Case Report

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An ignored cause of red urine in children: rhabdomyolysis due to carnitine palmitoyltransferase II (CPT-II) deficiency

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Abstract: Carnitine palmitoyltransferase II (CPT-II) deficiency is an autosomal recessively inherited disorder involving the β-oxidation of long-chain fatty acids, which leads to rhabdomyolysis and subsequent acute renal failure. The clinical phenotype varies from a severe infantile form to a milder muscle form. Here, we report a 9-year-old boy referred to our hospital for the investigation of hematuria with a 2-day history of dark urine and malaise. As no erythrocytes in the microscopic examination of the urine and hemoglobinuria were present, myoglobinuria due to rhabdomyolysis was the most probable cause of dark urine. After excluding the other causes of rhabdomyolysis, with the help of metabolic investigations, the patient was suspected to have CPT-II deficiency, the most common cause of metabolic rhabdomyolysis. Our aim in presenting this case is to emphasize considering rhabdomyolysis in the differential diagnosis of dark urine in order to prevent recurrent rhabdomyolysis and renal injury.

Keywords: carnitine palmitoyltransferase II deficiency; dark urine; hematuria; myalgia; red urine; rhabdomyolysis.

Introduction

Rhabdomyolysis is a common clinical syndrome. The majority of patients with rhabdomyolysis are admitted to hospitals with complaints of recurrent myalgia, fatigue, and dark urine. Acute kidney injury may develop in 7% of these patients [1, 2]. The attacks are initiated by prolonged exercise, fasting, fever, and exposure to cold [3]. The diagnosis is supported by elevated creatinine kinase (CK) levels and confirmed by the measurement of myoglobin levels in urine and serum [4, 5]. Although there are many etiologic factors of rhabdomyolysis, the most common cause of recurrent rhabdomyolysis in childhood is inherited metabolic disorders. Among inherited metabolic disorders, disorders of lipid metabolism are the most common ones [1]. The deficiency of carnitine palmitoyltransferase II (CPT-II), which is localized in the inner mitochondrial membrane, is an inherited disorder of long-chain fatty acid (LCFA) oxidation [1, 6, 7]. Its deficiency presents three different clinical pictures: neonatal, infantile, and mild myopathic forms of the disorder [3, 7, 8]. Here, we report on a patient who was referred to our pediatric emergency service from another hospital for the evaluation of hematuria and diagnosed with CPT-II deficiency.

Case report

A previously healthy 9-year-old boy had complaints of malaise, cough, and nasal congestion 1 week before admission. He also had sore throat and lower limb pain after playing football. The patient's symptoms did not improve despite antibiotic and ibuprofen therapy. When the patient also presented with fever and dark urine, he was referred to our pediatric nephrology department for evaluation of hematuria. His past medical history was

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unremarkable for trauma, surgery, renal, or any other inherited disease. He was the second child of nonconsanguineous parents and the family history did not give a clue for renal or other chronic systemic diseases. On admission, his body temperature was 36.3 °C, blood pressure 100/70 mmHg, and heart rate 90 beats/min. His height and weight were between the 50th–75th and 25th–50th percentiles, respectively. Physical examination was completely normal except for tenderness of the lower limbs. Urine analysis with dipstick revealed a 3+ blood reaction. Due to the lack of erythrocytes in the microscopic examination, rhabdomyolysis was the suspected diagnosis. Other laboratory findings were as follows: hemoglobin: 14.4 g/dL, hematocrit: 43.9%, platelet count: $256 \times 10^3/mm^3$, blood urea nitrogen (BUN): 11 mg/dL (5–22 mg/dL), creatinine (cr): 0.62 mg/dL (0.3–1 mg/dL), serum aspartate aminotransferase (AST): 2105 U/L (22–58 U/L), alanine aminotransferase (ALT): 389 U/L (8–39 U/L), CK: 183,623 U/L (38–277 U/L), CK-MB: 224.6 ng/mL (0.97–4.94 ng/mL), lactate dehydrogenase (LDH): 3505 U/L (115–304 U/L), and serum myoglobin: 298.1 ng/mL (28–72 ng/mL) (Table 1). Coagulation tests, blood gas, and blood ammonium levels were within normal limits. The patient was hospitalized with the diagnosis of rhabdomyolysis, and intravenous fluid and bicarbonate infusions were initiated. Cefuroxime acetyl was initiated for sinusitis. As the CK-MB level was elevated up to 304 ng/mL (0.97–4.94 ng/mL) (Table 1), electrocardiography and echocardiography were performed and normal results were obtained. Despite the intense hydration and bicarbonate infusion, the CK level continued to rise. All viral markers, chlamydia pneumonia IgM, mycoplasma pneumonia IgM, and salmonella-brucella agglutination tests were negative. After excluding the infectious and toxic causes of rhabdomyolysis, acylcarnitine profile and urine organic acid were analyzed for the inherited metabolic causes of rhabdomyolysis. The elevation of long-chain acylcarnitines is compatible with the diagnosis of CPT-II deficiency. The genetic analysis of the *CPT-II* gene revealed homozygosity for SI13L mutation. The patient's symptoms have improved, and he was discharged on the 9th day of hospitalization.

Discussion

It is well known that if there is a blood reaction on a urine dipstick with a lack of erythrocytes on microscopic examination, myoglobinuria or hemoglobinuria must always be considered. But when a patient is admitted with complaints of dark urine, physicians primarily examine the etiology of hematuria before considering rhabdomyolysis in differential diagnosis. Performing a complete urine analysis is absolutely needed in order to prevent delay in the specific diagnosis of dark urine. Our patient had also been referred to our hospital for evaluation of hematuria as he had complaints of dark urine after an infection. After excluding hematuria with a microscopic analysis of the urine, we noticed that the cause of dark urine was rhabdomyolysis. Being diagnosed with rhabdomyolysis in the first attack is very important in preventing triggering factors and undesirable renal and cardiac complications. Rhabdomyolysis in childhood may be due to trauma, drugs such as cocaine and amphetamines, hyperthermia, severe dehydration, inherited muscle diseases, excessive exercises like marathon running, and long surgical procedures. However, inherited metabolic diseases are the most frequent causes of recurrent rhabdomyolysis. Among inherited metabolic diseases, disorders of lipid metabolism and McArdle's disease are the most frequent ones [1]. CPT-II is localized in the inner mitochondrial membrane and is part of an enzyme complex that mediates LCFA transport from the cytosol into the mitochondria [1, 6, 7]. During catabolic processes, the main source of extra energy demand is LCFAs [6, 9]. In CPT-II deficiency, the transportation of hydrophobic LCFAs from the cytosol into the mitochondrial matrix for the production of energy via β-oxidation cannot occur. CPT-II deficiency presents three different clinical pictures:

Table 1: Laboratory values of the patient.

	CK, U/L	CKMB, ng/mL	AST, U/L	ALT, U/L	LDH, U/L	Myoglobin, U/L	Creatinine, U/L
On admission	183,623	224.6	2105	389	3505	224.6	0.62
1st day	215,054	304.0	3250	861			0.40
2nd day	235,097		3193	778	2594		0.66
3rd day	205,500	22.6	872	328	1297	298.1	0.66
4th day	24,493		1203	627		525.7	0.46
7th day	1185	21.5	206	66			0.30

neonatal, infantile and mild myopathic forms of the disorder. Neonatal and infantile forms have severe clinical manifestations such as seizures, liver failure, hypoketotic hypoglycemia, and cardiomyopathy [3, 7, 8]. On the other hand, the classical myopathic form has a milder clinical manifestation, characterized by recurrent episodes of muscle pain, weakness, and rhabdomyolysis triggered by prolonged exercise, fasting, fever, infection, high fat intake, exposure to cold, heat shock, and emotional stress [7, 10]. Our patient had a severe attack of rhabdomyolysis following the triggering factors of infection and heavy exercise.

Although CPT-II deficiency can be diagnosed by the determination of CPT activity in muscle, platelets, or fibroblasts, a definitive diagnosis requires the identification of mutations in the *CPT-II* gene. In patients with the myopathic form of CPT-II deficiency, a common p.SI13L mutation is identified in about 70% of mutant alleles as in our patient [8, 11–13].

There is no definitive treatment of CPT-II deficiency except prevention of rhabdomyolysis attacks. Carbohydrate-rich intake before exercise and a restricted intake of long-chain fatty acids along with medium-chain fatty acid supplementation are recommended [6, 12, 14]. In addition, patients with the classical myopathic form of CPT-II deficiency need to modify their lifestyle and avoid prolonged fasting and heavy exercises that increase energy demand [15]. For all etiological factors of rhabdomyolysis, intense hydration is very important to prevent renal complications [2, 6, 14]. Fluid therapy increases renal perfusion, inhibits the precipitation of myoglobin, and prevents further ischemic damage to the kidney [13, 15, 16]. Although our patient had heavy muscle destruction, complications did not occur due to early intense fluid and bicarbonate therapies.

In conclusion, this case revealed two striking things about the differential diagnosis of dark urine: one is considering rhabdomyolysis and the importance of a complete analysis of urine; the other is the diagnosis of CPT-II deficiency, the most common inherited metabolic cause of rhabdomyolysis in the first attack, for the prevention of recurrence and further undesirable renal, hepatic, and cardiac complications with proper treatment.

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