



**HAL**  
open science

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

Donato Rigante, Giulia Bersani, Adele Compagnone, Anna Zampetti, Alessia Nisco, Emanuela Sacco, Raffaella Marrocco

### ► To cite this version:

Donato Rigante, Giulia Bersani, Adele Compagnone, Anna Zampetti, Alessia Nisco, et al.. Exercise-induced rhabdomyolysis and transient loss of deambulation as outset of partial carnitine palmitoyl transferase II deficiency. *Rheumatology International*, 2009, 31 (6), pp.805-807. 10.1007/s00296-009-1221-z . hal-00615340

**HAL Id: hal-00615340**

**<https://hal.science/hal-00615340>**

Submitted on 19 Aug 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Donato Rigante · Giulia Bersani · Adele Compagnone · Anna Zampetti · Alessia De Nisco · Emanuela Sacco · Raffaella Marrocco

D. Rigante (✉) · G. Bersani · A. Compagnone · A. De Nisco · E. Sacco  
Department of Pediatric Sciences, Università Cattolica Sacro Cuore, Largo A. Gemelli no. 8 I-00168 Rome, Italy  
E-mail: drigante@gmail.com

A. Zampetti  
Department of Dermatology, Università Cattolica Sacro Cuore, Rome, Italy

R. Marrocco  
Department of Orthopaedics and Traumatology, Università Cattolica Sacro Cuore, Rome, Italy

**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 were appreciated in the short-term. The recurrence of rhabdomyolysis required a muscular biopsy showing a disturbance of fatty acid  $\beta$ -oxydation pathway.

**Keywords** Rhabdomyolysis · carnitine palmitoyl 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 1000 U/L, whilst 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.

## **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 were noted in his lower extremities. Osteo-tendinous reflexes were symmetrically elicitable, while blood analysis revealed leukopenia (white blood cell count  $2740/\text{mm}^3$ , neutrophil granulocytes  $770/\text{mm}^3$ , with normal platelet count and normal hemoglobin), massive myoglobinemia (5917 ng/ml, n.v. 10-95), myoglobinuria (7580 mg/L) and increased levels of myo-specific enzymes (CK 12012 IU/l, n.v. 10-70; lactate dehydrogenase 1010 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 brown-coloured 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  $2290/\text{mm}^3$  (neutrophil granulocytes  $390/\text{mm}^3$ ) on the 2<sup>nd</sup> 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 14400 on the 3<sup>rd</sup> day, 6338 on the 7<sup>th</sup>, 113 on the 14<sup>th</sup>; LDH 1608 on the 5<sup>th</sup> day, 781 on the 14<sup>th</sup>; SGOT 546 on the 3<sup>rd</sup> day, 30 on the 14<sup>th</sup>) and so myoglobinemia (1906 on the 3<sup>rd</sup> day, 209 on the 5<sup>th</sup>, 69 on the 14<sup>th</sup>) with myoglobinuria (24 mg/L on the 2<sup>nd</sup> day). Only an isolated hyperphosphoremia was recorded on the 5<sup>th</sup> day (5.7 mg/dl, n.v. 3-4,5), while white blood cell count raised to  $4260/\text{mm}^3$  (neutrophil granulocytes  $1430/\text{mm}^3$ ) on the 10<sup>th</sup> 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 palmyl transferase II (CPT II, 35.72 nm/min/g, n.v.  $75.69 \pm 18.28$ ). 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  $\beta$ -oxydation 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 hepatocardiomyopathy form. In the latter, a neonatal presentation leads invariably to early infantile death [8]. Episodic muscle necrosis and paroxysmal myoglobinuria after prolonged exercise with prolonged 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 oxydation, 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 report 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]. It is not known the rate of myoglobinuric acute renal failure occurring in rhabdomyolysis associated with CPT II deficiency. 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 1000 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.

## References

1. Luck RP, Verbin S (2008) Rhabdomyolysis. A review of clinical presentation, etiology, diagnosis and management. *Pediatr Emerg Care* 24:262-268
2. Dekeyser B, Schwagten V, Beaucourt L (2009) Severe rhabdomyolysis after recreational training. *Emerg Med J* 26:382-383
3. Zager RA (1996) Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int* 49:314-326
4. Baxter RE, Moore JH (2003) Diagnosis and treatment of acute exertional rhabdomyolysis. *J Orthop Sports Phys Ther* 33:104-108

5. McGarry JD, Brown NF (1987) The mitochondrial carnitine palmitoyltransferase system. From concept to molecular analysis. *Eur J Biochem* 244: 1-14
6. Angelini C, Trevisan C, Isaya G, Pegolo G, Vergani L (1987) Clinical varieties of carnitine and carnitine palmitoyltransferase deficiency. *Clin Biochem* 20:1-7
7. Tonin P, Lewis P, Servidei S, Di Mauro S (1990) Metabolic causes of myoglobinuria. *Ann Neurol* 27:181-185
8. Di Mauro S, Di Mauro PM (1973) Muscle carnitine palmitoyltransferase deficiency and myoglobinuria. *Science* 182:929-931
9. Smelt AH, Poorthuis BJ, Onkenhout W, Scholte HR, Andresen BS, van Duinen SG, Gregersen N, Wintzen AR (1998) Very long chain acyl-coenzyme A dehydrogenase deficiency with adult onset. *Ann Neurol* 43:540-544
10. Zepeda-Orozco D, Ault BH, Jones DP (2008) Factors associated with acute renal failure in children with rhabdomyolysis. *Pediatr Nephrol* 23:2281-2284
11. Better OS, Stein JH (1990) Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med* 322:825-829

**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