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Brief report

Severe rhabdomyolysis with hypoglycemia in an adult patient with carnitine palmitoyltransferase II deficiency

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Abstract

Carnitine palmitoyltransferase II (CPT2) deficiency is an inherited disorder associated with rhabdomyolysis. The adult form of CPT2 deficiency is usually "benign", characterized by episodes of rhabdomyolysis without extramuscular manifestations and with a good outcome, while the infantile type characteristically presents with severe metabolic symptoms such as hypoketotic hypoglycemia. We present here a case of severe rhabdomyolysis with acute renal failure and hypoglycemia in an adult patient with CPT2 deficiency.

Keywords: Carnitine palmitoyltransferase II; Rhabdomyolysis; Hypoglycemia

1. Introduction

Rhabdomyolysis is an important clinical syndrome that leads to myoglobinuria and acute renal failure in 8-25% of cases. When common causes of rhabdomyolysis (crush, infections, drugs) are excluded, especially in the case of recurrent episodes, inherited disorders of energy metabolism should be considered [1]. The most common inherited disease associated with rhabdomyolysis is carnitine palmitoyltransferase II (CPT2) deficiency. Patients with CPT2 deficiency present recurrent episodes of myoglobinuria, usually triggered by physical stresses. Of the three forms of CPT2 deficiency that have been described (adult, infantile, and neonatal), the "benign" adult form is characterized by episodes of rhabdomyolysis and a usually good outcome, while only the infantile type characteristically presents with severe metabolic symptoms such as hypoketotic hypoglycemia. Adult patients with CPT2 deficiency rarely present extramuscular symptoms.

We present a case of severe rhabdomyolysis with acute renal failure and hypoglycemia in an adult patient with CPT2 deficiency.

2. Case report

A 27-year-old male patient presented with fatigue, myalgia, and reddish-brown urine after an episode of upper respiratory infection. The patient was a professional soccer player and he complained of similar mild episodes since the age of 10, usually after prolonged exercise.. He did not smoke, drink alcohol, or use illicit drugs. His parents were in good health and he had no siblings.

At admission, the patient appeared to be ill. His body temperature was 36.6 °C, heart rate 96 bpm, blood pressure 110/70 mmHg, and respiratory rate 18/min. Laboratory testing showed Hct 44%, Hb 15 g/dl, WBC 12,000/mm^3, and PLT 160,000/mm^3. ESR was 61 mm/h and CRP 86 mg/L. Blood glucose was 64 mg/dl, urea 90 mg/dl, serum creatinine

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3.4 mg/dl, uric acid 7.4 mg/dl, Na 133 meq/l, and K 5.2 meq/l. CPK was 127,000 IU/l with 5952 IU/l CPK-Mb and negative troponin I. ALT was 670 IU/l (normal <40 IU/l), AST 2940 IU/l (normal <40 IU/l), and LDH 2274 IU/l (normal 120-230 IU/l). Prothrombin time was 11' (INR 1), partial thromboplastin time 23.5 s, and fibrinogen 210 mg/dl with negative fibrinogen degradation products. Thyroid hormone levels were normal.

The patient was put on intravenous hydration. In the days that followed, his renal function deteriorated and required three sessions of hemodialysis. Moreover, he had sustained hypoglycemia lasting for 5 days despite continuous infusion of dextrose water 10% (Fig. 1). After recovering slowly, he was discharged in good health 14 days after admission. One month later, a skeletal muscle biopsy was taken that morphologically revealed increased lipid storage and biochemically decreased CPT2 enzyme activity. Subsequent molecular analysis detected homozygotic Ser113Leu mutation of the CPT2 gene.

3. Discussion

Mitochondrial β-oxidation of long chain fatty acids is a major source of energy production. The long chain fatty acids are imported into the mitochondrial matrix by the carnitine-palmytoil (CPT) system, which is made up of two separate proteins located in the outer (CPT1) and inner (CPT2) mitochondrial membranes.

CPT2 deficiency is an autosomal recessive disorder of lipid metabolism [2]. There are three distinct CPT2-deficient phenotypes with different clinical manifestations according to the age of disease presentation. The infantile type has a severe presentation with attacks of hypoketotic hypoglycemia associated with cardiac damage, liver failure, and sudden death before the age of 1 year. Neonatal CPT2 deficiency presents with dysorganogenesis and is almost always lethal during the first months of life.

The adult form, also called the "classic", "benign", myopathic type, is characterized by recurrent episodes of rhabdomyolysis triggered by exercise. The age of onset of the first episode varies widely, 70% of the time occurring between 1 and 12 years of age, while 26% of patients report the first attack during adolescence [3]. Myoglobinuria occurs in 75% of cases, but acute renal failure requiring dialysis is rare. Between attacks, most affected individuals are asymptomatic. Usually the patients are mildly affected, reporting only a few severe attacks; some of these patients are serious athletes.

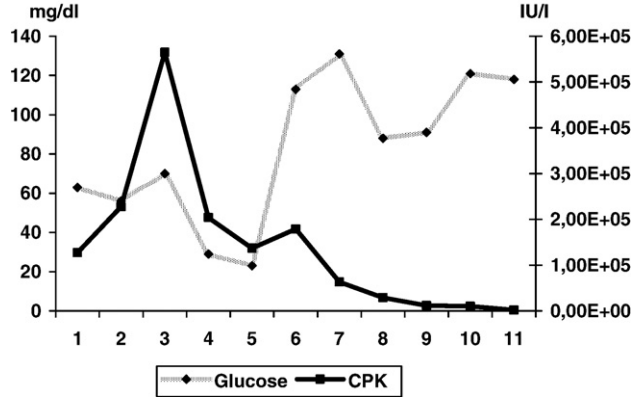

Fig. 1. Serum glucose and creatine-phosphokinase levels during follow-up.

Our patient was 26 years old but had had some mild episodes of myalgia and reddish-brown urine in the past. Nevertheless, he continued to play football. The acute respiratory tract infection that he experienced before admission seemed to trigger a severe life-threatening episode that led to the diagnosis. Classical adult type CPT2 deficiency is very rarely associated with symptoms other than rhabdomyolysis. There are only anecdotal reports of "non-classic" adult type CPT2 deficiency. Disturbances of carbohydrate metabolism (insulin resistance or hypoglycemia) have very rarely been observed in adult cases [4].

In our patient, sustained severe hypoglycemia was documented despite hypertonic glucose infusions. The hypoglycemia resolved concomitantly with improvement in the rhabdomyolysis (Fig. 1). The patient had no diabetes mellitus and he took no antidiabetic drugs. Other usual causes of hypoglycemia were ruled out. The rare possibility of spontaneous uremic hypoglycemia could also be considered, but this syndrome occurs in chronic dialysis patients with malnutrition and is never associated with acute renal failure [5]. In our patient, hypoglycemia could have been associated with the severe rhabdomyolysis representing another symptom of the same disease.

Whether adult patients with CPT2-deficiency and extramuscular symptoms present specific CPT gene mutations is not known. The most prevalent mutation in patients with CPT2 deficiency is the S113L mutation [6]. This mutation is found in 60% of patients with the adult type of rhabdomyolysis; it has not been described in patients with the infantile or neonatal form of CPT2 deficiency. Our patient had the classic mutation although his clinical presentation could be considered "non-classic". It seems he had an unusual genotype-phenotype correlation causing this severe clinical form of the disease. Thus, we present a rare case of CPT2 deficiency with severe rhabdomyolysis and hypoglycemia in a 26-year-old patient.

4. Learning points

- CPT2 deficiency may be the cause of severe rhabdomyolysis.
- Although usually "benign" and without extramuscular symptoms, the adult type of CPT2 deficiency may sometimes present with metabolic symptoms such as hypoglycemia.

References

[1] Gabow PA, Kaehny WD, Kelleher SP. The spectrum of rhabdomyolysis. Medicine (Baltimore) 1982;61:141–52.
[2] DiMauro S, DiMauro PMM. Muscle carnitine palmytoiltransferase deficiency and myoglobinuria. Science 1973;182:929–31.

[3] Wieser T, Deschauer M, Olek K, Hermann T, Zierz S. Carnitine palmytoiltransferase deficiency: molecular and biochemical analysis of 32 patients. Neurology 2003;60:1351–3.
[4] Fontaine M, Briand G, Largilliere C, Degrand P, Divry P, Vianey-Saban C, et al. Metabolic studies in a patient with severe carnitine palmytoiltransferase type II deficiency. Clin Chim Acta 1998;273:161–70.
[5] Arem R. Hypoglycemia associated with renal failure. Endocrinol Metab Clin North Am 1989;18:103–21.
[6] Taroni F, Verderio E, Fiorucci S, Cavadini P, Finocchiaro G, Uziel G, et al. Molecular characterization of inherited carnitine palmitoyltransferase II deficiency. Proc Natl Acad Sci 1992;89:8429–33.