anj clinicalupdate 96
AUGUST 06

By Sharon Wilson

Rhabdomyolysis made easy

About the author

Sharon Wilson is a clinical nurse consultant for surgery at Liverpool Hospital, Sydney, NSW.

Introduction

Rhabdomyolysis results from either a direct muscle injury or a mismatch between energy production and energy consumption. These in turn, result in a breakdown of muscle cells, and a spillage of their contents into the systemic circulation. While numerous causes have been reported for rhabdomyolysis, the most common are likely to be trauma (Walls 2002), drugs, and strenuous exercise (Russell 2005).

One type of exertional rhabdomyolysis is 'white collar rhabdomyolysis', which is observed in people such as physicians, businessmen and attorneys who participate in competitive sports without being adequately conditioned to keep pace with a conditioned athlete (Russell 2005).

The first reported incidence of rhabdomyolysis came from Germany in 1911, with reported symptoms including muscle pain, weakness and brown urine. It was called the Meyer Betz disease (Meyer-Betz 1911). Following the bombing of London in World War II, further cases were reported (Cunningham 1997).

What are the effects of rhabdomyolysis?

Many case studies have revealed rhabdomyolysis most commonly affects the lower half of the body – although a number of authors state many patients have no muscle pain or weakness at all (Rush et al 1999; Baggaley 1997). It also has been reported in polo ponies and race horses (Lane et al 1997).

Incidence of rhabdomyolysis

While few papers discuss rhabdomyolysis, there are several that report incidence. Walls reported 26,000 cases of rhabdomyolysis in the United States annually, with crush injury being the most common cause (Walls 2002). Black and Jick reported an incidence of 25 per 2.5 million people over a nine-year period in the United Kingdom, with 28% of these cases resulting from drug overdose, and 20% attributable to septicaemia (Black et al 2002).

Szewczyk et al conducted a review of the literature over 45 years (1998). They found 44 pressure-induced case studies from their search. The age of the patients ranged from 22-83 years, with most being around 46 years old. There was almost a 5:1 ratio in favour of males. Sixty two per cent of the cases were caused by alcohol or drug overdose, while 27% developed rhabdomyolysis following surgery where patients remained in one position for an average of 7.5 hours. Ninety three per cent of patients developed compartment syndrome in the affected muscles, demonstrating the close relationship between compartment syndrome and rhabdomyolysis.

Lane et al stated there are no prospective studies of the incidence of rhabdomyolysis, and many mild cases go unrecognised (Lane et al 2003).

Rhabdomyolysis – the disease process

Rhabdomyolysis has been broken down by some authors into four stages (Russell 2005).

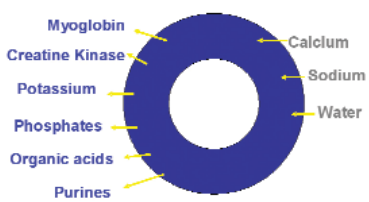

Figure 1. Damaged muscle cell

Stage one is the primary injury. This could be a motor vehicle accident which causes direct muscle injury, although there are other ways in which this disease can begin. Toxins can be released into the body following a snake bite; or muscle compression during an overdose can also cause primary injury. The other principle cause is when the energy supply to a muscle runs out during a tonic-clonic seizure for example, or during a marathon when the body has exhausted its energy supply and muscle starts to break down.

In stage two, normal function is disrupted in muscle cells. Energy for cellular function

is normally derived through aerobic (where glucose is broken down into CO2 and H2O giving rise to energy) or anaerobic (glycolysis) cellular metabolism.

Failure of this process leads to muscle cells leaking required elements (including potassium and phosphates) and permitting the entry of calcium, sodium and water from the blood supply (see figure 1).

In stage three, the side effects of this disruption can be seen as the muscle cells swell due to increased water uptake. Together with the resulting interstitial oedema, the patient develops third spacing, and hypovolaemia.

The resulting damage to the cell leads to further functional impairment at the cellular level, ultimately leading to cell death.

During this time, the intracellular contents leak into the blood stream causing systemic disruption.

Stage four is the final stage of the cascade, when the muscle cell death and systemic complications may lead to renal dysfunction (Russell 2005).

Clinical manifestations

Some patients do not initially have symptoms (Rush et al 1999). Others have muscle pain, weakness, tenderness, stiffness, and sometimes contractures. They can also have decreased tendon reflexes and a 'doughy' feeling in those muscles involved (Walls 2002).

Blood tests reveal elevated creatinine kinase (CK) levels. Other symptoms may include general malaise, fever, tachycardia, nausea, vomiting, agitation, confusion, decreased level of consciousness and low urine output. Most of these symptoms are due to muscle cell breakdown and its systemic effects and electrolyte abnormalities (Meister et al 2002). There have also been reports of soft tissue calcification on x-ray (Dhawan et al 1997).

The patient may be oliguric or anuric and have myoglobin in their urine. This causes the urine to become reddish-brown.

Myoglobinuria however, is dependant on four main conditions:

1. Plasma level of myoglobin. If there has been a large release of myoglobin from the cells, then there is a higher chance of myoglobin presenting in the systemic circulation and the urine.
2. Extent of plasma protein binding of myoglobin. Proteins are large, and are unlikely to be able to pass through the glomerular capillaries of the nephron in the kidney. So the more proteins binding to the myoglobin, the more likely they are to stay in the systemic circulation, and the less often myoglobin in the urine is seen.
3. Glomerular filtration rate. If the rate is slow, then the substances will not get pushed (by circulating pressure) through the filter of the nephron, and will end up back in the circulating blood volume. Hypovolaemia can decrease the filtration rate.
4. Rate of urine flow. If the patient is not passing urine, then the presence of myoglobin is unable to be detected.

It is therefore important to remember that an absence of myoglobinuria does not eliminate a diagnosis of rhabdomyolysis. In one study, 26% of patients had no myoglobin on microscopy (Dhawan et al 1997). However, all patients with myoglobin in their urine had rhabdomyolysis (Szewczyk et al 1998). So although a patient may have rhabdomyolysis without myoglobin in their urine, if myoglobin is detected in their urine it is likely that they have rhabdomyolysis.

Diagnosis

Most agree that clinical history and manifestations make the diagnosis, but these must be supported by laboratory studies (Russell 2005). The rationale for this is that reddish-brown urine may be due to haematuria, and CK elevation could be muscle damage other than skeletal muscle.

In cases of myoglobinuria, urinalysis is positive for blood and has an acid pH, but when sent to the laboratory, no red blood cells are evident (Lane et al 2003).

CK elevation five times the normal value is an indicator that rhabdomyolysis is likely, although many agree that an elevation of 2-3 times the normal limit should prompt further investigation (Meister et al 2002). CK tests may be repeated every 6-8 hours during the acute phase. It usually rises 2-12 hours after injury, peaks at 1-3 days and declines after 3-5 days (Dhawan et al 1997).

Lappalainen et al (2002) have suggested looking at serum myoglobin, instead of CK, however this was a small study (13 patients), and this suggestion has not been widely embraced.

Treatment

Mainstream treatment is fluid replacement. The consensus seems to be normal saline or crystalloid solution and therapy should be set to achieve 200mLs urine output per hour (Saad 1997; Cohen et al 1997), although some recommend at least 300mLs/hr until myoglobinuria has ceased (Walls 2002; Meister et al 2002). Boluses of crystalloid solution assist in maintaining circulating blood volume, increased renal perfusion and flushing myoglobin through the renal tubules.

The use of Mannitol (an osmotic diuretic that preserves intravascular volume, while flushing out cellular debris by vasodilating the kidneys) is controversial (Cohen et al 1997). Administering this osmotic diuretic without volume replacement might worsen hypovolaemia (Saad 1997).

Frusemide is a well known loop diuretic that can assist in promoting diuresis, however it acidifies the urine (Cohen et al 1997). Acidic urine can make the renal tubule injury worse. Use of this drug, like Mannitol, is not without risk.

From the literature review, the preferred current treatment is fluid, and then if urine output remains poor, a diuretic may be used (Meister et al 2002).

Clinical trials using sodium bicarbonate suggest that alkalising the diuresis helps prevent acute renal failure (ARF) in myoglobinuria, by preventing the break-down of myoglobin into a substance toxic to the proximal tubules (Cunningham 1997). However, sodium bicarbonate can cause metabolic alkalosis, and therefore worsen the hypocalcaemia.

Conventional therapy such as glucose/insulin infusions and sodium bicarbonate may not be effective due to the damage to the muscle cell wall. Therefore dialysis may be necessary.

Potential complications

Acute Renal Failure (ARF) is the sudden onset of impaired ability to secrete waste products in a patient whose renal function was previously normal.

Although no one is completely sure why rhabdomyolysis causes renal failure, there are a number of hypotheses.

The first possible cause of renal failure is due to vasoconstriction or hypoperfusion of the kidneys (Szewczyk et al 1998). This may arise when kidney function is impaired due to exhausted cellular energy supply,

or due to hypovolaemic shock where blood is shunted to the most vital organs – the heart, brain and lungs – leading to vasoconstriction in the kidneys and impaired function as a consequence.

The second theory for renal failure suggests that the large myoglobin molecules get stuck in the small tubules of the nephron, causing impaired renal function (Baggaley 1997).

The third suggestion is myoglobin nephrotoxicity (Lane et al 1997). When myoglobin breaks down, its components can be toxic to the tubules of the nephron, especially when the urine is acidic, causing acute tubular necrosis and ARF. This is the main reason for considering the use of sodium bicarbonate.

Dialysis may be required in 50-70% of cases (Walls 2002), however this number may not be accurate given the lack of reliable data regarding the incidence of rhabdomyolysis.

Although dialysis doesn't reduce the levels of myoglobin, it is useful in treating uncontrolled hyperkalaemia, acidosis and fluid overload. Peritoneal dialysis is not an option because it fails to clear solutes faster than they appear. Haemodialysis is the preferred method of treatment, and may be required for several days, or for longer periods in severe cases, in elderly patients or in the presence of existing renal dysfunction.

Hyperkalaemia. Skeletal muscle represents 60-70% of the total cellular mass, and more than 98% of potassium resides within cells, so even a small amount of cellular damage can result in a massive release of potassium into the blood stream.

Hyperkalaemia may cause fatal cardiac dysrhythmias. Progressive ECG changes can start occurring when serum potassium becomes greater than 5.5mmol/L. Peaked T waves, ST segment depression, and first degree AV block are the first changes. This can develop into widened QRS complexes when potassium is around 7mmol/L. In the final stages the patient develops complete heart block, VF, and asystole (Rush et al 1999).

A moderately high potassium can be cardiotoxic when the serum calcium is profoundly decreased because calcium opposes potassium. Therefore it is important to look at the patient and their clinical signs, as well as their potassium.

Other complications

Hypovolaemic shock may result from fluid influx into the damaged cells or other injuries as a result of trauma.

Metabolic acidosis may result from release of phosphate and lactic acid from the muscle cell, and from an inability of the kidney to buffer the acidosis (Cunningham 1997).

Fluid overload or underload may occur especially in elderly patients. Many patients need volume monitoring by way of a CVP or PA catheter. Patients need close monitoring of their electrolytes and appropriate treatment.

Disseminated intravascular coagulopathy (DIC) is a late complication of rhabdomyolysis and probably results from the activation of the clotting cascade by the damaged cells. It should be monitored by screening prothrombin, partial prothrombin levels, platelets and fibrinogen (Meister et al 2002).

Compartment syndrome may arise if the injured muscle cells swell, and the muscle cells are in a fascial compartment. This causes a rise in compartmental pressures, leading to a 'second wave effect' including decreased blood flow, ischaemia, and further muscle and nerve damage (Saad 1997). Patients can initially have a compartment syndrome, that leads to rhabdomyolysis, that leads to another compartment syndrome, or they may develop a rhabdomyolysis and then develop a compartment syndrome.

Although hypocalcaemia is also a complication of rhabdomyolysis, calcium infusions for a low extracellular calcium can worsen the deposition, and result in hypercalaemia during recovery, so infusions of this nature are generally used as a last resort.

Summary

Patients with rhabdomyolysis may present in any clinical situation, often through the emergency department, but also post operatively, in intensive care units, on general wards or even following the application of plaster to a broken limb.

The true incidence of rhabdomyolysis remains unknown.

Diagnosis should be made following laboratory testing, but urinalysis and clinical awareness are of paramount importance.

Treatment with crystalloid solutions (normal saline or Hartmann's) is the preferred treatment although other forms of therapy are often used depending on the patient, however these remain controversial.

The patient's signs and symptoms should be treated and the patient monitored for complications of treatment such as ARF and hyperkalaemia.

References

Baggaley, P.A. 1997 Rhabdomyolysis. http://members.tripod.com/~baggas/rhabdo.html. Date Accessed 7th July 2006.

Black, C. and Jick, H. 2002. Etiology and frequency of rhabdomyolysis, *Pharmacotherapy*, 22(12):1524-1526.

Cohen, R.I. and Rao R. 1997. A 41-year-old man with thigh pain and loss of sensation in the toes, *Chest*, 111(3):810-812.

Cunningham, M. 1997. Ecstasy-induced rhabdomyolysis and its role in the development of acute renal failure. *Intensive and critical care nursing*, 13(4):216-223.

Dhawan, R., Jyothinagaram, M.G. and Schwartz, A.B. 1997. Pathogenesis and management of rhabdomyolysis. Available at http://webcampus.drexelmed.edu/cme/monographs/MonographsDescription.asp?Series=0702. Accessed 22 March 2006.

Lane, R. and Phillips, M. 2003. Rhabdomyolysis, *British Medical Journal*, 327(7407):115-116.

Lappalainen, H., Tiula, E., Votila, L. and Mantari, M. 2002. Elimination kinetics of myoglobin and creatine kinase in rhabdomyolysis: implications for follow-up. *Critical Care Medicine*, 30(10):2212-2215.

Meister, J. and Reddy, KI. 2002. Rhabdomyolysis: an overview. *American Journal of Nursing*, 102(2):75-79.

Meyer-Betz, F. 1911. Beobachtungen an einem eigenartigen mit Muskellähmungen verbundenen Fall von Hämoglobinurie, *Deutsches Archiv Fur Klinische Medizin*, 101:85-127.

Rush, C. and Thomas, J. 1999. A 42-year-old man with rhabdomyolysis from substance abuse and minor trauma. *Journal of Emergency Nursing*, 25(1):7-11.

Russell, T.A. 2005. Acute renal failure related to rhabdomyolysis: pathophysiology, diagnosis and collaborative management. *Nephrology Nursing Journal*, 32(4):409-419.

Saad, E.B. 1997 Intensive Care: rhabdomyolysis and myoglobinuria. http://www.medstudents.com.br/terinh/terin3.htm. Accessed 22 March 2006.

Szewczyk, D., Ovadia, P., Addullah, F. and Rabinovici, R. 1998. Pressure-induced rhabdomyolysis and acute renal failure. *Journal of Trauma*, 44(2):384-388.

Walls, M. 2002. Orthopedic trauma! RN, 65(7):52-56, 58.