CASE REPORT

From recurrent rhabdomyolysis in a young adult to carnitine palmitoyltransferase II deficiency

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ABSTRACT

Metabolic myopathies are a diverse group of rare genetic disorders associated with recurrent episodes of rhabdomyolysis, induced by triggers such as fever or exercise. In these disorders, the energetic metabolism is compromised resulting in damage of the muscle cells. The diagnosis can be challenging but is essential for the correct treatment. Carnitine palmitoytransferase II (CPT-II) deficiency is the most common long-chain fatty acid oxidation defect, with the adulthood form requiring additional external triggers. The authors present a case of a young-male adult with recurrent episodes of rhabdomyolysis, one of them presented with acute renal failure and acute hepatitis. The diagnostic is demanding, which requires a high level of suspicion. The adequate treatment of these patients improves the muscle function and prevents other episodes of severe rhabdomyolysis.

KEYWORDS: rhabdomyolysis; acute renal failure; hepatitis; CPT II deficiency

INTRODUCTION

Rhabdomyolysis occurs from injury of muscle fibers and its clinical symptoms are myalgia, muscle weakness and muscle swelling [1]. Severe cases may also present fever, renal failure, liver failure, arrhythmias and even death [1–3]. The etiology of this condition includes fever, trauma, immobilization, infections, drugs (cocaine), medications (statins), and some immune conditions [1]. Some physiological conditions, like those induced by strenuous exercise and fever, can induce severe myolysis. Hereditary causes, such as dystrophies and metabolic myopathies (glycogenosis, beta oxidation deficits, mitochondrial diseases), are rare causes of rhabdomyolysis [4,5].

The CPT II deficiency (OMIM #600650) is the most common long-chain fatty acid oxidation defect [6]. It is an autosomal recessive disorder [5] and are known 3 forms, which are a lethal neonatal, a severe infantile and a myopathic that can be presented from infancy to adulthood [3,7]. The adult CPT II phenotype implies additional external triggers [8]. A case of a young adult male with recurrent severe rhabdomyolysis and the challenging diagnosis is presented by the authors in this paper.

CASE PRESENTATION

A 22 years-old male presented himself to the emergency department (ED) with fever, myalgia, fatigue, and dark urine (brown-colored). His previous medical history consisted in infantile asthma, an episode of hospitalization for rhabdomyolysis in adolescence and another episode of rhabdomyolysis of unknown cause six months before. The patient was evaluated in an Internal Medicine consultation and had total normalization of the previous alterations, being asymptomatic. The patient did not take regular medication and was vaccinated according to the country vaccine planning, in this case Portugal. The patient family medical history was unremarkable, and consanguinity was excluded.

At observation in the ED, his blood pressure (BP) was 120/75 mmHg, heart rate of 110bpm in sinus rhythm, a peripheral oxygen saturation of 96% without oxygen supplementation and an auricular temperature of 38.9ºC. His lungs and heart sounds were normal and there was not peripheral oedema. His muscle strength was normal, and no alterations were identified on the neurological exam.

His blood chemistry was consistent with severe rhabdomyolysis with transaminases elevation compatible with muscular lysis, and the urine test was consistent with myoglobinuria (Table 1). Since it was flu season and the patient had fever, he was tested for influenza virus A, which was positive. The patient was admitted and started on oseltamivir and support treatment, evolving in acute kidney injury without need for renal substitution therapy.

Due to the recurrent episodes of rhabdomyolysis (1 episode in adolescence and 2 episodes in adulthood) with renal lesion and after excluding the most frequent causes, the hypothesis of a metabolic cause was suspected, leading to an enlarged study to exclude non-common etiologies. Ultrasonography examination of the liver and kidneys showed no

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Table 1. Laboratory findings during patient's hospitalization

	Admission	Highest peak	Discharge	Reference value
Leucocytes (x10^3/mm^3)	5.10	13.80	10.20	4,5-11
Platelets (x10^3/mm^3)	96	-	246	150-400
Hemoglobin (g/dl)	14.4	-	13.7	13,5-16,5
Urea (mg/dl)	65	117	43	< 50
Creatinine (mg/dl)	1.04	3.44	1.04	0,7-1,10
Potassium (mmol/L)	4.4	4.4	4.2	3,5-5,5
Calcium (mg/dl)	10.3	-	9.1	8,6-10,2
Phosohat (mg/dl)	4.1	-	3.5	2,7-4,5
Albumin (g/dl)	4.8	-	3.3	3,5-5,0
Creatinkinase (U/L)	143406	143406	66	35-204
Myoglobin (U/L)	25020	25020	21	28-72
LDH (U/L)	267	5065	676	125-220
AST (U/L)	1500	2842	20	10-45
ALT (U/L)	942	942	116	< 44
Total Bilirubin (mg/dl)	0.6	0.7	0.6	< 1,1
INR	0.86	0.94	0.81	< 1,1
Protein C Reactive (mg/dl)	5.56	5.56	0.5	< 0,8

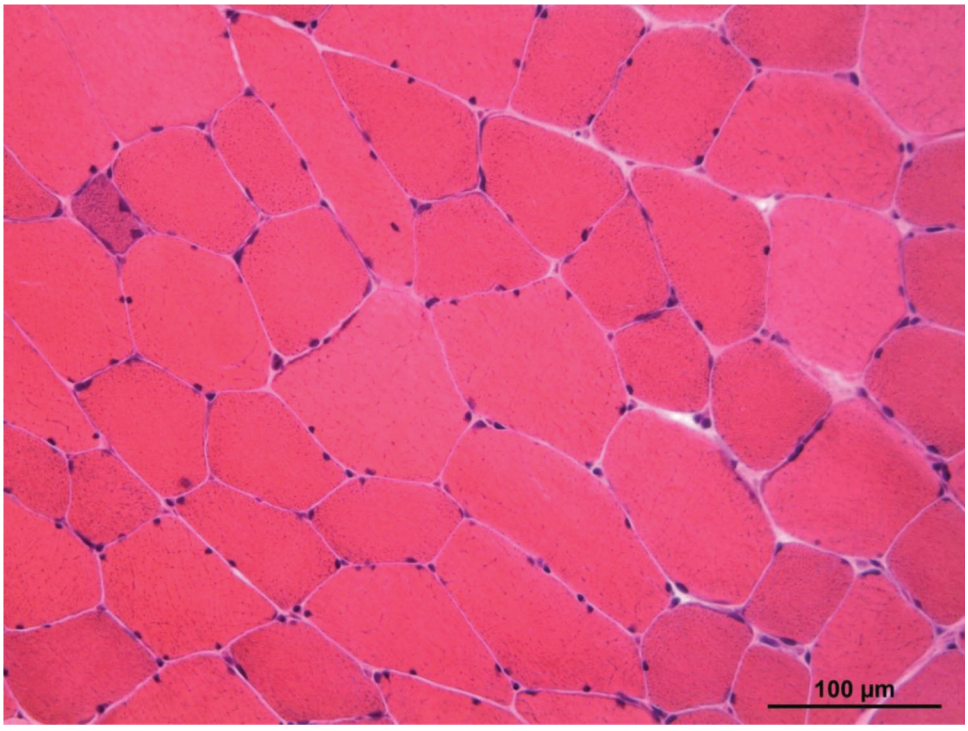

Fig. 1. Normal fiber variability, identifying a single basophil fiber (HE, 200x).

alterations. A chest CT was performed with no alterations documented. An echocardiogram was done reveling a normal heart function without a structural disease. From the immune study, the patient presented weak positive anti-PM/scl75 titles and low C3; with negative tests for ANA, ANCA, anti-dsDNA, anti-Jo, anti-Mi2 and normal levels of C4 and immunoglobulins A, M and G. An enzymatic dryspot test was performed and Pompe's disease was excluded. The electromyography was normal. The muscle biopsy, routinely processed, was inconclusive with unspecific non-significant inflammatory alterations and an increased level of lipid droplets (normal myophosphorylase and COX) revealed in Oil Red O staining; no glycogen accumulations were observed in Periodic acid-Schiff (PAS) staining (Figures 1-3). Normal myophosphorylase staining excluded McArdle disease. After the results of the tests initially done, metabolic myopathy was the most probable diagnosis.

The patient was discussed with the reference center of metabolic disorders and a methodic study was performed: normal lactate, basal CK level elevated. The acylcarnitine panel was done with a negative result and carnitine in serum were within normal range. A next generation sequency panel was done with detection of the variant c.338C > T, homozygotic on the exon 3 of the gene CPT2. The patient started with carnitine supplement, dietary restriction of long fatty acids, supplementation with median chain fatty acids and

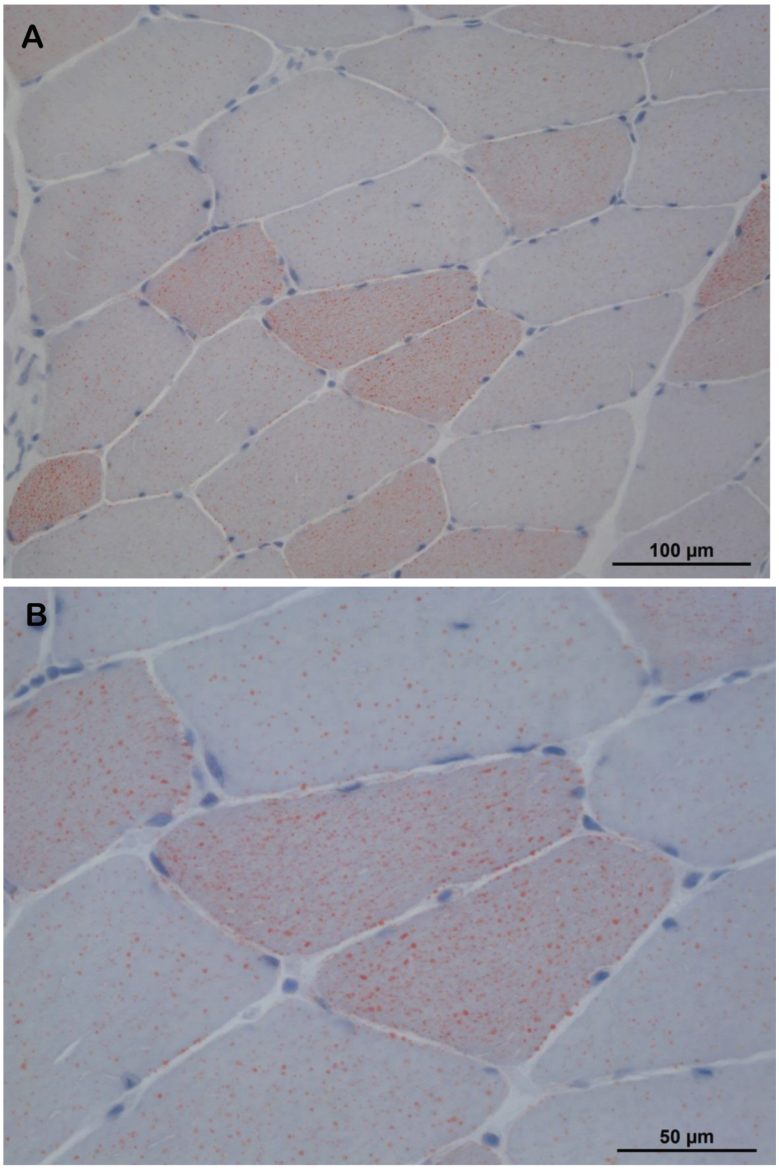

Fig. 2. A. Slight accumulation of lipid droplets in the sarcoplasm (Oil Red O, 200x); B. Detail of slight accumulation of lipid droplets in the sarcoplasm (Oil Red O, 400x).

triggers eviction (fasting, strenuous exercise, cold eviction). A new episode of hospitalization has occurred 6 months later after doing intense physical exercise and deficient compliance of treatment. After and adequate compliance of treatment, no acute episodes have been observed in the last 2 years.

DISCUSSION

Rhabdomyolysis is a common clinical syndrome, with the majority of patients being admitted with complaints of recurrent myalgia, fatigue, and dark urine [7]. There are multiple causes for rhabdomyolysis, but the final common pathway results in muscle injury and necrosis is the consequence of direct myocytes injury or energy supply failure in the muscle cell [9]. It is a state of muscle injury that can lead to several forms of systemic insult, namely acute kidney injury, electrolyte imbalance, and disseminated intravascular coagulation [10]. Rhabdomyolysis may occur as an isolated or as recurrent episodes, being caused by severe precipitants (fever, infection, or drugs) and these should be pursued systematically.

Approaching a patient with rhabdomyolysis requires a high index of suspicion and a thorough history and physical examination. Once the most common causes, as fever, trauma, immobilization, infections, drugs, medications as statins or atypical antipsychotics, are excluded, other conditions such as immune diseases – dermatomyositis and myositis-polymyositis, neurological diseases – status epilepticus and *delirium tremens*, and metabolic myopathies – McArdle disease, disorders of lipid metabolism and disorders of the glycolysis –, should be taken into account, and complementary studies should be done accordingly [9,10].

Amidst inherited metabolic diseases, disorders of lipid metabolism and McArdle's disease are the most common [11]. The metabolic causes, for instance those caused by fatty

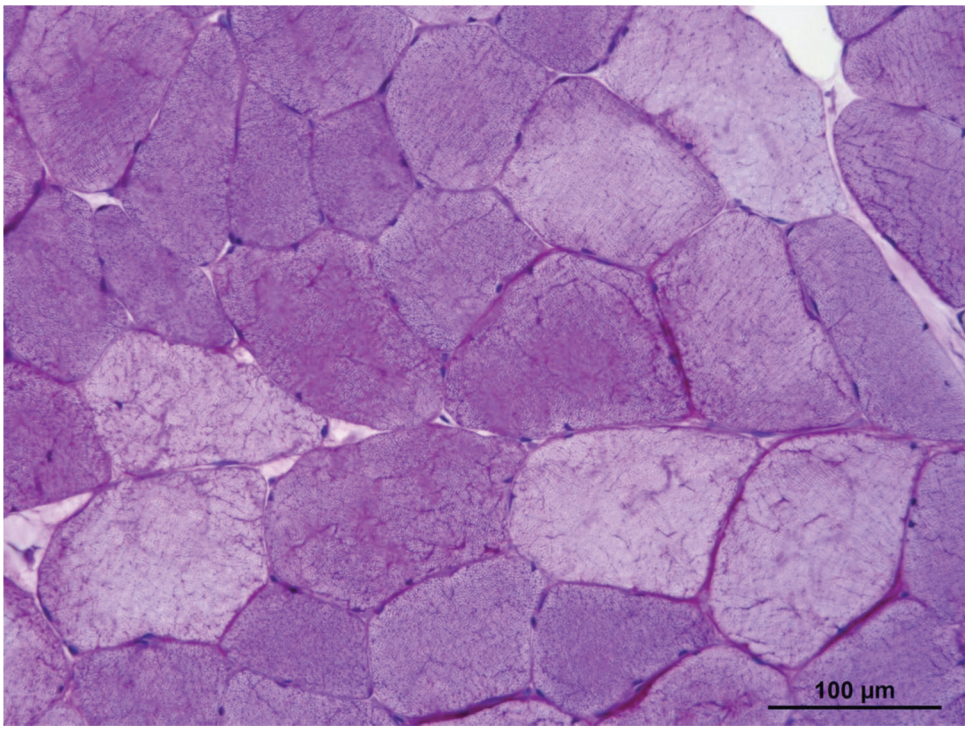

Fig. 3. Absence of abnormal glycogen accumulation. There is normal myophosphorylase activity and NADH, SDH and COX enzymatic activity (not shown) (PAS, 200x).

acid oxidation defects [1,5], are also triggered by these events and, despite being rare, should be considered when the clinical and familiar history, clinical examination and other laboratory findings are suggestive of these disorders.

CPT-II deficiency is one of the most frequent hereditary causes of rhabdomyolysis and myoglobinuria [1,8], and the most common long-chain fatty acid oxidation defect [2]. The spectrum of the clinical presentation and its severity depends on the remaining enzyme activity [2]. Three forms of CPT-II deficiency are known [3] – the perinatal, the infantile and the adult [8], all with autosomal recessive inheritance pattern [6]. The long-chain fatty acid is required as fuel to the muscles since they represent the main source of energy [2]. CPT-II is localized in the inner mitochondrial membrane and is part of an enzyme complex that mediates long-chain fatty acids transport from the cytosol into the mitochondria. During catabolic processes, the main source of extra energy demand is the long-chain fatty acids that can cross the inner mitochondrial membrane only after esterification with carnitine in a CPT II enzyme reaction [3,11]. In CPT-II deficiency, the production of energy via β-oxidation cannot occur [11].

Myalgia and myoglobinuria with brown-colored urine are the most common signs during the attacks [3], with the patient being asymptomatic between episodes [1,4]. The sequence of investigative steps is always directed by the clinical history [4]. To diagnose a metabolic myopathy, a muscle biopsy and a genetic test are required [9,11]. According with most recent literature, the muscle biopsy should be performed after complete recovery from rhabdomyolysis, since obtaining a biopsy during acute injury may overlook the underlying myopathy [9]. Our patient underwent the muscle biopsy before the complete resolution of the episode and therefore the result could be impacted by it. In those with high suspicion of metabolic myopathy an acylcarnitine profiling and a genetic test should be performed. Prevalence of the mutations that have been discovered is still unknown [3], being the Ser113Leu variant, present in exon 3, the most common [4], which is the case of the patient here discussed.

The management is mainly focused on preventing renal and hepatic failure during a crisis and involves avoiding triggers, specifically exercise, fasting, long-duration exercise, adequate hydration, reducing dietary long-chain fats [6]. Also, in some cases, L-carnitine supplementation and nutritional support is needed. These actions will provide the energetic fuel that the cell can use and avoid potential toxic metabolites and disruptive of normal metabolism [5,11]. In CPT II, the adjustments are based in an adequate glucose and median chain fatty acids and avoid fatty acids that need the carnitine shuttle to enter the mitochondria [3,4,7].

CONCLUSION

To conclude, the common causes of rhabdomyolysis need to be sought in the initial approach of the patients. At the same time, other rarer causes with specific treatment should not be obliterated. Inherited genetic metabolic disorders, like the CPT II deficiency, should be suspected in adult patients with recurrent episodes of rhabdomyolysis, due to its rapidly evolution and potential severity. In the case presented by the authors, an infection was the cause of the acute presentation of rhabdomyolysis that rapidly evolved to acute kidney injury. Although our patient had a weekly positive anti-PM/scl75 titles, the need of triggers to set off the episodes of rhabdomyolysis was not compatible with an autoimmune disease. In this case, the genetic testing gave the definitive diagnosis. The treatment of these cases only requires the treatment of the cause, organ support and specific treatment that revert the

metabolic stress on muscle. To this day, no definitive treatment of CPT-II deficiency is known. Nonetheless, it is important to be aware of the rare etiologies of rhabdomyolysis, especially in those cases where more than one episode has occurred.

DECLARATIONS

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Conflict of Interest
No conflict of interest to disclose.

Informed Consent
Written informed consent was obtained from the patient for publication of this case report.

Images Contributions
All images where kindly provided by Ricardo Taipa, MD, PhD, Head of the Neuropathology Unit / Portuguese Brain Bank.

Data Availability
The authors declare that data supporting the findings of this study are available within the article.

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