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CASE REPORT

Carnitine Palmitoyl Transferase Deficiency – Unrecognized Cause of Recurrent Acute Kidney Injury

Mirna Alečković-Halilović[1], Enisa Mešić[1], Osman Sinanović[2], Sanela Zukić[2] and Jasminka Mustedanagić[3]

[1]Nephrology, Dialysis and Kidney Transplantation Department, University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina; [2]Neurology Department, University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina; [3]Pathology Department, University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina

Abstract

Metabolic myopathies represent a small percentage of rhabdomyolysis causes that could lead to acute kidney injury (AKI). This could be prevented if this condition is suspected and timely treated. Carnitine palmityl transferase (CPT) deficiency is the most frequent metabolic myopathy and should be considered whenever recurrent myoglobinuria is suspected, and distinguished from the second frequent one, McArdle disease. We present a case of a patient with two medically misinterpreted episodes of AKI in whom the subsequent diagnosis of CPT deficiency was established based on high index of clinical suspicion and correlation of clinical manifestations to specific metabolic defects. Application of simple measures and lifestyle changes improved our patient's life quality and prevented potential new life-threatening complications.

Keywords: acute kidney injury, rhabdomiolysis, carnitine palmitoyl II deficiency, metabolic myopathies, hem pigment nephropathy

INTRODUCTION

Acute kidney injury (AKI) caused by heme pigment nephropathy can occur in patients with rhabdomyolysis and, less commonly, hemolysis. The reported percentage of rhabdomyolysis cases complicated by AKI ranges from 15% to over 50%.[1] Rhabdomyolysis can be the symptomatic expression of a wide variety of pathological processes, among which are trauma, toxins, drugs, infections, and endocrinopathies. Rhabdomyolysis can be divided into three categories: traumatic, nontraumatic exertional, and nontraumatic nonexertional.[2] Patients with exertional rhabdomyolysis tend to have recurrent attacks with onset in young adulthood, often with a positive family history of recurrent myoglobinuria.[3] This group includes patients with inherited enzyme deficiencies (metabolic myopathies) with history of exercise intolerance beginning in childhood, and episodes of pigmenturia occurring in adolescence. Although the metabolic myopathies represent a very small percentage of cases of rhabdomyolysis, they should be suspected in patients with recurrent episodes of rhabdomyolysis after exertion.[2]

CASE REPORT

A 40-year-old male, a worker at a shoe factory with occasional part-time job as a construction worker, was referred to the nephrology outpatient clinic complaining of back pain and voiding dark red urine. Physical examination and renal and abdominal ultrasound were unremarkable. Laboratory tests disclosed normal blood count, serum creatinine, eGFR (MDRD) of 117 mL/min/1.73 m^2, elevated transaminases (AST 245 U/L and ALT 126 U/L), and hyperlipoproteinemia (CHOL 6.9 mmol/L, LDL 4.72 mmol/L, HDL 0.71 mmol/L, and TGL 2.09 mmo/L), normal ALP, GGT, bilirubins, and proteins. Urinalysis showed positive dipstick for heme (++), but empty urinary sediment. On closer questioning, the patient remembered that since childhood he had intolerance of prolonged physical activity,

Address correspondence to Enisa Mešić, Nephrology, Dialysis and Kidney Transplantation Department, University Clinical Centre Tuzla, Trnovac bb 75000 Tuzla, Bosnia and Herzegovina. Tel: +00387 35 303395; E-mail: nisa@bih.net.ba; enisa.mesic@ukctuzla.ba

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especially if hungry, stressed out, or performed in cold weather, which manifested as weakness, myalgia, sometimes stiffness, with occasional cramps emerging at rest. He experienced first severe episode at 18, while in army, when he felt like his muscles would explode and had dark red urine for the first time in his life. He was discharged from the army, but wasn't further medically examined. He denied any other chronic or acute illness, trauma, intoxication, or abuse of illicit drugs, but reported occasional usage of ibuprofen. He had two episodes of acute kidney injury (AKI), at 4 years' interval, both during winter. His sister was chronic dialysis patient (suspected chronic glomerulonephritis due to kidney injury during acute postinfectious glomerulonephritis).

Five years ago he was hospitalized with AKI and suspicion of hemorrhagic fever with renal syndrome, when he presented with severe myalgia, general muscle weakness, and prostration accompanied by low-grade fever, oliguria, and dark red urine few days after prolonged work in a barn. He had marked elevation of creatinine, elevated transaminases, sedimentation rate, and CRP, with hyperlipoproteinemia, leukocytosis, but normal platelets and coagulation studies, with normal ALP and bilirubins. Urine dipstick showed positive protein (+) and heme (++), with pyuria (15–20 leukocytes) and hematuria (10–12 pale, dysmorphic erythrocytes). Abdominal ultrasound was consistent with AKI. Eight sessions of hemodialysis were performed and patient was discharged fully recovered. Subsequently arrived tests for *Leptospira* species, hantaviruses, hepatitis viruses, and immunological tests were normal.

He was again seen by a nephrologist only at his second hospitalization 4 years later, with similar scenario, this time during his part-time job as a construction worker. Initial and additional laboratory testing results and clinical course resembled those seen at previous hospitalization. This time IgA nephropathy was suspected. An oliguric AKI was treated with hemodialysis again (seven sessions); the patient fully recovered and was discharged without confirmation of IgA nephropathy.

We met our patient 1 year after that second AKI, when he showed up at our nephrology outpatient clinic with back pain and dark red urine. Based on the obtained information, we suspected new episode of nontraumatic exertional rhabdomyolysis and decided to hospitalize him. Besides the aforementioned elevated transaminases, CK (6053 U/L), CKMB (100 U/L), and LDH (576 U/L) were also high, with normal troponin level and mild hypocalcemia. Electro- and echocardiography, chest X-ray, and repeated abdominal ultrasonography were normal. Electromyoneurography showed borderline neuropathy, with normal visual and auditory evoked potentials. Immunological tests were normal, as well as testing for hepatitides and repeated urine culture. Peripheral blood smear was unapparent, and coagulation tests, haptoglobin, and iron and hormonal testing of thyroid gland were normal. Urine dipstick showed positive heme reaction with normal urinary sediment on repeated testing. His creatinine clearance and 24 h protein excretion were normal and he was normotensive. After few days of rest, hydration, and urine alkalinization, all tests returned to normal and myalgia and back pain subsided.

At this point, we suspected metabolic myopathy as the underlying condition and performed a forearm ischemic test in order to distinguish between the two most frequent forms. The test resulted in expected blood lactate and ammonia rise. Muscle biopsy (rectus femoris muscle), performed after 30 min of exercise showed myopathic lesions with accumulation of lipids. Succinat dechidrogenase and cyclooxygenase staining were compatible with carnitine palmityl transferase (CPT) deficiency. Muscle biopsy of the patient's sister was normal. We discharged our patient with recommendations for diet and physical activity and have followed up him for 3 years now. No new episodes of myoglobinuria and AKI were noted and his renal function remains normal.

DISCUSSION

Metabolic myopathies refer to a group of hereditary muscle disorders caused by specific enzymatic defects due to defective genes that result in skeletal muscle dysfunction.[4] According to literature, this preventable cause of AKI is often medically misinterpreted and it sometimes takes decades to establish this diagnosis. In case of our patient, at his first hospitalization, clinical presentation and the fact that patient came from rural area raised suspicion for hemorrhagic fever with renal syndrome. After complete patient recovery, his doctors were unfortunately satisfied with this theory even though other tests, together with serologic tests for leptospirae and hantaviruses, remained negative. The second episode of AKI was explained by possible IgA nephropathy due to appearance of recurrent hematuria during winter, that time with confirmed intercurrent urinary infection. AKI can occur during episodes of gross hematuria in IgA nephropathy. The most common histological lesion is ATN, which has been ascribed to tubular obstruction by red cell casts and may be induced by the iron released from lysed red cells in the tubules.[5,6] Any trace of academic curiosity necessary in search for underlying diagnosis vanished when additional serological and immunological tests of our patient came negative and when on few subsequent visits to the nephrologist, the patient presented with normal liver and renal function, urinary tests, and blood pressure, not necessitating renal biopsy. When we met the patient at our outpatient clinic, the collected data on chronic exertional intolerance with weakness and myalgia, together with recurrent episodes of dark red urine, normal blood count, and elevated transaminases, and two episodes of AKI, in absence of other common causes of rhabdomyolysis, raised our suspicion about nontraumatic exertional rhabdomyolysis.

The commonest cause of nontraumatic exertional rhabdomyolysis are metabolic myopathies, with CPT deficiency being the most frequent one[7] and the most frequent cause of recurrent myoglobinuria without clear trigger.[5] Lipids are an important energy source for resting muscles and during submaximal exercise. In case of CPT deficiency, fatty acids do not enter mitochondria to be oxidized and no energy is obtained. The consequence is muscle destruction or rhabdomyolysis. CPT deficiency belongs to the group of metabolic myopathy with exclusively dynamic symptoms[6] and that fact additionally narrowed our differential diagnosis. There are CPT I and CPT II deficiencies, with the latter being the more common and benign form with onset of symptoms in adolescence or adulthood, inherited as an autosomal recessive trait. In addition to the adult myopathic form, CPT I and II deficiency may cause a rare but severe and fatal disease in the neonatal period and during early infancy.[4] The time of onset of disease and lack of evidence of systemic involvement in our patient pointed out at the diagnosis of adult myopathic form of CPT II deficiency. Our diagnosis was additionally supported by the normal ischemic exercise test, CK elevation during symptomatic and normal in interictal periods, EMNG showing only borderline neuropathy, and the pathohistological picture in accordance with CPT deficiency.

CPT deficiency should be differentiated from the second most frequent metabolic myopathy—McArdle disease or glycogen storage disease—[4], but the final diagnosis usually is established through biochemical demonstration of CPT deficiency in the muscle or by identification of the genetic defect. We were not discouraged by the fact that in our center, or in any other centers in the region, we were not able to perform the required sophisticated confirmatory tests, so we went on and established diagnosis based on the high index of clinical suspicion and correlated certain clinical manifestations to specific metabolic defects.

The incidence of CPT deficiency has been reported to be between 1 in 15,000 and 1 in 30,000 births.[8] Bearing in mind that this condition is the most probable cause of nontraumatic rhabdomyolysis, one can assume that it is not as rare as much as underdiagnosed. Even when we talk about the relatively benign myopathic form of CPT II deficiency, if not recognized and treated, besides poor quality of life and work efficiency, there are potentially serious complications such as AKI, which can be sometimes very confusing on first presentation in apparently healthy individuals after stressors such as general anesthesia[9] or even fatal in some cases.[10,11] No specific treatment for CPT deficiency exists except avoidance of the factors that can trigger rhabdomyolysis, like prolonged aerobic exercise, exposure to cold, fasting, and stress; avoidance of some medications[12] (ibuprofen in case of our patient); and prevention of pigment nephropathy if rhabdomyolysis develops. Dietary management is the mainstay of treatment. A high-carbohydrate low-fat diet, frequent meals, and extra carbohydrate intake before and after sustained exercise appear to improve exercise intolerance.[13]

In conclusion, we hope that this case report will contribute to raising the awareness of CPT deficiency that should be considered whenever recurrent myoglobinuria is suspected from history of exertional myalgia and recurrent episodes of "nonhematuric" dark red urine, but should not be ruled out even in case of dysmorphic erythrocyturia in setting of ATN. We also intended to encourage our colleagues from other centers without sophisticated confirmatory tests for this disease to add it to their list of preventable causes of AKI because application of simple measures and lifestyle changes would improve their patient's quality of life and prevent potential life-threatening complications.

***Declaration of interest*:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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