

## Exercise: not always a benefit?

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### ■ ABSTRACT

Rhabdomyolysis is a known cause of acute kidney injury which can occur in different settings. While strenuous physical exercise, especially under extreme heat, is one possible cause, it is not clear whether exercise in itself, depending on intensity and length, is a sole cause, or if other contributing mechanisms are necessary. Rhabdomyolysis in the context of intense exercise can mask other underlying causes which merit attention in order to prevent recurrences and acute kidney injury. In cases involving young athletes, metabolic and toxic causes of rhabdomyolysis and infectious myopathies must be kept in mind.

The authors present the case of a young male, a regular sports practitioner, who was admitted to the emergency department with an oliguric acute kidney injury following strenuous physical exercise. His laboratory evaluation revealed rhabdomyolysis and acute renal failure, which progressively improved with medical therapy, but persistent CK elevation led to the suspicion of a metabolic myopathy, later confirmed through a muscle biopsy.

#### Key-Words:

Acute renal failure; exercise; myopathy; rhabdomyolysis.

### ■ INTRODUCTION

While exercise is seen as a health-promoting measure for most people, too-strenuous physical exercise can have serious consequences, one of which is

rhabdomyolysis<sup>1</sup>. Rhabdomyolysis can occur whenever energy needs exceed the existing reserve, but it is usually asymptomatic<sup>1,2</sup>. However, in more severe cases it can cause localised or diffuse myalgias, and acute kidney injury (AKI) may occur, sometimes with need for dialysis, with serious health risks<sup>3,4</sup>.

It is not clear if exercise in itself or other contributory mechanisms determine which patients will develop rhabdomyolysis as a response to strenuous exercise. These determinants may be related to exogenous factors, such as the intensity of the exercise, environmental temperature, medications or toxic substance abuse<sup>1</sup>, but also to endogenous factors, such as metabolic myopathies or genetic polymorphisms in muscle enzymes or growth factors that may explain individual susceptibility to exercise-induced rhabdomyolysis<sup>5-7</sup>.

Young athletes can be more vulnerable to rhabdomyolysis, especially if they have an associated contributing mechanism, such as a metabolic myopathy<sup>1</sup>. Indeed, rhabdomyolysis can reveal an underlying cause, which, if undiagnosed, can cause recurrent rhabdomyolysis and AKI<sup>3,4</sup>.

### ■ CASE REPORT

Male, 26 years, Caucasian, competition athlete (triathlon), admitted to the emergency department with unspecified illness, tiredness and oliguria. In the previous 24 hours he had practiced strenuous physical exercise (16 km, 6 hours running and cycling) under heat (30°C) and afterwards began feeling

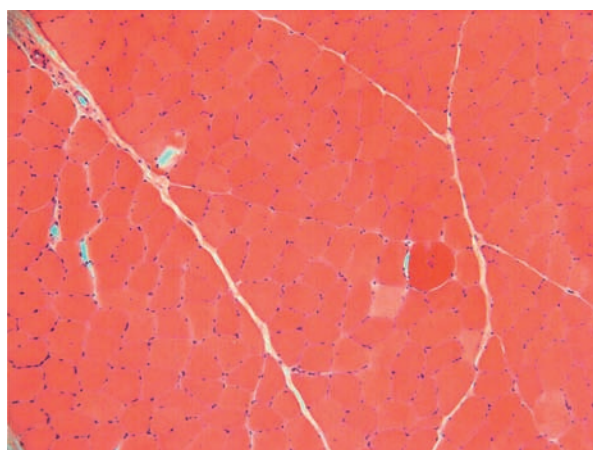
unspecified sickness, widespread muscle pain, dark (brown) urine, and progressively diminishing urinary output. His past medical history revealed no similar previous episodes, no medication or toxic substances abuse, no known diseases, no familial history of similar cases. He was dehydrated and oliguric. Relevant laboratory abnormalities were serum creatinine 8.4 mg/dL; blood urea nitrogen 178 mg/dL, CK 19.791 IU/L, LDH 990 IU/L with uric acid, total bilirubin, calcium, phosphate, acid-base and electrolyte levels in the normal range. Urinary sediment was normal, with heme-positive urine. Renal echography showed no obstruction or morphologic abnormalities. The patient underwent vigorous oral and intravenous hydration, (6 litres of isotonic saline solution in the first 12 hours and 3 litres/day in the following days, both accompanied by daily ingestion of 2 litres of water) with progressive and complete renal function recovery (diuresis recovery in the first 72 hours, serum creatinine: 1.4 mg/dL at the 10<sup>th</sup> day of hospitalisation). Viral serologies (HIV 1 and 2, BHV, CHV, adenovirus, influenza, enterovirus) were negative, immunologic studies (ANA, anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-Scl 70, anti-Jo-1, AMA, p-ANCA, c-ANCA, anti-thyroid antibodies) negative; thyroid function evaluation: normal. However, CK was persistently high (1100 to 1200 IU/L), without changes in any other parameter, which led us to suspect an underlying

myopathy. A muscle biopsy was performed, revealing a glycogen storage disease. The following colorations were performed: haematoxylin-eosin (Fig. 1) and Gomori's trichromium, which showed slightly more evident muscle-fibre size variability, with the presence of scarce atrophic fibres interspersed throughout muscle bundles and no perivascular inflammatory infiltrates or interstitial connective tissue increase. Oxidative reactions were also performed (Adenosine triphosphate 4,6 and 9,7) and revealed no changes, as well as immunohistochemical staining for myophosphorylase and phosphofrutokinase, which were positive. The Periodic Acid Schiff coloration showed the typical features of a glycogen storage disease (Fig. 2). The search for other glycogenosis was not performed because their diagnostic methods are not available at our hospital.

The patient no longer practices competition sports, and has had no recurrences of the rhabdomyolysis.

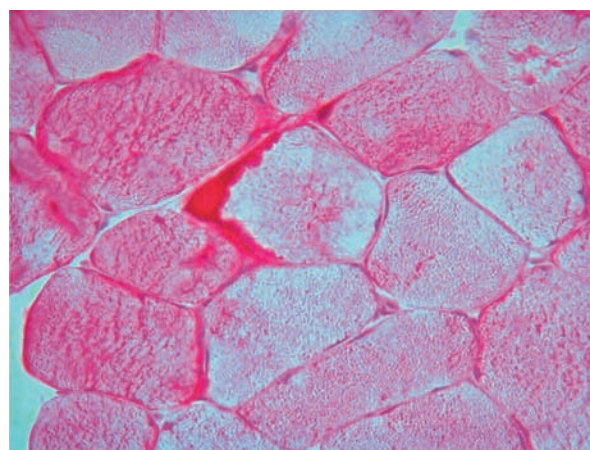
## ■ DISCUSSION

Rhabdomyolysis causing AKI in a patient who has previously practiced strenuous physical exercise



**Figure 1**

**Muscle biopsy (deltoid muscle) under H&E coloration (x100):** slight increase in the variability of length of the fibres, with the presence of scarce atrophic fibres in the muscle. No perivascular inflammatory infiltrates, no increase in interstitial conjunctive tissue.



**Figure 2**

**Muscle biopsy (deltoid muscle) under PAS coloration (x400):** several muscle fibres with positive PAS material overload (glycogen), undersarcolemmic and in intermyofibrillary space.

leads us to the immediate establishment of a link between exercise, rhabdomyolysis and AKI. According to the existing literature, in the cases of AKI caused by rhabdomyolysis in marathon runners, there were concomitant renal aggressions, such as analgesic ingestion, viral or bacterial infections, or underlying myopathy in a significant number of cases<sup>1</sup>. Therefore, the rare cases of AKI in high competition athletes may be the result of several factors<sup>1,2</sup>. However, it has been noticed that response to physical exercise can differ among individuals, conferring individual susceptibility to exercise induced rhabdomyolysis (ER)<sup>5</sup>; some individuals exhibit extreme increases in blood CK after exercise and have been characterised as high responders, an as yet undefined condition, whose possible physiological links are not understood. Genetic polymorphisms of muscle-specific enzymes, such as creatine kinase (CK-MM) NcoI, namely the CK-MM AA genotype, ACTN3 and MLCK, and growth factors such as IGFII, and percent body fat may be part of the constellation of mechanisms that explain the magnitude of the CK response to exercise, and, consequently, individual susceptibility to ER<sup>5-7</sup>.

In the case of athletes, toxic substances abuse must be kept in mind as a possible cause of rhabdomyolysis<sup>2</sup>. In the absence of an obvious cause of rhabdomyolysis, such as drug abuse or toxicity, severe trauma, or strenuous physical exercise, an underlying metabolic myopathy should be investigated<sup>1,2,8,9</sup>.

Among metabolic myopathies, we must consider enzymatic defects affecting fatty acids metabolism, glycogenosis and mitochondrial DNA deletions<sup>10</sup>. The most common cause of recurrent myoglobinuria is carnitin-palmitoil transferase deficit, an enzyme involved in fatty acid metabolism. There are six glycogenosis associated with recurrent myoglobinuria: myophosphorylase deficiency (type V), phosphofrutokinase deficiency (type VII), phosphoglycerate-kinase deficiency (type IX), phosphoglycerate-mutase deficiency (type X), lactate dehydrogenase deficiency (type XI) and phosphorylase b kinase deficiency. McArdle's disease, or myophosphorylase deficiency, is the most common cause of exercise intolerance. All these enzyme defects are autosomal recessive, except for phosphoglycerate-kinase deficiency, which is X-linked recessive, and phosphorylase b kinase deficiency, which is genetically heterogeneous, X linked or autosomal in its myopathic form. McArdle's

disease and phosphofrutokinase deficiency occur predominantly in males; certain clinical aspects aid in the differential diagnosis of glycogenosis (variable degrees of haemolysis with phosphofrutokinase deficiency, and severe haemolysis with phosphoglycerate-kinase deficiency, seizures and mental retardation in phosphoglycerate-kinase deficiency, rare cases of exercise intolerance with enzymatic defects), but the definitive diagnosis is made through muscle biopsy<sup>10,11</sup>.

In this case, the persistent rise in CK levels, and the severity of rhabdomyolysis raised the suspicion of metabolic myopathy. The muscle biopsy performed at our hospital diagnosed a glycogenosis, but did not specify which one; we could only exclude McArdle's disease and phosphofrutokinase deficiency. We hypothesise that it could be a phosphoglycerate-mutase (type X), lactate-dehydrogenase (type XI) or phosphorylase b kinase deficiency, because myophosphorylase and phosphofrutokinase deficiency were excluded through muscle biopsy, and there were no haemolysis, seizures or mental retardation, which are typical of phosphoglycerate-kinase deficiency.

The fact that the patient was a regular sports practitioner without previous complaints might be explained by the beneficial effect of aerobic training on exercise capacity, through a progressive increase in intensity, allowing the use of fatty acids as a source of energy<sup>11,12</sup>. There are no specific therapies for glycogenosis, but aerobic training and oral ingestion of sucrose immediately prior to exercise may be of benefit<sup>13</sup>.

AKI in this context is caused by volume depletion, renal vasoconstriction, tubular obstruction and direct cytotoxicity to tubular epithelial cells<sup>14</sup>. Myoglobin is a freely filtered 17 kDa protein, which precipitates in renal tubules, causing tubular obstruction to urinary flow and cytotoxicity to tubular cells through either lipid peroxidation by the haeme group, or as released free iron catalyses hydroxyl radicals production through the Fenton reaction, causing free radical lesion. Simultaneously, there is an enormous fluid retention in the sick muscle (15 to 20 litres), with subsequent intravascular volume depletion, renin-angiotensin-aldosterone system activation and sympathetic nervous system activation resulting in renal vasoconstriction. This can be aggravated by nitric oxide consumption by circulating haeme proteins<sup>14-16</sup>.

The main aim of therapy in this situation is to prevent the causes of AKI: volume depletion, tubular obstruction, aciduria and free radical release. The therapy of rhabdomyolysis in the acute phase is independent of its cause: vigorous hydration, and, if AKI has not occurred, urinary alkalisation and mannitol, according to some authors<sup>14</sup>. When AKI is installed, the need for renal replacement therapy is dictated when there is uraemia, or metabolic acidaemia or hyperkalaemia refractory to medical therapy<sup>14-16</sup>.

In a patient with AKI and rhabdomyolysis after strenuous physical exercise, it is important to exclude an underlying disease, namely metabolic, toxic or infectious myopathy.

**Conflict of interest statement.** None declared.

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