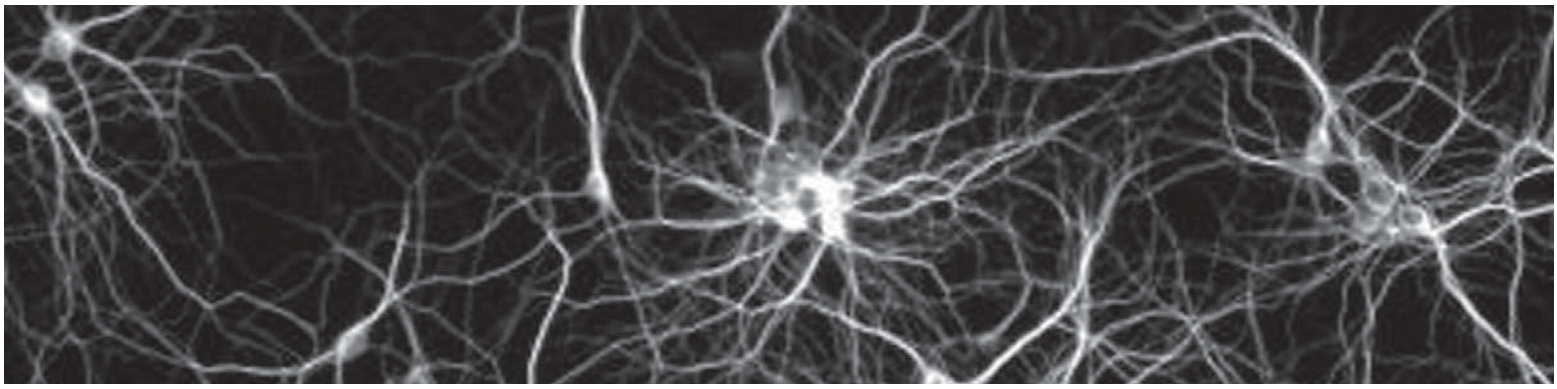

Carnitine palmitoyl transferase type 2 deficiency - case report and review of the literature

Erv. Bilić, M. Deliu[1], V. Brinar[2], D. Čerimagić[3], Ern. Bilić[4], V. Delimar[1], A. Zemba Čilić, M. Žagar

ABSTRACT - Carnitine palmitoyl transferase (CPT) deficiency is a relatively rare disease of fatty acid oxidation inherited autosomal recessively. CPT2 deficiency presents frequently in adults with rhabdomyolysis and myoglobinuria triggered most often by prolonged exercise. Carnitine is required for the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for their oxidation. Strenuous exercise is known to increase serum creatine kinase (CK) in nearly all healthy people and can be elevated often over ten times the upper limit of normal. Rhabdomyolysis can be of inherited etiology (disorders of glycogenolysis, fatty acid oxidation, mitochondrial respiratory chain pathways) or acquired (trauma, compartment syndrome, drugs, caffeine, toxins, infections, inflammatory muscle diseases, and exertion). Here we present a female patient with CPT2 deficiency diagnosed after recurrent rhabdomyolysis upon physical exertion and carbohydrate-restrictive diet. With the implementation of dietary measures and lifestyle changes that included more frequent but shorter interval exercise and avoidance of inappropriate physical exertion, the patient had a normal neurological status with only slightly elevated CK levels. This example illustrates the importance of careful monitoring of patients with increased levels of CK, even when there are no evident clinical, histopathologic or electromyoneurography (EMNG) indicators of myopathy.

Key words: palmitoyl transferase, rhabdomyolysis, carnitine

Zagreb University Hospital Center, School of Medicine, University of Zagreb, Clinical Department of Neurology, Zagreb, Croatia
[1]Student, School of Medicine, University of Zagreb, Zagreb, Croatia
[2]Cortex Outpatient Clinic for Neurology and Internal Medicine, Zagreb, Croatia
[3]Dubrovnik General Hospital, Department of Neurology, Dubrovnik, Croatia
[4]Zagreb University Hospital Center, School of Medicine, University of Zagreb, Clinical Department of Pediatrics, Zagreb, Croatia

INTRODUCTION

Carnitine palmitoyl transferase (CPT) deficiency is a relatively rare disease of fatty acid oxidation inherited autosomal recessively. CPT1 deficiency presents with recurrent attacks of fasting hypoketotic hypoglycemia but not affecting the heart and the muscle. The more common of the two, CPT2, presents frequently in adults with rhabdomyolysis and myoglobinuria triggered most often by prolonged exercise. More severe forms will present during the neonatal period. This report will review the features of CPT2 deficiency caused by exertional rhabdomyolysis in a genotype-verified adult patient.

Carnitine is required for the transfer of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for their oxidation (1). For fatty acids to enter the mitochondria, they must undergo conjugation to carnitine, which will then accumulate inside the cell by the action of organic cation transporter type 2 (OCTN2) carnitine transporter in the heart, muscle, and kidney. CPT, located in the inner part of the outer mitochondrial membrane, will induce the formation of a high-energy ester bond with long chain carboxylic acids. Acylcarnitine is translocated across the inner mitochondrial membrane *via* carnitine acylcarnitine translocase and cleaved by CPT2 in the inner aspect of the inner mitochondrial membrane. Carnitine is then released to the mitochondrial matrix for the cycle to repeat itself. Consequently, fatty acids are conjugated back to coenzyme A (CoA) in order to enter beta-oxidation with the production of acetyl-CoA for oxidative phosphorylation or production of ketone bodies in the liver (2). Deficiencies can also arise in OCTN2 carnitine transporters and carnitine-acylcarnitine translocase, however, these will not be discussed here.

CPT 1 deficiency

Three different isoforms exist including the liver, muscle and brain, with only the liver-type showing deficiency in humans. It usually presents itself in infancy with altered mental status, hepatomegaly, nonketotic hypoglycemia, elevated free fatty acids, elevated heart function tests, increased plasma carnitine levels, and mild hyperammonemia triggered by fasting or viral illness (2). Diagnosis is based on the elevation of free and short-chain acylcarnitine, with low levels of long-chain acylcarnitine, and confirmed by the assay of CPT1 in fibroblasts whose activity is reduced to 5%-20% (2).

CPT2 deficiency

CPT2 deficiency is seen more frequently, and often presents in adolescents or young adults with evident muscle involvement. Presentation in infancy indicates a more severe form of the disease, usually with respiratory distress, seizures, altered mental status, hepatomegaly, cardiomegaly, arrhythmia, dysmorphic features, renal dysgenesis, and neuronal migration defects (2). The myopathic form can present with or without myoglobinuria and elevated serum CK triggered by exertional exercise, cold, fever, infection, or prolonged fasting. Diagnosis is based on an abnormal acylcarnitine profile obtained from blood spotted on filter paper with increased (C16 + C18:1)/C2 ratio (3). Regarding their genotype, most patients have at least one copy of S113L, P50H, or Q413fs-F448L mutation. This creates an accumulation of fatty acids in fibroblasts (4). However, histologic analysis fails to show any myopathologic hallmarks.

Rhabdomyolysis

Strenuous exercise is known to increase serum CK in nearly all healthy people and can often be elevated often ten times the upper normal limit (5). However, there are differences in baseline between races and genders (6,7). Nevertheless, elevated levels of CK indicate a breakdown of striated muscle, otherwise known as rhabdomyolysis. Clinically, rhabdomyolysis presents with features such as myalgia, tenderness, muscle weakness, swelling of involved muscles and myoglobinuria, manifesting as dark or tea colored urine. It can be of inherited etiology (disorders of glycogenolysis, fatty acid oxidation, mitochondrial respiratory chain pathways) or acquired (trauma, compartment syndrome, drugs, caffeine, toxins, infections, inflammatory muscle diseases, and exertion) (8-10). Consequently, recurrent rhabdomyolysis can lead to acute kidney injury, disseminated intravascular coagulopathy, arrhythmias, hyperkalemia, and other metabolic disorders.

Elevated levels of CK after strenuous exercise typically occur in subjects who, besides the typical soreness after exercise, are otherwise asymptomatic, although there is a wide variation between individuals engaged in the same degree of exertion. CK levels parallel the increase in myoglobin and are used clinically as a surrogate marker of muscle injury to determine whether to administer treatment to prevent renal failure (11). Greater increases also occur after excessive muscle activity.

CASE REPORT

Here we present a female patient with CPT2 deficiency diagnosed after recurrent rhabdomyolysis upon exertion and carbohydrate-restrictive diet. First signs of myalgia due to physical activity occurred at the age of ten and usually subsided within 2-3 days. Upon subsequent recurrences, EMNG and immunologic testing were performed but produced normal results. Muscle biopsy showed inflammatory myopathy. After yet another episode of physical exertion in 2010 (prolonged dancing), the patient described weakness in her legs, nausea, and renal insufficiency was diagnosed with a CK of 11000. Genetic analysis was performed, which demonstrated two gene mutations: c.338 C to C/T; p. S113S/L c.534-558 del 25 bp and ins T {del AACCCTGCAAAAAGTGACACTATC ins T]. Both mutations have been previously described in the literature (4). Our patient is a heterozygote with two recessive mutations, which confirm the diagnosis of muscle CPT2 deficiency. With appropriate dietary measures (frequent smaller meals rich in carbohydrates), hydration, and antipyretics, our patient now shows no signs of the disease, with only slightly elevated CK levels.

DISCUSSION

Leg pains and exercise intolerance are common complaints in children and young adults. In most cases, the cause will be considered benign and idiopathic, especially when symptoms occur at nighttime, after unaccustomed intense exercise, or in the course of a concurrent viral illness (12,13). Myopathic diseases presenting with leg pain and cramps carry a risk of either acute rhabdomyolysis or progressive muscle weakness and can be easily missed. Milder episodes of rhabdomyolysis presenting with myoglobinuria can go unnoticed or be mistaken for hematuria and investigated by nephrologist, leading to a delay in the correct diagnosis (12,13). When a history of dark urine in association with muscle aches is given, biochemical assessment of urine during an episode is essential to confirm myoglobinuria. All neurologists, especially those dealing with neuromuscular diseases, are faced with elevated CK values in patients with an unknown muscle disease origin. Chronically elevated CK of unknown origin is otherwise known as benign hyper-CK-emia. In patients with muscle dystrophies, muscle aches usually occur after, but not during, exercise and myoglobinuria is usually mild with no severe rhabdomyolysis or renal failure (13). In Becker muscle dystrophy, exercise-induced cramps and myoglobinuria may be the only symptoms before muscle weakness develops and the diagnosis is established (14,15). Exertional myalgia and rhabdomyolysis may also be a presenting feature in female carriers of X-linked dystrophinopathies (16). Disorders of glycogen metabolism may also cause muscle pain and elevated CK values caused by exercise. McArdle disease is the most common disorder of glycogen metabolism and is caused by homozygous mutations in the PYGM gene, resulting in complete or almost complete absence of the muscle glycogen phosphorylase enzyme (17). Patients with this disease experience muscle fatigue followed by discomfort in the first few minutes of aerobic activity and they are vulnerable to rhabdomyolysis following isometric muscle activity (weights lifting, squatting) (18). Other, less frequent inherited metabolic diseases, including phosphorylase B kinase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, beta enolase deficiency and lactate dehydrogenase deficiency, may also cause rhabdomyolysis after exercise (19). In rare cases, congenital myopathies such as malignant hyperthermia susceptibility, central core disease, centronuclear myopathy or multi-minicore disease may cause rhabdomyolysis after exercise (20-25). Disorders of fatty acid oxidation are rare and often present in infancy with episodes of hypoglycemia and liver and cardiac involvement but milder cases may cause first symptoms (elevated CK values, muscle pain, exercise intolerance or rhabdomyolysis) in adolescent age, usually provoked by exercise, prolonged fever or reduced food intake. CPT2 deficiency presenting in adolescents and young adults is characterized by recurrent myoglobinuria, high CK values, muscle aching, stiffness induced by prolonged aerobic exercise, fasting, infections, emotional stress or cold (13). The condition may appear silent until the first episode of rhabdomyolysis with CK value above 100000 IU/L (26). Very long-chain acyl-CoA deficiency has similar presentation to CPT2 deficiency (27).

The value of CK, like myoglobin, may be elevated in various states and diseases (28) (Tables 1 and 2).

Myopathy, leg pains, exercise intolerance and elevated levels of CK may also be a consequence of certain drug side effects. Statin-induced myopathy is a common side effect of these vastly prescribed drugs. However, it is important to mention that different, often prescribed, drugs, or a combination of drugs (antiarrhythmics, antihypertensives, benzodiazepines), which compete for the same meta-

Table 1. *Differential diagnosis of myoglobinuria*

Differential diagnosis of myoglobinuria	• Prolonged physical exertion • Viral and bacterial infections • Toxins (alcohol) • Neuroleptic malignant syndrome • Heat shock • Trauma • Prolonged febrile state • Inflammatory myopathy • Limb girdle muscular dystrophy • Malignant hyperthermia • Metabolic myopathy

Table 2. *Differential diagnosis of increased CK value*

Myopathies	Muscle dystrophies Congenital myopathy Metabolic myopathy Inflammatory myopathy Drug-induced myopathy Healthy gene carriers for muscular dystrophy
Ion channel disorders	
Motor neuron disorders (in case of muscle mass deterioration due to denervation)	Amyotrophic lateral sclerosis Spinal muscular atrophy Post polio syndrome
Neuropathy	Guillain-Barré syndrome
Viral diseases	Hepatitis C Flu
Drugs	Statins, niacin, gemfibrozil Chloroquine Colchicine Cyclosporine Zidovudine
Hypothyroidism Hypoparathyroidism	
Operative procedures	
Trauma injections, EMNG	
Increase in exercise	
Increase in muscle mass	
Racial differences	
Gender differences	
'Idiopathic hyper-CK-emia'	

bolic processes, may burden or change the way of acquiring metabolic energy in muscle and in this way make the muscle more sensitive to external damage, like strenuous exercise.

In this paper, we present a young woman with a long history of occasional elevations of CK with previously normal neurological and EMNG findings. Our patient suffered a life-threatening condition consisting of renal failure and rhabdomyolysis provoked by exercise and minimal food intake. With further metabolic and molecular genetic analysis, the diagnosis of CPT2 deficiency was made. After the diagnosis, the patient was given dietary recommendations that involved repeated intakes of small meals rich in carbohydrates, followed by clinical recovery. This example illustrates the importance of careful monitoring a patient with increased levels of CK, even when there are no evident clinical, histopathologic or EMNG indicators of myopathy. Every patient with elevated CK levels of unknown origin should obtain neurological monitoring and control when taking into account the different conditions, diseases, or other external factors that could be causing this sign. Recognizing the exact causes of elevated CK may prevent the development of more severe forms of muscle disease, serious drug complications, or related diseases of other organs. Leg pain and elevated CK values are common symptoms with many causes; however, myalgia associated with exercise intolerance may be the presenting feature of underlying metabolic or myopathic disease with potentially serious consequences. Careful history and examination should point to the most appropriate first-line investigations. Elevated CK values may reflect different disorders of energy metabolism in the demanding muscle cell and properly diagnosing the muscle disease can prevent the development of serious complications.

REFERENCES

1. Roe C DJ. Carnitine palmitoyl transferase deficiency. In: Scriver C BA, Sly W, Valle D, editors. The metabolic and molecular bases of inherited disease. 8th edn. New York: McGraw-Hill; 2001, 2297-326.
2. Longo N, Amat di San Filippo C, Pasquali M. Disorders of carnitine transport and the carnitine cycle. Am J Med Genet, Semin Med Genet 2006; 15: 77-85.
3. Gempel K, Kiechl S, Hofmann S *et al*. Screening for carnitine palmitoyltransferase II deficiency by tandem mass spectrometry. J Inherit Metab Dis 2002; 25: 17-27.
4. Deschauer M, Wieser T, Zierz S. Muscle carnitine palmitoyltransferase II deficiency: clinical and molecular genetic features and diagnostic aspects. Arch Neurol 2005; 62: 37-41.

5. Landau ME, Kenney K, Deuster P, Campbell W. Exertional rhabdomyolysis: a clinical review with a focus on genetic influences. J Clin Neuromuscul Dis 2012; 13: 122-36.
6. Olerud JE, Homer LD, Carroll HW. Incidence of acute exertional rhabdomyolysis. Serum myoglobin and enzyme levels as indicators of muscle injury. Arch Intern Med 1976; 36: 692-7.
7. Meltzer HY. Factors affecting serum creatine phosphokinase levels in the general population: the role of race, activity and age. Clin Chim Acta 1971; 33: 165-72.
8. Tsai CN, Liu MF, Lin TS, Lin LH, Wang CR. Rhabdomyolysis and acute renal failure in a polymyositis patient. Mod Rheumatol 2004; 14: 422-3.
9. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine 2005; 84: 377-85.
10. Warren JD, Blumbergs PC, Thompson PD. Rhabdomyolysis: a review. Muscle Nerve 2002; 25: 332-47.
11. Clarkson PM, Kearns AK, Rouzier *et al.* Serum creatine kinase levels and renal function measures in exertional muscle damage. Med Sci Sports Exerc 2006; 38: 623-7.
12. Quinlivan R, Jungbluth H. Myopathic causes of exercise intolerance with rhabdomyolysis. Dev Med Child Neurol 2012; 54: 886-91.
13. Garrood P, Eagle M, Jardine PF, Bushby K, Straub V. Myoglobinuria in boys with Duchenne muscular dystrophy on corticosteroid therapy. Neuromuscul Disord 2008; 18: 71-3.
14. Minetti C, Tanji K, Chang HW *et al.* Dystrophinopathy in two young boys with exercise-induced cramps and myoglobinuria. Eur J Pediatr 1993; 152: 848-51.
15. Figarella-Branger D, Baeta Machado AM, Putzu GA *et al.* Exertional rhabdomyolysis and exercise intolerance revealing dystrophynopathies. Acta Neuropathol 1997;94:48-53.
16. Mathews KD, Stephan CM, Laubenthal K *et al.* Myoglobinuria and muscle pain are common in patients with limb-girdle muscular dystrophy 2L. Neurology 2011; 76: 194-5.
17. Rubio JC, Lucia A, Fernandez-Cadenas I *et al.* Novel mutation in the PYGM gene resulting in McArdle disease. Arch Neurol 2006; 63: 1782-4.
18. Quinlivan R, Buckley J, James M *et al.* McArdle disease: a clinical review. J Neurol Neurosurg Psychiatry 2010; 81: 1182-8.
19. Kreuder J, Borkhardt A, Repp R *et al.* Brief report: inherited metabolic myopathy and hemolysis due to a mutation in aldolase A. N Engl J Med 1996; 334: 1100-4.
20. Durham WJ, Wehrens XH, Sood S, Hamilton SI. Diseases associated with altered ryanodine receptor activity. Subcell Biochem 2007; 45: 273-321.
21. Jungbluth H. Central core disease. Orphan J Rare Dis 2007; 2: 25.
22. Quinlivan RM, Muller CR, Davis M *et al.* Central core disease: clinical, pathologic and genetic features. Arch Dis Child 2003; 88: 1051-5.
23. Romero NB, Monnier N, Viollet L *et al.* Dominant and recessive central core disease associated with RYR1 mutations and fetal akinesia. Brain 2003; 126: 2341-9.
24. Jungbluth H, Sewry CA, Muntoni F. What's new in neuromuscular disorders? The congenital myopathies. Eur J Pediatr Neurol 2003; 7: 23-30.
25. Wilmshurst JM, Lillis S, Zhou H *et al.* RYR1 mutations are a common cause of congenital myopathies with central nuclei. Ann Neurol 2010; 68: 717-26.
26. Thuiller L, Rostane H, Droin V *et al.* Correlation between genotype, metabolic data and clinical presentation in carnitine palmitoyltransferase 2 (CPT2) deficiency. Hum Mut 2003; 5: 493-501.
27. Olsen RK, Dobrowolski SF, Kjeldsen M *et al.* High resolution melting analysis, a simple and effective method for reliable mutation scanning and frequency studies in the ACADVL gene. J Inherit Metab Dis 2010; 33: 247-60.
28. Jackson CE. A clinical approach to the patient with suspected myopathy. Continuum: Muscle diseases. Am Acad Neurol 2006; 12: 13-32.

Address for Correspondence: Ervina Bilić, MD, PhD. Clinical Department of Neurology, School of Medicine, University of Zagreb, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia; e-mail: ervina.bilic@mef.hr

Deficit karnitin palmitoil transferaze tipa 2 – prikaz bolesnice i pregled literature

SAŽETAK - Deficit karnitin palmitoil transferaze (KPT) je rijetka autosomno recesivno nasljedna bolest u osnovi koje je poremećaj oksidacije masnih kiselina i dobivanje energije iz masti. Simptomi deficita KPT tipa 2 obično se javljaju u odrasloj dobi nakon redukcijske dijete, febriliteta ili značajnog fizičkog opterećenja. Karnitin je neophodan za transport dugolančanih masnih kiselina iz citoplazme u mitohondrijski matriks za daljnju oksidaciju i proizvodnju energije. Iznimna fizička aktivnost može dovesti do porasta serumske kreatin kinaze u zdravih osoba, pri čemu ta vrijednost može biti i višestruko veća od normalnih vrijednosti. Rabdomioliza može imati različite uzroke (toksini, lijekovi, infekcije, upalna bolest mišića), a nasljedni poremećaji metabolizma su važna skupina ovoga ponekad životno ugrožavajućeg stanja. U ovom radu prikazujemo bolesnicu u koje je tijekom života u više navrata dokumentirana visoka vrijednost kreatin kinaze pa je zbog tog nalaza neurološki pregledana, a učinjena je i elektromioneurografija koja je bila urednog nalaza. U naše je bolesnice došlo do naglog razvoja životno ugrožavajućeg stanja, odnosno rabdomiolize s akutnom bubrežnom insuficijencijom, nakon redukcijske dijete i pojačanog fizičkog napora. Nakon postavljanja dijagnoze deficita KPT tipa 2 i provođenja odgovarajućih dijetetskih mjera bolesnica je dobro, urednog neurološkog statusa s minimalno povećanom vrijednosti kreatin kinaze. Ovaj primjer ilustrira važnost praćenja i dijagnostičke obrade bolesnika s povišenim vrijednostima kreatin kinaze u kojih u podlozi navedenog laboratorijskog nalaza mogu biti najrazličitiji uzroci pa i nasljedni poremećaj metabolizma.

Ključne riječi: palmitoil transferaza, rabdomioliza, karnitin