CASE REPORT

Wave of renal impairment

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Accepted 9 January 2018

SUMMARY

We present a case of a 51-year-old man who went to the emergency department after an almost-drowning episode, presenting with muscular weakness, myalgia and dark urine. Laboratory data showed a severe rhabdomyolysis (creatinine kinase 497 510 U/L). Despite aggressive fluid therapy, an oliguric acute kidney injury was established with temporary need of haemodialysis. The patient had a longtime history of exercise intolerance and family history of a metabolic myopathy, namely a sister with McArdle's disease. The genetic test was positive. McArdle's disease is an autosomal recessive disorder caused by mutations in the muscle glycogen phosphorylase gene that encodes the myophosphorylase. The main symptom consists in exercise intolerance and the most severe complication is rhabdomyolysis with acute renal failure. Metabolic myopathies, such as McArdle's disease, should be considered in patients with acute renal failure due to unexplained severe rhabdomyolysis, especially if there are chronic complaints of exercise intolerance and positive family history.

BACKGROUND

Rhabdomyolysis is a frequent cause of acute kidney injury (AKI). It results in the release of intracellular muscle constituents into the circulation causing an elevation of the levels of creatine kinase (CK) and myoglobin in the blood stream and sometimes electrolyte disturbances. CK is the most commonly used marker to guide the diagnosis. Although the mechanism of renal dysfunction is not completely understood, it is believed to result predominantly from myoglobin-direct tubular cytotoxicity, vasoconstriction and tubular obstruction. Volume depletion enhances both vasoconstriction and the formation of obstructing casts. Patients with severe rhabdomyolysis should be treated with adequate fluid administration to limit the degree of renal impairment or even prevent it. However, careful attention must be paid to fluid balance to avoid hypervolaemia and acute pulmonary oedema. The causes of rhabdomyolysis are multiple but are usually readily apparent from the clinical history. Some of the most common causes are trauma (eg, crush syndrome), prolonged immobilisation, extreme muscle exercise (eg, seizures, alcohol withdrawal, strenuous exercise), infections (eg, influenza), hypothermia and drug/toxin exposure (eg, statins, cocaine abuse). Unusual causes, such as metabolic muscle diseases, must be considered when the clinical history provides no apparent explanation, particularly when there are chronic complaints of exercise intolerance, positive

family history or when the muscle injury is disproportionate to the muscle exercise.^{1–3}

In our paper, we present the case of a patient who presented with a severe case of rhabdomyolysis secondary to McArdle's disease, briefly reviewing this entity and when to consider it in the differential diagnosis of rhabdomyolysis.

CASE PRESENTATION

We report the clinical case of a 51-year-old man without any relevant known medical condition or chronic medication. There was no history of illicit drug or alcohol abuse. He had a longtime history of exercise intolerance with several minor traumatic injuries due to falls.

He went to the emergency department with complaints of muscular weakness, myalgia and darkening of his urine. The first symptoms had appeared previously that day when he was standing near the sea and had been caught by a bigger wave. He recalled feeling severe limitation in moving himself and almost drowning, being rescued in time by some locals.

On admission, the physical examination was unremarkable except for brownish urine colouration.

Laboratory data showed a small elevation in serum creatinine, significant elevation of hepatic enzymes and a severe rhabdomyolysis (creatinine kinase 497 510 U/L). He was kept in the emergency department and treated with aggressive fluid therapy. However, during the following 2 days, oliguric AKI developed and urgent consultation to a nephrologist was sought.

INVESTIGATIONS

On our first evaluation, on physical examination, his temperature was 36.3°C, heart rate 90 bpm, blood pressure 160/90 mm Hg, respiratory rate 24 bpm and oxygen saturation 92% while breathing ambient air. On chest examination, there were bilateral lung crackles; the cardiac examination revealed a normal rate and rhythm, with no murmurs. The abdomen was soft and non-tender. There was marked peripheral oedema.

There was a marked elevation in serum creatinine (565.3 µmol/L), a still severe rhabdomyolysis (creatinine kinase >160 000 U/L), a discrete hyperkalaemia (5.47 mmol/L), hypocalcaemia, hyperphosphataemia and hypernatraemia. The renal ultrasound showed no abnormalities. There was no diuretic response to bolus intravenous loop diuretics, and emergency haemodialysis was initiated.

The patient was admitted in the nephrology ward, and the subsequent evolution was favourable.

To cite: Pinto H, Teixeira AC, Oliveira N, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-223437

Figure 1 Temporal evolution of laboratory values of serum creatinine and creatine kinase (CK).

The patient rapidly recovered diuresis during the first week and slowly recovered from both the rhabdomyolysis and the kidney injury (figure 1 and table 1). Haemodialysis was stopped after four sessions.

The complete clinical history revealed that one of the patient's sisters had been diagnosed with McArdle's disease. This fact and the previously mentioned history of chronic muscular fatigue led us to propose a genetic disease, namely the McArdle's disease, as the cause of the severe rhabdomyolysis. A blood sample was sent to Instituto Nacional de Saúde Dr. Ricardo Jorge and the diagnosis of McArdle's disease was confirmed through genetic testing of a specific mutation of the gene *PYGM*, the c.2392T>G (p.W798R), that was previously found in his sister.

TREATMENT

The patient began supplementation with vitamin B₆, and during his hospital stay, he needed prolonged fluid therapy to correct hydroelectrolytic disturbs. He received counselling about physical activity and diet.

OUTCOME AND FOLLOW-UP

After discharge, there was continuous improvement of kidney function with complete recovery. There were no other episodes of severe rhabdomyolysis.

DISCUSSION

Rhabdomyolysis is a clinical condition involving the damage of skeletal muscle and the release of its breakdown products into

the bloodstream and extracellular space. It usually presents with a triad of symptoms, including myalgia, weakness and myoglobinuria (typically described as tea-coloured urine). Treatment is primarily supportive with emphasis on vigorous fluid administration. Most authors agree that in the first hours, we should use crystalloid solutions such as isotonic saline (NS) at a high rate, for example 500–1000 mL/hour, reducing the rate administration if there is any sign of volume overload. The majority of authors advise to correct the metabolic acidosis, alternating NS with isotonic bicarbonate. The use of bicarbonate can also lead to urinary alkalinisation that is believed to protect against myoglobin toxicity. If there is no diuretic response, the fluid administration must be limited to avoid fluid overload. Careful attention must be paid to serial measurement of serum potassium levels as they can rise fast in cases of severe rhabdomyolysis. Fluids containing potassium should not be used. During the initial phase of rhabdomyolysis, serum calcium levels usually fall due to calcium deposition on damaged tissue; on recovery, the calcium is again mobilised and there is usually transient hypercalcaemia. Intravenous calcium administration is only required during acute phase if the hypocalcaemia is symptomatic and otherwise should be avoided, as calcium supplementation may increase muscle injury. Criteria for dialysis initiation are the standard: fluid overload unresponsive to loop diuretics, electrolyte disturbances (namely hyperkalaemia), metabolic acidosis and uremic encephalopathy. The level of myoglobin or creatine kinase should not be used to guide the initiation of renal replacement therapy.^{1–5}

There are multiple causes to rhabdomyolysis and generally the cause is evident from the clinical history or exam. The most common causes are trauma and compression (eg, Crush syndrome, motor vehicle accidents or prolonged immobilisation), excessive muscle activity (strenuous exercise, seizures or delirium tremens), major artery occlusion (embolus, thrombus), infections (eg, influenza, Legionella), hypothermia, drug/toxin exposure (eg, statins, ethanol, cocaine). Other less frequent causes of rhabdomyolysis are endocrine or metabolic disorders, such as McArdle's disease. The severity of rhabdomyolysis can vary from asymptomatic to life threatening, with extreme CK elevations and AKI. Usually, AKI is not present when rhabdomyolysis is caused by excessive muscle activity unless there has been concomitant volume depletion or if there was previous renal insufficiency. If there is more than 1 episode of exercise-induced

Table 1 Laboratory data

Laboratory data	Normal range (units)	Results at admission	Results at day 2	Results at discharge
Haemoglobin	13.0–17.5 (g/dL)	16.8	13.9	11.8
Urea	3.2–7.1 (mmol/L)	9.5	23.5	10.8
Creatinine	58–110 (μmol/L)	105	565.3	147.9
Sodium	137–145 (mmol/L)	139	142	148
Potassium	3.5–5.1 (mmol/L)	4.1	5.47	4.78
Calcium	2.10–2.55 (mmol/L)	–	1.91	2.47
Phosphorus	0.81–1.45 (mmol/L)	–	1.74	1.45
Creatine kinase	10–171 (U/L)	497510	>16000	411

rhabdomyolysis, when there are chronic complaints of exercise intolerance, positive family history or when the muscle injury is disproportionate to the muscle exercise, hereditary muscle enzyme defects should be suspected.⁶

McArdle's disease, also known as glycogen storage disease type V, glycogenosis type V or myophosphorylase deficiency, is one of the most common disorders of muscle glycogenosis.^{7,8} McArdle's disease is transmitted in an autosomal recessive pattern and is caused by mutations in the muscle glycogen phosphorylase gene (*PYGM*), located at chromosome 11q13 that encodes the muscle isoform of glycogen phosphorylase, also called myophosphorylase. This enzyme catalyses and regulates the cleavage of glycogen to glucose-1-phosphate in skeletal muscle. In case of mutation, patients are unable to use their muscle glycogen stores to produce energy.^{7,9}

Symptoms usually present in childhood but clinical heterogeneity exists. Some individuals have mild symptoms as fatigue, whereas others have a severe and rapidly progressive form that manifests shortly after birth. The typical clinical manifestations consist in exercise intolerance with early fatigue, muscle stiffness and contractures, myalgia and sometimes episodes of 'dark urine' (myoglobinuria). The most severe complication is rhabdomyolysis with AKI, eventually leading to chronic kidney disease, although this is a rare occurrence. Patients often describe the second wind phenomenon. It occurs when the patient rests or diminishes the intensity of the exercise after the first minutes, being then capable of continuing the exercise with symptomatic improvement. This occurs probably because of the activation of fatty acid metabolism and the release of hepatic stores of energy.^{8,10,11} Our patient had a late diagnosis, although he had muscular weakness and some falls due to exercise intolerance long before the admission in our hospital. Several clues in this case could lead us to the diagnosis of McArdle's disease, such as the complaints of exercise intolerance since childhood, the severe rhabdomyolysis disproportionate to the muscle exercise, the high serum level of total CK activity, even at rest and without heavy exercise in the previous hours or days and the existence of positive family history.

Muscle biopsy or molecular genetic testing of *PYGM* can make the diagnosis. McArdle's disease is genetically heterogeneous, but the majority of patients can be diagnosed without the need of muscle biopsy, by testing the most frequent mutations.^{7,12–15} The forearm exercise test, during which serum ammonia and lactate levels are measured, is a simple and sensitive test that can be used when there is a suspect case of McArdle's disease.¹⁶

A diet high in fat and/or protein has not been found to lead to significant improvement in patients with McArdle's disease. However, a high-carbohydrate diet may replenish hepatic glycogen stores and help in its mobilisation during exercise. Some studies demonstrate an improvement in symptoms and a decrease of exercise-induced rhabdomyolysis with the consumption of simple carbohydrates (eg, sucrose or fructose) before dynamic/aerobic exercise. It is necessary however to take in consideration the possibility of increasing weight and the potential loss in exercise capacity.^{17,18} Strenuous exercise should be avoided but, on the other hand, studies suggest that routine moderate exercise can be beneficial by increasing cardiovascular capacity and reduce symptoms.^{19–21} Some authors believe that dietary supplementation with low-dose creatine (60 mg/kg per day) may be beneficial.²² One study suggested that treatment with the ACE inhibitor ramipril improved exercise tolerance in a group of McArdle's disease mutations.²³

Two case reports propose that vitamin B₆ supplementation can be valuable in patients with McArdle's disease. They recommend oral vitamin B₆ supplements (60–90 mg/day), which they believe can restore some stability to the mutant phosphorylase and enhance its residual activity in the skeletal muscle of patients.^{24,25}

It remains unproven the potential effect of therapeutics such as D-ribose, glucagon, verapamil, branched-chain amino acids, dantrolene sodium, aminoglycosides (eg, gentamicin) or high-dose creatinine (150 mg/kg/day).¹⁸

In conclusion, AKI is rare in McArdle's disease since the symptoms often limit the degree of physical activity. However, when episodes of acute effort do occur, patients can develop severe rhabdomyolysis and should promptly be treated in hospital environment. The diagnosis of McArdle's disease and other metabolic myopathies should be suspected in symptomatic young adults or adolescents and when there is family history. The second wind phenomenon is characteristic of this disease.¹⁰

Although there is no specific treatment, an early diagnosis is important to promote lifestyle changes. Even though preventive measures such as avoiding acute physical efforts should be enforced, recent evidence suggests that careful exercise training with moderate aerobic exercise may help to reduce symptoms of exercise intolerance.^{10,26} There is not enough evidence about the efficacy of dietary changes: although some authors support the advantage of a high protein diet, the majority refer that a rich carbohydrate diet is preferable.^{7,18} There is also some evidence about the benefits of vitamin B₆ supplementation.²⁴ Patients should also receive genetic counselling.

Learning points

- ▶ Rhabdomyolysis is a frequent cause of renal impairment, and in severe cases, haemodialysis may be required.
- ▶ When the cause of the rhabdomyolysis is not evident or the severity is disproportionate to the muscle damage, hereditary muscle enzyme defects should be suspected.
- ▶ McArdle's disease and other metabolic myopathies should be suspected in symptomatic young adults or adolescents and when there is family history.
- ▶ The second wind phenomenon is characteristic of McArdle's disease.
- ▶ Early diagnosis is important to promote lifestyle changes and to avoid unnecessary efforts that can result in life-threatening episodes of rhabdomyolysis.

Contributors HP contributed to the article with the conception of the manuscript, acquisition, analysis and interpretation of data and drafting the work. ACT contributed to the article with the conception of the manuscript and to the acquisition, analysis and interpretation of data. NO contributed to the article with the conception of the manuscript, with bibliographic research and revising it critically for important intellectual content. RA contributed to the article revising it critically for important intellectual content and to approval of the final version of the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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