Rhabdomyolysis

Rhabdomyolysis is the destruction of a significant amount of striated muscle, leading to disruptions in fluid balance, electrolytes and renal function. It may have either traumatic (such as crush injury) or non-traumatic causes. Diagnosis is typically made through the timely determination of the serum creatine kinase activity in a patient with a suggestive history or clinical features. Treatment is supportive, with generous intravenous hydration and correction of electrolyte abnormalities. Sometimes haemofiltration or dialysis is required, but the renal prognosis is generally good.

The first complete description of rhabdomyolysis was famously made by London physicians Bywaters and Beall, who observed the classic sequence of symptoms in patients extracted from collapsed buildings during the London blitz in 1941, identified the central role of myoglobin in its pathogenesis, and promoted the use of intravenous bicarbonate solutions as a treatment (Bywaters, 1990).

Clinical assessment

The most common cause of rhabdomyolysis worldwide is crush injury (*Table 1*). Typically, the patient has been released from a collapsed building or wrecked car, and may have other injuries. Upon release of pressure, the damaged muscles become oedematous and extract fluid from the circulation, leading to hypotension (Huerta-Alardín et al, 2005; Bosch et al, 2009). Swollen muscles can also lead to compartment syndrome, characterized by severe pain with loss of fine touch and distal perfusion, which can become limb threatening (Warren et al, 2002).

Table 1. Causes of rhabdomyolysis in hospital practice

Prolonged immobilization (elderly, drug abuse, complex surgery)
Crush injury
Prolonged seizures
Strenuous exercise
Statin-related
Infections (cytomegalovirus, Epstein–Barr virus, influenza)
Hyperglycaemic crises (diabetic ketoacidosis and hyperosmolar hyperglycaemic state)
Electrolyte abnormalities (hypokalaemia, hypophosphataemia)

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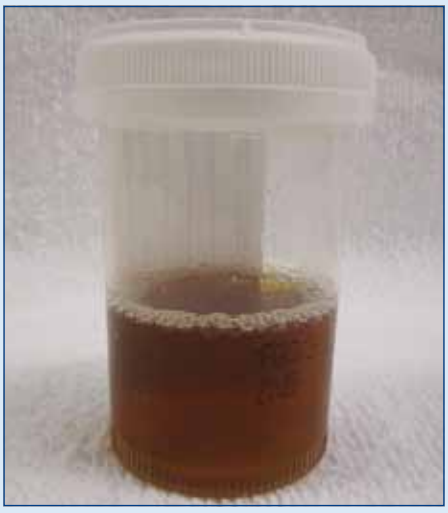
Even in the absence of a history of trauma, people with rhabdomyolysis report myalgia and muscular tenderness, often with varying degrees of muscular weakness (Warren et al, 2002). The various associated electrolyte abnormalities may cause confusion, cardiac arrhythmias and vomiting. The presence of dark brown ('tea-' or 'cola-coloured') urine may have been noted (Huerta-Alardín et al, 2005) (*Figure 1*). Alternatively, urinalysis may show 'blood – lysed' without red blood cells on urine microscopy, as myoglobin reacts with the haemoglobin strip. This occurs in 80% of cases (Bosch et al, 2009).

Symptoms of acute renal impairment, such as oliguria, develop up to 24–48 hours after the original insult (Warren et al, 2002). Other sequelae of rhabdomyolysis include an increased risk of disseminated intravascular coagulation (Warren et al, 2002; Huerta-Alardín et al, 2005).

Some cases of rhabdomyolysis may reflect an underlying myopathy, such as McArdle's disease (glycogen storage disease type V). It is therefore useful to enquire about previous episodes of dark urine or hospital attention after exercise, surgery or illness. Furthermore, a family history may be valuable (Warren et al, 2002).

Figure 1. Tea- or cola-coloured urine is characteristic for myoglobinuria.



Diagnosis

Given that most laboratories do not determine creatine kinase (CK) activity routinely on biochemical samples, the diagnosis needs to be suspected and creatine kinase measurement requested. Elevations of creatine kinase levels above 5–10 times the upper limit of normal are conventionally regarded as diagnostic of rhabdomyolysis, although not all cases of 'hyper-CK-aemia' proceed to significant acute kidney injury (Bosch et al, 2009). The risk of acute kidney injury is low if the creatine kinase activity is only moderately raised, but can be augmented if there are other contributing factors such as sepsis (Bosch et al, 2009). Creatine kinase activity starts falling after several days (Huerta-Alardín et al, 2005). There is little value in determining myoglobin in either urine or serum, because it has a short half life and it does not offer added information in determining disease severity (Rodríguez-Capote et al, 2009).

Once diagnosed, rhabdomyolysis requires ongoing assessment for electrolyte derangements and renal impairment. Hyperkalaemia can be severe, probably because the damaged myocytes release intracellular potassium into the circulation, in addition to the hyperkalaemia one would expect in the context of acute kidney injury (Huerta-Alardín et al, 2005). Hyperphosphataemia, from phosphates released by myocytes, can cause hypocalcaemia by precipitation (Huerta-Alardín et al, 2005). Both hyperkalaemia and hypocalcaemia are associated with arrhythmias, and a 12-lead electrocardiogram and continuous electrocardiogram monitoring may be required.

The renal function may be normal at baseline, and if the patient is otherwise reasonably well it may be appropriate to monitor urine output without an indwelling catheter, although this may still be

required if the renal function deteriorates or there is any doubt about urine output. Oliguria (defined as urine output below 0.5 ml/kg/hour) is an early indication of impaired renal function. Renal function, electrolytes and bone profile should be determined frequently (once or twice daily, depending on suspicion).

Causes

In the majority of cases, the underlying cause of the rhabdomyolysis is quite obvious. The most common causes in hospital practice are related to prolonged immobilization (e.g. elderly patients found on the floor after a fall, intravenous drug users and alcoholics), with a smaller proportion resulting from rarer causes such as prolonged seizures, strenuous exercise, statin use, infections (such as influenza, cytomegalovirus or Epstein–Barr virus), severe hypokalaemia or other electrolyte abnormalities, diabetic ketoacidosis, hyperglycaemic hyperosmolar state, neuroleptic malignant syndrome (Bosch et al, 2009) and inflammatory myositis (dermato- and polymyositis). A comprehensive list of rarer causes can be found in Warren et al (2002).

Statin-associated rhabdomyolysis is uncommon (0.44 cases per 10 000 patient years), but given the widespread use of statins in the population it is certainly encountered in clinical practice. The risk is increased in the elderly (over 80 years of age), women, those with a low body mass index, a background of multisystem diseases, chronic liver and kidney disease, untreated hypothyroidism, co-ingestion of particular drugs (fibrates, ciclosporin, macrolides among others) and dietary substances (grapefruit and cranberry juice). Genetic factors may contribute to the risk. Episodes may be precipitated by exercise, excessive alcohol, an intercurrent infection, major surgery or trauma (Sathasivam and Lecky, 2008).

The risk of rhabdomyolysis is also increased in those with underlying myopathies. Enzyme defects in the muscle energy supply (glycogenolysis, lipid metabolism, mitochondrial enzymes, pentose phosphate pathway, purine nucleotide cycle) can all lead to a lowered threshold for muscle cell damage and events of exertional rhabdomyolysis (Bosch et al, 2009).

Pathophysiology

The initial damage to the myocytes results from either direct trauma to the sarcolemma or interference with intracellular ion channels. Both lead to raised intracellular calcium ions and unremitting contraction, depletion of adenosine triphosphate, and disintegration of the cell. The intracellular milieu is rich in potassium, phosphate, muscle enzymes (such as creatine kinase, lactate dehydrogenase, aminotransferases, aldolase) and the oxygen-carrying haem protein myoglobin. Free phosphate precipitates into insoluble crystals with calcium, leading to calcium depletion. Potassium is redistributed into tissues by the Na/K-ATPase pump, but this may be overwhelmed and lead to hyperkalaemia (Warren et al, 2002). Muscle enzymes are not known to cause significant problems but can be detected in peripheral blood. Finally, myoglobin is the main cause of acute kidney injury in rhabdomyolysis. Capillary leakage into oedematous muscle also depletes fluid, albumin and haemoglobin from the circulation (Warren et al, 2002).

In the kidney, the combination of hypoperfusion as a result of hypovolaemia and the glomerular excretion of myoglobin leads to the formation of granular casts that obstruct flow through the tubules. The glomerular filtration rate is reduced, and oliguria is often present (Bosch et al, 2009). Myoglobin interacts with the Tamm–Horsfal protein, particularly when the urine is acidic and concentrated. A cytotoxic injury occurs at the level of the proximal tubule, while obstruction occurs distally (Bosch et al, 2009).

Management

The management of rhabdomyolysis is supportive, in the sense that there is no way of slowing the muscle cell breakdown. The first priority after ensuring a safe airway and adequate respiratory function is the restoration of circulating volume. In crush injuries, this process should ideally be started even before the patient is extracted to prevent hypotension (Sever et al, 2006), provided venous or interosseous access can be obtained. Irrespective of the cause, adequate hydration should be provided as soon as possible. If compartment syndrome is suspected, timely orthopaedic input is crucial.

The next priority is normalizing the plasma electrolytes. Severe hyperkalaemia, particularly when associated with electrocardiogram changes, requires immediate administration of calcium to prevent arrhythmias, followed by temporizing measures to shift potassium intracellularly. Insulin and dextrose can reliably lower the potassium by 0.6 mmol/litre. High doses of nebulized salbutamol have a similar and additive effect, but are less effective if the patient takes beta blockers, and work in only about 60% of people (Weisberg, 2008). Most benefit is to be expected from increasing urine output. Bicarbonate-containing fluids are of limited benefit over and above other fluids in improving hyperkalaemia (Weisberg, 2008). Very severe hyperkalaemia can be a valid indication for continuous veno-venous haemofiltration on the intensive care unit, or for haemo-dialysis if available (Weisberg, 2008). Correction of mild hypocalcaemia is not always required, and indeed increases the risk of an 'overshoot' hypercalcaemia during the resolution phase of the disease (Huerta-Alardín et al, 2005) and further deposition of calcium-containing crystals in tissues (Bosch et al, 2009).

Intravenous hydration is thought to decrease the risk of myoglobin-associated acute tubular damage and acute kidney injury. In crush injury, a urine output of 300 ml or more is recommended, and volumes of up to 12 litres/24 h may be required (Sever et al, 2006). Given that much of the infused fluid is absorbed by oedematous muscle, a positive fluid balance is almost inevitable (Sever et al, 2006). In hospital practice, where most patients with rhabdomyolysis are older or have multiple comorbidities, such amounts of fluid are likely to be excessive and may lead to fluid overload. If the patient is oliguric, especially after a fluid challenge, or there are concerns about ability to handle large volumes of fluid (e.g. possible history of heart failure or elderly), a central venous pressure line may be useful to guide fluid management (Ramrakha and Moore, 2004). Boluses of fluid are administered while assessing the central venous pressure. If the central venous pressure rises but subsequently falls, the patient is likely to still require further intravenous fluids, while if the central venous pressure remains elevated the

patient is intravascularly fluid replete, and further fluid administration may lead to fluid overload.

There are theoretical reasons why alkalinizing the urine with bicarbonate-containing fluids (e.g. 1.26% $NaHCO_3$) to a urine pH >6.5 may reduce the aggregation of myoglobin in the kidney, but this has not been consistently borne out by clinical studies (Bosch et al, 2009). Most benefit from alkalinization is to be expected in the first few hours of treatment (Ramrakha and Moore, 2004). Bicarbonate solutions have the advantage of containing less chloride compared to normal saline and therefore have a smaller risk of hyperchloraemic acidosis, but bicarbonate can also worsen hypocalcaemia (Bosch et al, 2009).

Many cases of rhabdomyolysis proceed to require renal replacement therapy. The indications for renal replacement therapy are not materially different from any other scenario: refractory hyperkalaemia, severe acidosis, fluid overload or uraemia leading to end-organ dysfunction such as uraemic encephalopathy or pericarditis (Lameire et al, 2005). In a patient who has received large volumes of fluid but remains oliguric or is showing signs of fluid overload, there is a strong temptation to use loop diuretics to drive diuresis; several meta-analyses show no benefit from this approach, and professional recommendations discourage the practice (Joannidis et al, 2010). There is also a concern that furosemide increases myoglobin precipitation in the tubules (Ramrakha and Moore, 2004). Most patients regain their renal function, even after an episode of rhabdomyolysis that has required renal replacement therapy. In a small proportion, the renal function does not recover completely, and some remain dialysis-dependent.

Discharge and follow up

A patient can usually be considered for discharge if there was hyper-CK-aemia but the renal function has remained stable for several days. If there has been acute kidney injury, the decision on discharge depends on a sustained improvement of the renal function and electrolytes and effective treatment of any complications.

If statins were thought to be involved in an episode of rhabdomyolysis, it may still be appropriate to recommence statin therapy, particularly if the risk of cardiovascular disease is deemed high. Many people with statin-induced rhabdomyolysis will tolerate a re-challenge with a statin (even the same agent) at a lower dose (Sathasivam and Lecky, 2008).

In a single episode of rhabdomyolysis with a clear-cut cause (e.g. immobilization as a result of marked inebriation or heat stroke as a result of exercise in the hot weather), no further investigations are required. Repeated episodes in the context of relatively minor insults or exercise, a single episode with no clear explanation, or a strong family history, all warrant investigation by a neurologist with an interest in neuromuscular disease. A muscle biopsy, blood and urine biochemistry, and particular provocation tests (Warren et al, 2002) may assist in diagnosis. If an inflammatory myopathy (i.e. dermatomyositis or polymyositis) is suspected, rheumatology input is required.

Conclusions

Rhabdomyolysis may occur in a proportion of acutely admitted patients, and early recognition and adequate treatment is important in preventing morbidity and mortality. BJHM

Figure 1 *is reproduced courtesy of Dr James Heilman. Conflict of interest: Dr JF de Wolff is one of the main authors of the Wikipedia entry on rhabdomyolysis (en.wikipedia.org/wiki/Rhabdomyolysis).*

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KEY POINTS

- Rhabdomyolysis may result from various insults to striated muscle, such as trauma and prolonged immobilization, as well as various other physical, chemical or biological causes. Muscle breakdown products, particularly myoglobin, can precipitate in the kidney and cause acute kidney injury, and there is a high risk of electrolyte abnormalities.
- The diagnosis is typically made when the history prompts a request for creatine kinase activity. Have a low threshold for doing so in patients with a history of immobilization, myalgias or unexplained acute kidney injury.
- After basic stabilization, correcting electrolyte abnormalities (especially hyperkalaemia) and maintaining an adequate fluid balance are most likely to lead to a good outcome. Sometimes surgical intervention is required for compartment syndrome.
- A proportion of patients need renal replacement therapy for acute kidney injury, but the renal prognosis is good.
- In rhabdomyolysis that is insufficiently explained, recurrent, or associated with a strong family history, further investigations may yield evidence of an underlying myopathy.

TOP TIPS

- In rhabdomyolysis, hyperkalaemia can be disproportionate to the severity of renal impairment.
- Repeat the renal function and electrolytes frequently in someone with biochemical evidence of rhabdomyolysis.
- Think about invasive venous pressure monitoring if the patient is oliguric despite good blood pressure and adequate filling, particularly in those with a background of cardiac failure.