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CASE REPORT

Exercise-induced rhabdomyolysis and transient loss of deambulation as outset of partial carnitine palmityl transferase II deficiency

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Abstract We report the case of a 13-year-old boy with an abrupt onset of leg pain and muscle weakness, incapability of deambulation and a laboratory picture of exercise-induced acute rhabdomyolysis. Intravenous hyperhydration and forced diuresis were adopted to avoid renal complications. No evidence of articular or residual muscular damage was appreciated in the short-term. The recurrence of rhabdomyolysis required a muscular biopsy showing a disturbance of fatty acid β-oxidation pathway.

Keywords Rhabdomyolysis · Carnitine palmityl transferase II deficiency

Introduction

Rhabdomyolysis is a systemic disorder characterized by skeletal muscle necrosis resulting in the release of muscle cell contents into the blood as creatine kinase (CK) and myoglobin [1]. Diagnosis is based on more than fivefold increase above normal in serum muscle enzymes and specifically on elevated CK levels (usually more than 1,000 U/L, while lower levels may define more appropriately a state of myositis) with pathologic evidence of myoglobin in blood and urine [2]. Multiple etiologies have been described (Table 1) and the various forms of rhabdomyolysis can present without symptoms or as life-threatening conditions with electrolyte imbalance, disseminated intravascular coagulation and acute renal failure, which are the most serious complications [3]. A progressive fatigue with diffuse joint pain and reduced articular range of motion may be present especially in the drug-associated forms of rhabdomyolysis [4]. The possibility that a state of rhabdomyolysis might hide an underlying metabolic disease is often taken into consideration with retardation.

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Case report

A previously healthy 13-year-old boy was brought to the pediatric emergency room due to debilitating bilateral myalgias and hypostenia at the lower limbs, manifested after a football match, which forbade him from walking. Physical examination revealed an alert and cooperative boy, afebrile, with normal vital signs. No tenderness, swelling or deformity was noted in his lower extremities. Osteo-tendinous reflexes were symmetrically elicitable, while blood analysis revealed leukopenia (white blood cell count 2,740/mm^3, neutrophil granulocytes 770/mm^3, with normal platelet count and normal hemoglobin), massive myoglobinemia (5,917 ng/ml, n.v. 10–95), myoglobinuria (7,580 mg/L) and increased levels of myo-specific enzymes (CK 12,012 IU/l, n.v. 10–70; lactate dehydrogenase 1,010 IU/l, n.v. 340–450; glutamic oxaloacetic transaminase 344 IU/l, n.v. 5–45; aldolase 50 IU/l, n.v. 1.3–8.2). His electrolytes were normal, while urine was

Table 1 Causes of acute rhabdomyolysis

Traumas
Crush and electrical injuries
Physical abuse
Compression from prolonged immobilization
Prolonged exercise (in military recruits, trained athletes or daily runners)
Neuromuscular and metabolic diseases
Glycogen storage disease type V (McArdle disease)
Glycogen storage disease type VII (Tarui disease)
Muscular dystrophies (dystrophinopathies)
Mitochondrial myopathies
Polymyositis/dermatomyositis
Short-chain acyl-coenzyme A dehydrogenase deficiency
Medium-chain acyl-coenzyme A dehydrogenase deficiency
Long-chain acyl-coenzyme A dehydrogenase deficiency
Phosphorylase kinase deficiency
Phosphofructokinase deficiency
Phosphoglycerate mutase deficiency
Carnitine palmityl-transferase II deficiency
Infections
Viral
Influenza/parainfluenza virus
Herpes virus
Cytomegalovirus
Epstein-Barr virus
Enterovirus
Rotavirus
Adenovirus
Human immune deficiency virus
Bacterial
Staphylococcus aureus
Streptococcus pneumoniae
Salmonella typhi
Escherichia coli
Pseudomonas aeruginosa
Haemophilus influenzae
Mycoplasma pneumoniae
Legionella pneumophila
Neisseria meningitidis
Leptospira interrogans
Francisella tularensis
Drugs
Alcohol
Amphetamines
Heroin
Antipsychotics
Statins
Anesthetics (ketamine, propofol)
Sedatives (benzodiazepines, lamotrigine)
Antibiotics (erythromycin, trimethoprim/sulfamethoxazole, isoniazid)
Antimycotics (amphotericin B, itraconazole)
Corticosteroids
Salicylates
Cocaine
Status asthmaticus
Diabetic ketoacidosis
Thyroid diseases
Malignant hyperthermia
Venomous snake bites
Chronic ingestion of natural licorice

brown-colored and urinalysis negative for red blood cells. His past medical history was otherwise unremarkable with the exception of recurrent upper airway infections in the foregoing years. In addition, the boy had been adopted in his first infancy (his origins were Moroccan) by two Italian parents. Since the 3 days prior to his muscle complaints he received full-dosage amoxicillin/clavulanate for a febrile tonsillopharyngitis. Intravenous hyperhydration (3 L/day) and forced diuresis with furosemide were the only therapeutic interventions.

His white blood cell count decreased to 2,290/mm^3 (neutrophil granulocytes 390/mm^3) on the 2nd day, so that ceftriaxone was started empirically. Autoimmune screen (enclosed anti-Jo1 antibodies) and serology for common (viral, bacterial and rickettsial) pathogens were negative. Doppler ultrasonography ruled out venous thrombosis and abdominal echography was normal. He remained hemodynamically stable. All the cultural, cardiologic, metabolic and immunologic examinations gave negative results. Hyperhydration was maintained for a total of 4 days. Muscle enzymes showed a progressive normalization (CPK 14,400 on the 3rd day, 6,338 on the 7th, 113 on the 14th; LDH 1,608 on the 5th day, 781 on the 14th; SGOT 546 on the 3rd day, 30 on the 14th) and so myoglobinemia (1,906 on the 3rd day, 209 on the 5th, 69 on the 14th) with myoglobinuria (24 mg/L on the 2nd day). Only an isolated hyperphosphoremia was recorded on the 5th day (5.7 mg/dl, n.v. 3–4.5), while white blood cell count raised to 4,260/mm^3 (neutrophil granulocytes 1,430/mm^3) on the 10th day. Blood urea nitrogen, creatinine, cystatin C, parathormon and blood gas analysis were constantly normal.

During the hospital stay, myalgia completely resolved and the possibility of deambulation became normal, but these signs recurred acutely 2 weeks after the first admission. On this occasion all blood and urinary investigation resulted negative, except for myoglobinemia and myoglobinuria.

The severity and the recurrence of the myopathic presentation justified the recourse to muscle biopsy: the histochemical/enzymatic analysis and the dosage of glycolytic enzymes resulted negative; the evaluation of mitochondrial enzymes showed a partial deficiency of carnitine palmityl transferase II (CPT II, 35.72 nm/min per gram, n.v. 75.69 ± 18.28). The boy attended for review one month later: his muscle complaints had resolved, he was able to walk and there was no evidence of generalized muscle weakness on manual muscle test with blood parameters completely normalized.

Discussion

The CPT II enzyme is a ubiquitous enzyme localized at the internal mitochondrial membrane and is responsible for the mitochondrial oxidation of long-chain fatty acids bound to carnitine, following transport across the intermitochondrial membrane [5]. CPT II deficiency (OMIM 600650) is the most common, though rare, autosomal recessive inherited disorder of the fatty acid β-oxidation cycle with a widely heterogeneous phenotype and different clinical pictures: the result is the accumulation of long-chain acylcarnitine in the mitochondrial matrix [6]. This enzyme deficiency has also resulted the most frequent associated disorder in a series of 36 patients with idiopathic myoglobinuria [7]. Two clinical phenotypes of CPT II deficiency have been reported: an adult muscular form characterized by exercise intolerance and myoglobinuria and a more severe, infantile hepatocardiomuscular form. In the latter, a neonatal presentation leads invariably to early infantile death [8]. Episodic muscle necrosis and paroxysmal myoglobinuria with severe muscular weakness might be modalities of presentation of CPT II deficiency in young adults, especially in cases of partial deficiency, when additional external triggers increasing the requirement for fatty acid oxidation, such as low-carbohydrate and high-fat diet, fasting, exposure to excessive cold and prolonged major exercise, are required before the predominantly myopathic symptoms are elicited [9].

Our case highlights that the presenting symptom of late-onset CPT II deficiency might be exercise-induced rhabdomyolysis through the appearance of leg pain, severe weakness and transient loss of deambulation. In our patient leukopenia has been interpreted as a post-infectious effect, as it is not expected in CPT II deficiency.

In patients with rhabdomyolysis the risk of acute renal failure, prevention or treatment of which is a major factor in determining management of these patients, has been estimated to be between 17 and 35% in the adult series; two small series in children indicated a risk of 42% and 50% [10]. The rate of myoglobinuric acute renal failure occurring in rhabdomyolysis associated with CPT II deficiency is not known. In these cases a vigorous fluid resuscitation (in isotonic saline boluses) should be started early in the management of these patients, even before a definitive etiology of rhabdomyolysis is known: this fluid therapy increases renal perfusion, inhibits cast formation and prevents further ischemic damage to the kidney [11]. Once rhabdomyolysis is established, high uric acid concentration and low urinary pH must be prevented to avoid the precipitation of myoglobin and diuresis should be monitored until plasma CK levels are less than 1,000 U/L. Furthermore, patients with adult-onset form of CPT II deficiency need to modify their lifestyle, avoiding prolonged fasting and refraining from demanding exercises.

Conclusive aim of this report is alerting the clinician to the need for prompt medical management of patients displaying signs of rhabdomyolysis and emphasizing that individuals who have recurrent episodes of muscle necrosis or those with a personal or family history of exercise intolerance should be evaluated for underlying myopathies as CPT II deficiency.

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