acute kidney injury; however, there is no clear evidence as to its benefit or whether it is any better than simple aggressive hydration with intravenous fluids.\cite{4}

If renal function fails to improve, patients are at risk of acute tubular necrosis, in which case haemodialysis may be necessary.\cite{10}

Hypocalcaemia and hyperphosphataemia need not be corrected unless dangerously low - they improve as CK falls.

Treat the underlying cause if needed.

**Statins and myotoxicity**

- Statins are widely used and their use has been associated with a reduction in mortality and morbidity in ischaemic heart disease and cerebrovascular disease.
- They are associated with muscle aches and pains and can cause myositis and rhabdomyolysis which can be fatal.\cite{11, 12, 13}
- Cerivastatin was the most frequently used statin with associated rhabdomyolysis and was subsequently withdrawn.\cite{14, 15}
- The risk of rhabdomyolysis with statins is increased in the elderly, with use of interacting medications (eg, fibrates) and hypothyroidism.
- If patients on statins develop myositis (muscle pain, muscle tenderness and weakness) or myalgia then the statin should be stopped and CK checked urgently. If CK level is normal, consider changing to another member or restart at a lower dose with cautious monitoring. Presence of rhabdomyolysis will require termination of treatment, and management as described above.

**Further reading & references**

1. Rhabdomyolysis - Resident Grand Rounds; Turner White Communications Inc, Jan 2008

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