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Case Report

Carnitine Palmitoyltransferase II Deficiency (CPT II) Followed By Rhabdomyolysis and Acute Kidney Injury

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Abstract

BACKGROUND: Carnitine palmitoyltransferase II deficiency (CPT II) is an autosomal recessive disorder and the most common inherited disorder of mitochondrial long-chain fatty acid oxidation, characterised by attacks of myalgia and myoglobinuria. The most common “classic” myopathic form occurs in young adults and is characterised by recurrent episodes of rhabdomyolysis triggered by prolonged exercise, fasting or febrile illness.

CASE PRESENTATION: We present a case of a 22-year-old Caucasian male admitted to our hospital with fever, dyspnea, fatigue, myalgia and dark urine (brown-coloured). The symptoms appeared after viral infection followed by fever. Acute kidney injury (AKI) developed as a complication, and there was a need for treatment with hemodialysis. At the clinical presentation, the patient had plasma creatine kinase (pCK) level of 130.383 U/L and plasma myoglobin level over 5000 μg/L. Genetic testing (molecular analysis) confirmed the diagnosis of inherited rhabdomyolysis, a metabolic disorder of carnitine palmitoyltransferase II deficiency. A previous episode with the same symptoms, the patient had four years ago but did not ask for medical treatment. The patient was discontinued from hemodialysis because of the resolution of acute kidney injury. The patient was discharged from the hospital in good condition, with a recommendation about his future lifestyle in order to prevent similar episodes.

CONCLUSION: Every patient presenting with myalgia, dark urine (brown-coloured), high level of pCK and development of AKI requiring hemodialysis, should be explored for inherited rhabdomyolysis induced by CPT II deficiency.

Introduction

Carnitine palmitoyltransferase II (CPT II) deficiency is a genetic disorder of mitochondrial fatty acid oxidation. Long-chain fatty acids are required for fueling the skeletal muscles, and they are only able to cross mitochondrial membrane after esterification with carnitine in a reaction with the enzyme CPT II [1] [2]. The damages are the result of an increased intracellular free ionised cytoplasm and mitochondrial calcium. This might be caused by depletion of adenosine triphosphate (ATP), and/or by direct injury and rupture of the plasma membrane. ATP depletion leads to myocyte injury and the release of intracellular muscle constituents, including creatine kinase (CK) and other muscle enzymes, myoglobin, and various electrolytes [3]. Three types of CPT II deficiency are recognised: a lethal neonatal form, a severe infantile hepatocardiomuscular form and myopathic form in which the onset ranges from infancy to adulthood [1] [2] [4]. The third one is the most common disorder of lipid metabolism affecting skeletal muscle and is the most frequent cause of hereditary myoglobinuria.

In vivo investigation of fatty acid oxidation in CPT II deficiency individuals, by indirect calorimetry and stable isotope methodology, shows impaired oxidation of long chain fatty acids during low-intensity exercise, with normal oxidation at rest. In addition, this method can only highlight low-fat oxidation but not diagnose CPT II deficiency. Almost all individuals with the myopathic form suffer from myalgia. Approximately 60% of them have muscle weakness during the attacks. The muscle cramps also occur

during the attacks, although they are not typical of this disease [5]. Myoglobinuria with brown-coloured urine occurs during the attacks in approximately 75% of the patients [6]. The first description of this disease in adults with exercise-induced rhabdomyolysis was made by Di Mauro in 1973 [7]. The symptoms start in childhood, whereas the attacks with myoglobinuria mostly emerge in adolescence or early adulthood. The most severe complications are massive rhabdomyolysis followed by acute kidney injury (AKI) requiring hemodialysis, acute hepatic lesion, respiratory insufficiency and paroxysmal heart arrhythmias.

Case presentation

We present a case of a 22-year-old Caucasian male, who until this hospital admission, had never asked for medical treatment. From the family medical history, the father of the patient died 10 years ago from cancer. The patient presented with fever, dyspnea, myalgia, fatigue, and dark urine (brown-coloured), followed by the development of acute kidney injury with oliguria. The laboratory analyses showed: plasma creatine kinase (pCK) level of 130.383 U/L, plasma myoglobin level over 5000 µg/L, plasma lactate dehydrogenase (pLDH) level of 2607 U/L, plasma alanine aminotransferase (pALT) level of 1104 U/L, plasma aspartate aminotransferase (pAST) level of 2920 U/L, plasma creatinine level of 574 µmol/L, and plasma blood urea nitrogen level of 20.6 mmol/L. The patient was initiated with hemodialysis treatment via a temporary vascular access-venous femoral catheter. The hemodialysis sessions were performed without complications.

Genetic testing (molecular analysis) for an inherited metabolic disorder was done, and there was a confirmation of the diagnosis CPT II deficiency. Deoxyribonucleic acid (DNA) sequencing analysis of exons 3 of the CPT II gene revealed that the patient had homozygote active mutation TCG>TTG for Ser 113 Leu and it was associated with family myoglobinuria.

During the hospitalisation, six hemodialysis treatments were performed. At day 12 of the hospitalisation, the patient was discontinued from the hemodialysis because of recurrence of diuresis with declining plasma levels of creatinine and blood urea nitrogen (Table 1). Ultrasonography examination of the kidneys showed normal kidney size and echogenic structure. Urine culture was sterile. The immunological testing (ANA, anti-dsDNA, cANCA) were negative. Continuous abdominal pain in the epigastric region with vomitus was also present. With upper digestive endoscopy, chronic gastritis with superficial ulcers was diagnosed. During the whole period, the plasma levels of calcium and potassium were in the normal range (Table 1). At the hospital admission the level of myoglobin was over 5000 µg/L, but at the end of the hospitalisation, it was 258.6 µg/L. Also, the level of pCK was 130.383 U/L, but at the end, it was 329 U/L (Table 1).

Table 1: Presentation of the laboratory findings during the patient's hospitalisation

	14 march	15 march	16 march	17 march	18 march	19 march	24 march	26 march	27 march	30 march
	Day (1)	Day (2)	Day (3)	Day (4)	Day (5)	Day (6)	Day (11)	Day (13)	Day (14)	Day (17)
P CK U/L		130.383	38.251	9.865		1.306	155			329
P CK-MB U/L		1626	473			30				
P Myoglobin µg/L		>500	>5000	>3000		1297	258.6			
P LDH U/L		2607	1554			471	460			
P AST U/L		2920	1590	869		139	46			
P ALT U/L		1104	955	697		357	134			
P Creatinine µmol/L	574	555	601					641	671	480
P Urea mmol/L		20.6	21.7					11.5		
P Potassium mmol/L	4.7	5		4.2		4.1		3.8	3.9	4
P Calcium mmol/L		2.08		2.32		2.3	2.33	2.34		2.35
P Phosohat mmol/L		2.2								
White blood cells count 10*9/L		25.2	16.1	13.4	15.9		18.1			10.1
Platelet count 10*9/L		214	198	194	246		341			412
P Total proteins g/L		58	62	61		59	67			
P Albumins g/L		38	37	35		35	38			
P Globulins g/L		20	25	26		24	29			
C3 g/L						1.27				
C4 g/L						0.204				
Diuresis ml		100		100		200	500	1900	2800	4800

The patient was discharged from the hospital in good condition, with recommendations about his future lifestyle in order to prevent similar episodes. The advice was given to his family members about the genetic metabolic disorder, CPT II deficiency.

Discussion

We presented a patient with fever, dyspnea, myalgia, fatigue, and dark urine (brown-coloured), with the acute hepatic lesion, without respiratory or heart failure. The symptoms occurred after a viral infection followed by fever. The patient also developed acute kidney injury requiring hemodialysis. Laboratory data suggested that it was due to massive rhabdomyolysis. The diagnosis was established by genetic testing (molecular analysis) for an inherited metabolic disorder which confirmed the diagnosis CPT II deficiency.

A few years ago, at the Hospital of Cardiology in Skopje-Macedonia, another patient (20 years old) with the same genetic inherited metabolic disorder (CPT II deficiency) was treated. The patient developed acute kidney injury, acute hepatic lesion, respiratory insufficiency and cardiomyopathy with volume overload. He was treated with plasmapheresis, hemodialysis and supportive therapy. The patient was discharged from the hospital in good condition with advice for a lifestyle modification [8]. One clinical study summarizes the clinical features of this disease, analysing data of 28 patients with

biochemically and genetically confirmed CPT II deficiency. It is noticeable that exercise was the most important trigger factor for attacks. The authors also noted that infections were more frequent trigger factors than fasting. CPT II deficiency was characterised with a male predominance of 86%, due to the X-chromosomal modifier genes or hormonal factors such as estrogen that might be a regulator of CPT [9]. Another clinical study presented that this enzymatic defect was detected in 47% of 77 patients, who underwent biopsy for idiopathic myoglobinuria. The carnitine palmitoyltransferase II deficiency was the most common disorder in the group of the biopsied patients [10].

It is necessary to detect the aetiology of rhabdomyolysis and start with the medical treatment**.** Although some genetic mutations have already been defined, the prevalence of these mutations is still unknown. It might be that the mutant enzyme is thermolabile in the adult form, causing the episodes of rhabdomyolysis during the acute febrile illness [11].

Diagnosing CPT II deficiency can be done by acylcarnitine analysis using tandem mass spectrometry (peak at C16 is indicative of the condition). Measurement of the CPT II activity can be performed as well as many laboratory findings, such as low carnitine levels, increased serum plasma creatine kinase and transaminase, which can be associated with the disease. For a definitive diagnosis, sequencing of the CPT II gene for mutation analysis is recommended [8]. Prenatal diagnosis may be offered for pregnancies at a 1/4 risk of infantile/severe-type CPT II deficiency [2].

Prevention includes protection from infections, avoidance of some medications (ibuprofen, diazepam, valproic acid) and general anaesthesia, toxins, heat and stress. Treatment is based on avoidance of fasting (more frequent meals) and exercise. A low-fat diet enriched with medium chain triglycerides and carnitine is recommended [12]. During acute infections, an infusion of glucose can be administered. Oral carnitine supplementation can be considered as an adequate therapy. The medium-chain fatty acid triheptanoin may be effective in the adult-onset CPT II deficiency [13].

In conclusion, inherited genetic metabolic disorder (CPT II deficiency) followed by massive rhabdomyolysis with acute kidney injury requiring hemodialysis might be a life-threatening condition. It could cause severe organ damage with a need for intensive medical treatment. The definitive diagnosis of this condition is achieved by genetic testing. Whenever a patient suffers from recurrent episodes of myalgia, followed by myoglobinuria due to rhabdomyolysis, the possibility of the presence of this rare condition should be considered.

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