A RARE CAUSE OF RHABDOMYOLYSIS AND ACUTE RENAL FAILURE IN AN ADULT PATIENT: CARNITINE PALMITOYLTRANSFERASE II DEFICIENCY

Introduction

The term rhabdomyolysis literally refers to dissolution of muscle tissue; in daily clinical practice, this term implies damage to the skeletal muscle cells due to traumatic and non-traumatic causes and dispersion of cellular elements into the circulation, which produces laboratory and clinical findings. Damage to the muscle cells results in the release of myoglobin, creatine kinase (CK), and other protein and non-protein cellular components into the plasma. These also include aldolase, lactic dehydrogenase (LDH), potassium, and aspartate aminotransferase (AST). Rhabdomyolysis can occur as a result of various etiologic factors including trauma, alcoholism, intoxication, coma, prolonged immobilization, excessive physical activity, epileptic seizures, hyperthermia, hypothermia, drug use, electrolyte disturbances (particularly hypopotassemia and hyperphosphatemia), and...
infections. Most patients present with the triad of myalgia, weakness, and dark-colored urine\(^\text{1}\). The diagnosis is based on elevated creatine kinase levels and elevated serum myoglobin levels in urine and serum. Acute renal failure is the most feared complication of rhabdomyolysis\(^\text{2}\).

Although there is a very limited data on the prevalence of rhabdomyolysis in adult population, annually 26,000 new cases of rhabdomyolysis are reported in the United States and these cases account for 5 to 7% of all cases with acute renal failure\(^\text{3}\). There is no epidemiological data in the literature regarding the prevalence, incidence, and male-to-female ratio of rhabdomyolysis. Inherited causes are mostly associated with deficiency or insufficiency of various enzymes that are involved in the catabolism of different macromolecules such as carbohydrates and lipids.

Although McArdle’s disease in the most common form in this group of disorders, CPT II deficiency is the most common inherited disorder in which oxidation of long-chain fatty acids is affected\(^\text{4}\). Classic carnitine palmitoyltransferase II deficiency is the most common cause of recurrent rhabdomyolysis in all age groups. Homozygous and compound heterozygous mutations in S113L and R503C genes are two common causes of disease\(^\text{5}\).

In clinical practice, there are three main forms of CTP II deficiency: a lethal neonatal form, a severe infantile form, and myopathic form\(^\text{6}\). A common p.S113L mutation has been detected in approximately 70% of mutant alleles in patients with carnitine palmitoyltransferase II (CPT II) deficiency\(^\text{7}\). The current report presents a 56-year-old male patient, who sustained recurrent episodes of rhabdomyolysis due to carnitine palmitoyltransferase II deficiency and who developed acute renal failure during the second episode.

**Case presentation**

A 56-year-old male patient without a known chronic disease presented to the emergency room complaining of abdominal pain. Upon observation of no pathological finding on physical examination and laboratory workup, the patient was discharged with a diagnosis of meteorism. However, the patient had been admitted to another hospital 3 days after due to unrelied complaints and he had been administered antibiotherapy (levofloxacin 500 mg once daily) with a diagnosis of pneumonia and then he had been discharged from the hospital.

After two days, the patient was re-admitted to the emergency department of our hospital due to unrelied complaints and addition of nausea, vomiting, and dark-colored urination. Laboratory tests revealed elevated creatine, blood urea nitrogen and potassium levels and metabolic acidosis for which the patient was hospitalized in a general ward for further analysis and treatment with the diagnosis of acute renal failure (Table 1).

<table>
<thead>
<tr>
<th>Patient’s Values</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine: 13.01 mg/dl</td>
<td>0.7-1.4</td>
</tr>
<tr>
<td>Blood urea nitrogen: 243 mg/dl</td>
<td>5-23 mg/dL</td>
</tr>
<tr>
<td>Sodium :128 mEq/l</td>
<td>135 - 148 mmol/L</td>
</tr>
<tr>
<td>Potassium: 5.4 mMOL/L</td>
<td>3.5 - 5.5 mmol/L</td>
</tr>
<tr>
<td>pH: 7.28</td>
<td>7.35 - 7.45</td>
</tr>
<tr>
<td>Bicarbonate: 11 mMOL/L</td>
<td>22-26 mMOL/L</td>
</tr>
<tr>
<td>Carbondioxide pressure: 20 mmHg</td>
<td>35 -45 mmHg</td>
</tr>
</tbody>
</table>

**Table 1**: Patient’s first laboratory values.

The patient’s past medical history was not remarkable. The patient reported dark-colored urination following vigorous exercise when he was 17 years. He was married with one child and he was a carpenter. He had a 30 packs/year smoking history (stopped smoking for 4 days). In his family history, his mother had died of chronic obstructive pulmonary disease, while the patient did not have a family history of malignancy. Laboratory tests and radiologic imaging studies upon admission revealed normal findings. On physical examination, the patient’s general condition was good; he was conscious, orientated, and cooperative. Arterial blood pressure was 130/70 mmHg and pulse rate was 78 bpm, and body temperature was 36.90C. There was no scleral icterus, conjunctivas appeared normal; there was no lymphadenopathy; thyroid gland was palpable with nor sign of nodularity; there was pretibial edema (++/+); lung auscultation revealed bilateral crepitant rales, no ronchi, and there was blunting of costophrenic angle; abdominal examination showed mild generalized tenderness. Examination of other systems revealed normal findings. Laboratory results of the patient are summarized in Table 2. The patient was hospitalized in a regular ward due to acute renal failure secondary to rhabdomyolysis.
A rare cause of rhabdomyolysis and acute renal failure in an adult patient: Carnitine palmitoyltransferase II deficiency

The patient was screened for all possible endocrine disorders such as diabetic ketoacidosis, and thyroid and parathyroid disorders. All tests showed normal findings. The patient was screened for polymyositis, scleroderma, and dermatomyositis. The patient tested negative for anti JO 2, anti mi 2, and anti SCL-70 antibodies. Electromyography revealed normal findings. The patient underwent whole body screening for a malignancy and all tests and imaging studies revealed normal findings. Additional tests were requested to rule out heavy metal intoxication. These tests showed levels within the normal ranges. The patient was investigated for possible pulmonary thromboembolism as the patient had acute respiratory failure; there was no finding suggestive of thromboembolism.

Further investigations were requested for rhabdomyolysis. C-ANCA, P-ANCA, and rheumatoid factor were within normal ranges. The patient tested negative for ANA and anti-ds DNA. Thoracic and abdominal computed tomography revealed normal findings. Kidney biopsy revealed acute tubular necrosis, mild interstitial inflammation, regular vascular structures, and normal glomerular structure without crescent and direct immunofluorescent examination showed no deposition (Figure-1).

Muscle biopsy was advised for differential diagnosis of muscle disorders; however, the patient rejected this procedure. Carnitine/acyl-carnitine analysis and urine organic acid analysis were performed using the tandem mass spectrometry (MS) method to evaluate the patient for fatty acid oxidation disorder. These tests showed normal levels of organic acid in urine, normal level of acyl/glycin, normal free carnitine levels in plasma, increased levels of estercarnitine/free carnitine, increased levels of acylcarnitine, and normal levels of C8-C18 free fatty acids; molecular genetic analysis was planned to evaluate the patient for mitochondrial enzyme deficiency. The patient was screened for genetic disorders including medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, carnitine palmitoyltransferase I (CPT I) deficiency, and CPT II deficiency using polymerase chain reaction with cDNA method in whole blood sample obtained from the patient. The patient was found to be homozygous for S113L gene mutation, which is associated with CPT II deficiency.

<table>
<thead>
<tr>
<th>Patient's Laboratory Values</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Alanineaminotransferase</td>
<td>&lt;31 U/L</td>
<td>International/NormalizedRate: 1.08</td>
<td>0.8-1.3</td>
</tr>
<tr>
<td>Albuimine</td>
<td>3.5-5.6 g/dl</td>
<td>Indirect bilirubin: 0.28 mg/dl</td>
<td>0.2-0.7 mg/dl</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>25-100 U/L</td>
<td>Kappa light chain 356 mg/dl</td>
<td>122-457 mg/dl</td>
</tr>
<tr>
<td>Amylase</td>
<td>25-125 U/L</td>
<td>Lactate: 1.2 mMOL/L</td>
<td>0.3-1.3 mmol/L</td>
</tr>
<tr>
<td>ANA</td>
<td>Negative</td>
<td>Lead: 0.1 μg/dL</td>
<td>0.20 μg/dL</td>
</tr>
<tr>
<td>Anti JO 2</td>
<td>Negative</td>
<td>Leukocyte: 7.54 K/μL</td>
<td>4.0-11.0 K/μL</td>
</tr>
<tr>
<td>Anti mi 2</td>
<td>Negative</td>
<td>Low-density lipoprotein: 97 mg/dl</td>
<td>&lt;130 mg/dl</td>
</tr>
<tr>
<td>Anti SCL-70</td>
<td>Negative</td>
<td>Mercury: 0.05 μg/dL</td>
<td>0-10 μg/dL</td>
</tr>
<tr>
<td>Anti-ds DNA</td>
<td>Negative</td>
<td>Neutrophil: 5.77 K/mL</td>
<td>2.6-6.9 K/mL</td>
</tr>
<tr>
<td>Aspartate aminotransaminase</td>
<td>&lt;31 U/L</td>
<td>P-ANCA: 12.5 IU/ml</td>
<td>0-12.5 IU/ml</td>
</tr>
<tr>
<td>B2 microglobulin</td>
<td>&lt;2500 ng/ml</td>
<td>Parathyroid hormone: 386 pg/ml</td>
<td>15-44 pg/ml</td>
</tr>
<tr>
<td>C reactive protein</td>
<td>&lt;0.8 mg/dL</td>
<td>Phosphorus: 7.9 mg/dL</td>
<td>2.4-4.4</td>
</tr>
<tr>
<td>C-ANCA</td>
<td>0-12.5 IU/ml</td>
<td>Platelet: 388,000 K/μL</td>
<td>150-450 K/μL</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.5-10.5 mg/dL</td>
<td>Rheumatoid factor: &lt;5 IU/μL</td>
<td>0-30 IU/ml</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/dl</td>
<td>Sedimentation: 8 mm/h</td>
<td>0-15 mm/h</td>
</tr>
<tr>
<td>Copper</td>
<td>70-140 μg/dL</td>
<td>Stimulating hormone thyroxine: 1.05 µIU/mL</td>
<td>0.35-4.94 µIU/mL</td>
</tr>
<tr>
<td>D-dimer</td>
<td>0-500 μg/dl</td>
<td>Thyroid stimulating hormone: 2.57 µIU/mL</td>
<td>0.35-4.95 µIU/mL</td>
</tr>
<tr>
<td>Ferritin</td>
<td>22-275 ng/ml</td>
<td>thyroxin : 1.05 pg/ml</td>
<td>0.58-1.64 pg/ml</td>
</tr>
<tr>
<td>Ferric</td>
<td>127 pg/ml</td>
<td>Total bilirubin: 0.45 mg/dl</td>
<td>0.2-1.2 mg/dl</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>200-400 mg/dl</td>
<td>Total iron binding capacity: 234 μg/dl</td>
<td>250-410 μg/dl</td>
</tr>
<tr>
<td>Folate</td>
<td>3-20 ng/ml</td>
<td>Triglyceride: 232 mg/dl</td>
<td>&lt;150 mg/dl</td>
</tr>
<tr>
<td>Gamma glutamyl transferase</td>
<td>&lt;32 U/L</td>
<td>Triiodothyronine: 2.11 pg/ml</td>
<td>1.71-3.71 pg/ml</td>
</tr>
<tr>
<td>HbA1c</td>
<td>4-6 %</td>
<td>Vitamin D: 4.3 mg/μL</td>
<td>25-100 mg/μL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.5-16.0 g/dl</td>
<td>Zinc: 92.9 μg/dL</td>
<td>70-127 μg/dL</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>35-65 μg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: All laboratory values of the patients.

The patient underwent emergency hemodialysis and further laboratory workup was planned to elucidate the etiology of rhabdomyolysis. His medical history was not remarkable for trauma, fever, confusion, heavy exercise, surgery, immobilization, electric shock or heat stroke, illicit drug use, and alcohol consumption. The patient underwent screening for brucellosis, cytomegalovirus infection, leptospirosis, tuberculosis, and hepatitis all of which can cause rhabdomyolysis. All screening tests showed negative findings. The patient had electrolyte disturbances such as hypocalcemia, hyperkalemia, and hyponatremia, and these were regarded as the consequences rather than being the causes of rhabdomyolysis.
The patient received a total of 14 hemodialysis sessions during this period and the patient was discharged after his general condition has improved and liver and kidney function tests have returned to normal, and the patient was advised to attend control visits at nephrology outpatient clinics.

**Discussion**

Rhabdomyolysis is a syndrome caused by skeletal muscle damage influencing the integrity of sarcolemma. Rhabdomyolysis was first described by Fleisher in 1881 as hemoglobinuria occurring with muscle exercises\(^8,9\). It is estimated that rhabdomyolysis accounts for 5 to 25% of cases with acute renal failure. However, approximately 10 to 40% of cases with rhabdomyolysis develop acute renal failure\(^10\). Elevated serum myoglobin level is the basic laboratory finding of rhabdomyolysis. However, this finding is of no diagnostic value as myoglobin has a half-life of 1-3 hours and it is totally eliminated from the plasma in approximately 6 hours. Elevated serum CK level is a typical indication for muscle damage. It was suggested that a CK value over 500, 1000 or 3000 units would be necessary to establish the diagnosis of rhabdomyolysis\(^11\).

There are traumatic and non-traumatic causes of rhabdomyolysis. The frequency of etiologic factors varies from one country to another. Drug abuse is the leading cause in western countries, whereas traumatic causes become important in the developing countries. In general, the most common causes of rhabdomyolysis include multiple trauma, crush syndrome, vascular and orthopedic interventions, coma, immobilization, burns, alcoholism, illicit drug use or drugs, infections, electrolyte disturbances, endocrine disorders, inflammatory myopathies, metabolic myopathies, mitochondrial myopathies, malignant hyperthermia, and neuroleptic malignant syndrome. Inherited disorders are the most common causes of recurrent rhabdomyolysis in adults and children. The most common causes among inherited metabolic disorders include lipid metabolism disorders, glycogen metabolism disorders, and myoadenylate deaminase deficiency\(^12\).

Carnitine palmitoyltransferase II deficiency is the most common inherited cause of recurrent myoglobinuria. Carnitine palmitoyltransferase II enzyme is located in the inner membrane of mitochondria and it catalyzes regeneration of carnitine-acyl-coenzyme A\(^13,12\). The disease has an autosomal recessive inheritance pattern. In clinical practice, it manifests in a broad spectrum from severe multisystemic infantile form to milder muscle form with late onset that is characterized by rhabdomyolysis and myoglobinuria. Unlike glycogen metabolism disorders, patients with carnitine palmitoyltransferase II deficiency may be completely asymptomatic between disease episodes. Muscle pain occurs in the childhood, whereas myoglobinuria episodes often occur in adolescence. Exercise, infections, starvation, and cold exposure are the most common causes of rhabdomyolysis in patients with CPT II deficiency. The severity of episodes is highly variable and some episodes may result in acute renal failure\(^12\).

In the present patient, first rhabdomyolysis episode had occurred in adolescence when the patient suffered from dark-colored urination after playing football; however, he developed acute renal failure during the second episode. Differential diagnosis in patients with recurrent episodes of rhabdomyolysis requires high index of suspicion and a thorough anamnesis. Patients with McArdle’s disease exhibit exercise intolerance and severe muscle pain in addition to rhabdomyolysis. Patients with McArdle’s disease suffer from fatigue, weakness, and muscle pain in the first few minutes of intense exercise; however, a short period of rest may improve exercise tolerance (second wind phenomenon).

Clinical appearance of Tauri’s disease may resemble that of McArdle’s disease; however, carbohydrate intake may further exacerbate exercise intolerance\(^13\). In contrast to patients with McArdle’s disease and Tauri’s disease, lactic acid is found within normal ranges during exercise in patients with CPT II deficiency. The wind phenomenon is not observed in patients with CPT II deficiency. The episodes of rhabdomyolysis in these patients are often exacerbated by low-intensity exercise for prolonged duration, cold exposure, starvation, and infections\(^13\).

The present patient did not exhibit second wind phenomenon and rhabdomyolysis episode was
associated with cold exposure and starvation. Further tests including forearm exercise test, muscle biopsy, and genetic tests can be performed in patients with exercise-induced rhabdomyolysis and those suspected of having metabolic myopathy.\(^1,\) The clinicians often resort to muscle biopsy in patients with recurrent episodes of rhabdomyolysis. In contrast to carnitine deficiency that is characterized by lipid deposition, muscle biopsy in patients with CPT II deficiency may show normal findings or non-specific myopathic changes.\(^2\)

Muscle biopsy could not be performed as the patient rejected this procedure; however, electromyography showed normal findings. Molecular genetic tests and biochemical analyzes are gold standard methods in the diagnosis. S113L mutation is the most commonly found genetic mutation in patients with CPT II deficiency. Other mutations include R503C, P50H, Q413fs, and F448L mutations. More than 95% of the patients carry S113L mutation in at least one allele. With the exception of P50H, Q413fs, and F448L mutations, diagnosing CPT II deficiency is not likely in patients who do not carry S113L mutation.\(^2\) Molecular tests can establish the diagnosis by detecting mutations in both alleles of the gene. The present patient was homozygous for S113L mutation. There is a genotype-phenotype correlation in patients with CPT II deficiency. Mild missense mutation as S113L mutation is associated with muscle form of the disease. However, truncating mutations such as Q413fs and F448L mutations are associated with lethal multisystemic infantile form of the disease.\(^2\) Compound heterozygous patients for mild and severe mutations may present with a mild muscle form or severe lethal form.\(^2\) Our patient had mild muscle form of the disease as expected from homozygous S113L mutation.

However, consumption of carbohydrate-rich diet before exercise, medium-chain fatty acid supplementation, and restriction of long-chain fatty acids are recommended in these patients. Intense hydration is of paramount importance to prevent renal complications.\(^1\) Inherited causes must be kept in mind after ruling out more common causes in patients presenting with rhabdomyolysis. However, clinicians are often prone to treat these patients as idiopathic rhabdomyolysis. CPT II deficiency and other inherited causes must be considered in adult patients particularly those presenting with recurrent episodes of rhabdomyolysis. Therefore, all patients with relevant anamnesis must undergo genetic screening. In conclusion, recurrent episodes of rhabdomyolysis induced by starvation and cold exposure should raise the suspicion of CPT II deficiency. Molecular genetic analysis of the relevant gene must be performed to elucidate disease etiology and genetic counseling must be provided to the families.

References


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