

Acute renal failure due to carnitine palmitoyltransferase II deficiency

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ABSTRACT

Carnitine palmitoyltransferase II (CPT-II) deficiency is the most common long-chain fatty acid oxidation defect, resulting in rhabdomyolysis and acute renal failure (ARF). There are three forms of CPT-II deficiency: the neonatal, infantile and adult form. We report an adult form of CPT-II deficiency in a patient who presented with attacks of exercise-induced rhabdomyolysis and ARF.

INTRODUCTION

Long-chain fatty acids (LCFA) are the main energy source of muscles during prolonged exercise.¹ LCFAs cannot diffuse into mitochondria passively; they must be activated by a long-chain fatty acyl-CoA synthetase on the outer mitochondrial membrane. Long-chain fatty acyl-CoAs are imported into the mitochondrial matrix by the carnitine palmitoyltransferase system. This system consists of two distinct enzymes: the outer membrane enzyme is carnitine palmitoyltransferase I and the inner membrane enzyme is carnitine palmitoyltransferase II (CPT-II). CPT-II deficiency is the most common long-chain fatty acid oxidation defect.² This deficiency results in energy depletion in myocytes during prolonged exercise leading to rhabdomyolysis. There are three different forms of CPT-II deficiency: the neonatal, infantile and adult form. The neonatal form is the most lethal and the adult form the most benign. In the adult form of CPT-II deficiency, episodic rhabdomyolysis attacks occur following prolonged exercise, infection or anaesthesia. When rhabdomyolysis occurs, acute renal failure (ARF) follows the cascade in proportion to the

involved muscle mass and hydration status of the subject. We report a case of adult form CPT-II deficiency induced rhabdomyolysis resulting in ARF.

CASE REPORT

A 20-year-old man presented with nausea, muscle cramps and darkening of his urine. Seven years ago he first noticed that after strenuous exercise he had brown urine which resolved within three days. He was an amateur football player at that time. He then started to train hard to play competitively. At that time, again after an attack, he consulted a physician and was told that his blood urea was high and he was advised not to take prolonged exercise. He kept on doing light exercise from time to time and found out that if he sweated too much during exercise, his urine turned brown. One year before, while he was asymptomatic, he was hospitalised in the Neurology Department of our faculty for aetiological investigations. At that time electromyographic studies and muscle biopsy were nondiagnostic. One week before he was admitted to our unit, he again engaged in prolonged exercise and he noticed discoloration of his urine. During that week he also noticed a decrease in his urine volume. We hospitalised the patient in our Nephrology Department with the diagnosis acute renal failure. He was in good condition. His blood pressure was 120/80 mmHg, pulse was 80 beats/min, axillary temperature was 36.7°C, breathing frequency was 16. His lung sounds and heart sounds were normal, without friction. There was no peripheral oedema. He had no neurological deficits and his muscle strength was normal.

He had diuresis, but he did have a history of an oliguric period before he was hospitalised. His blood chemistry was consistent with rhabdomyolysis (*table 1*). Urine examination by dipstick revealed blood in the urine, but microscopic examination of urine revealed two to three erythrocytes per high power field. This was consistent with myoglobinuria.

Table 1
Blood chemistry on admission

	VALUE	NORMAL RANGE
Urea	37.4 mmol/l	1.7-8.3
Creatinine	530 µmol/l	44-123
Creatine kinase	18,760 U/l	0-190
AST	2415 U/l	5-37
ALT	406 U/l	5-37
Myoglobin	356 nmol/l	11-41
Lactate dehydrogenase (LDH)	7685 U/l	150-350
Sodium	133 mmol/l	135-145
Potassium	4.2 mmol/l	3.5-5

AST = aspartate aminotransferase, ALT = alanine aminotransferase.

The patient had a 6000 cc diuresis. The patient was in the polyuric phase of ARF, and was only treated with oral hydration. We performed a muscle biopsy and sent it to Buffalo University, NY, USA for examination of muscle enzyme levels. The phosphorylase and citrate synthase activity were in the normal range, but carnitine palmitoyl-transferase (CPT) II activity was 12.0 nmol/min/g (normal 77.8±13.3). Ratio of CPT-II/ citrate synthase was 0.85 (normal 5.13±1.62). The diagnosis of CPT-II deficiency induced rhabdomyolysis was made. After five days his urine volume fell to 1700 cc, and his blood urea and creatinine levels normalised. He was discharged from hospital and started on a carbohydrate-rich diet. He was told not to do any exercise. Six months later, he again played in a football match on a hot day, which again resulted in rhabdomyolysis induced acute renal failure. He recovered from the last attack as well. During his follow-up CK levels remained within normal ranges.

Discussion

In normal metabolic conditions, the main energy source for muscles is glucose. To support the contraction of skeletal muscles, physical exercise increases total body metabolism to 5 to 15 times the resting rate. LCFAs become the major source of energy after 30 minutes of exercise, and thus they must be transported into mitochondria by specific enzymes, including CPT-II. In CPT-II deficiency the spectrum of the clinical presentation mainly depends on the remaining enzyme activity. The least activity results in the most energy depletion. The unique pathway

leading to rhabdomyolysis starts after depletion of energy within muscle cells (*figure 1*).

There are several factors that lead to myoglobin induced acute renal failure. The most important factor is dehydration.

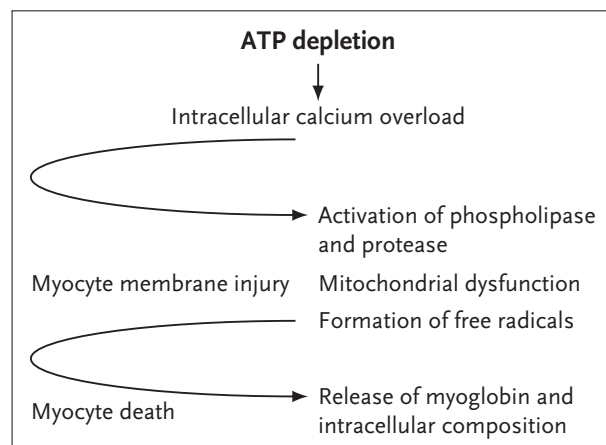


Figure 1
ATP depletion and myocyte death

ATP depletion results in intracellular calcium overload. Calcium activates phospholipase and protease enzymes, which lyse cellular membrane and alter the function of mitochondria. These enzymes also form free radicals that lead to myocyte death. Cellular ingredients including myoglobin, phosphorus and uric acid leak to outside of the membrane.³

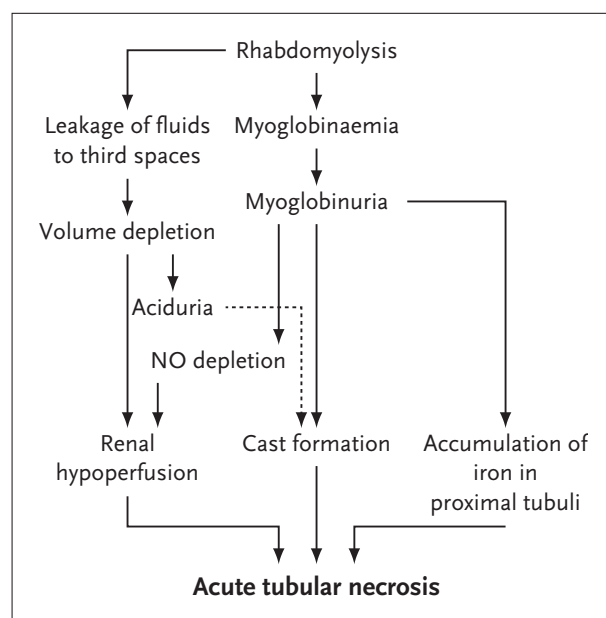


Figure 2
Rhabdomyolysis and tubular necrosis

Rhabdomyolysis results in myoglobinaemia. Myoglobinuria occurs when myoglobin exceeds 250 µg/ml (normal 5 ng/ml) and causes cast formation and accumulation of iron in proximal tubules. Sequestration of fluids in injured muscles results volume depletion, aciduria, nitric oxide depletion and renal hypoperfusion that altogether contribute to acute tubular necrosis.⁵

During physical exercise, especially in hot weather, the sweating rate is 1.0 to 2.5 l/h.⁴ This dehydration can be augmented to 5% of the body weight depending on the intensity of the exercise, clothing worn and how hot the weather is. In our patient's history, his urine only became discoloured if he sweated too much during exercise. An intervention, rehydration, at this point may potentially prevent the renal dysfunction.

The causes of rhabdomyolysis differ from country to country. In Turkey, after the major Marmara earthquake in 1999, the most common cause of rhabdomyolysis became crush syndrome.⁵ In USA, most cases of rhabdomyolysis are due to trauma, and in Poland alcohol abuse.^{6,7} Whatever the cause, the rhabdomyolysis may progress to myoglobin induced acute renal failure (figure 2). The incidence of myoglobin induced ARF has been reported to be 16 to 33%.

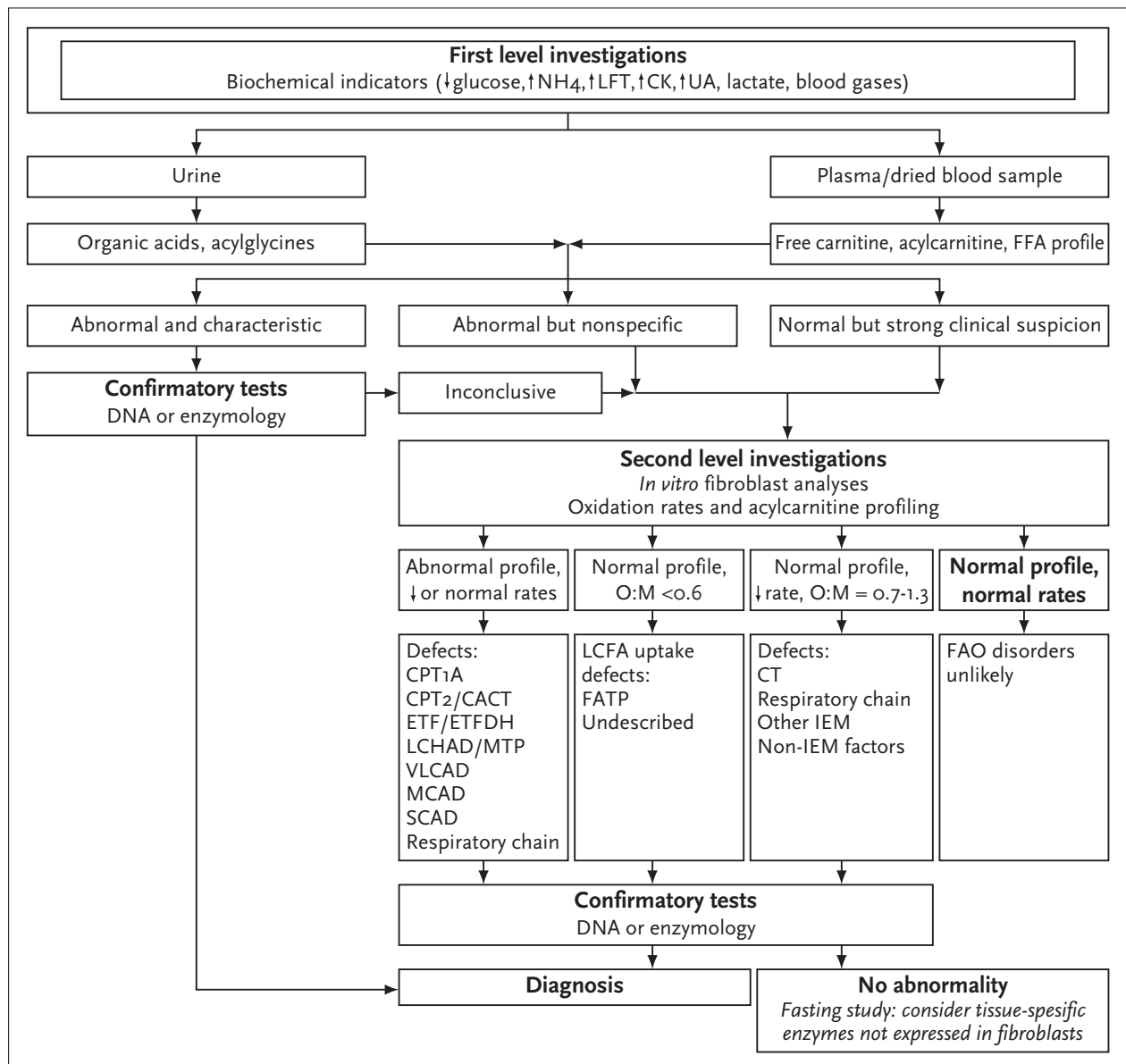


Figure 3
Diagnostic steps in suspected FAOD patients

NH₄ = ammonium, LFT = liver function tests, CK = creatine kinase, U = uric acid, O = oxidation rate of [9,10(n)-3H] Oleate, M = oxidation rate of [9,10(n)-3H] Myristate, CPT1A = hepatic carnitine palmitoyltransferase I, CPT2 = carnitine palmitoyltransferase II, CACT = carnitine acylcarnitine translocase, ETF = electron transfer flavoprotein, ETFDH = electron transfer flavoprotein dehydrogenase, LCHAD = longchain L-3-hydroxyacyl-CoA dehydrogenase, MTP = mitochondrial trifunctional protein, VLCAD = very long chain acyl-CoA dehydrogenase, MCAD = medium-chain acyl-CoA dehydrogenase, SCAD = short-chain acyl-CoA dehydrogenase, FATP = long-chain fatty acid transporter protein, CT = plasma membrane carnitine transporter, IEM = inborn errors of metabolism, FAO = fatty acid oxidation.⁸

Recurrent rhabdomyolysis is characteristic of the adult form of CPT-II deficiency, and is often associated with deficiency of L-3-hydroxyacyl-CoA dehydrogenase (LCHAD), mitochondrial trifunctional protein (MTP), very long-chain acyl-CoA dehydrogenase (VLCAD) and short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD).¹

Diagnosis of fatty acid oxidation disorder (FAOD) in a clinical case first requires the awareness and recognition of the disease. The introduction of tandem mass spectrometry (MS/MS) has substantially improved the ability to detect FAOD by acylcarnitine profiling. The diagnostic steps in a suspected FAOD include: routine blood chemistry, blood gases, acylcarnitine profiling by MS/MS, *in vitro* cellular-based screening assays (oxidation rate and quantitative acylcarnitine profiling), DNA analyses or biochemical measurement of the enzyme (*figure 3*). In CPT-II deficiency, urine organic acid profile, urine acylglycine and plasma C6-16 free fatty acids are normal, but free carnitine and acylcarnitine profiles of plasma or dried blood sample show an increase in C16, C16:1, C18:1 and C18:1.⁸ What is lacking in our case is that we were unable to perform an acylcarnitine profile.

The value of muscle biopsy in unexplained rhabdomyolysis, or its marker as elevated levels of creatine kinase, has been investigated by some authors. Certain diagnosis can be reached in 18.4 to 45% for persistent hyper-creatine kinase-aemia (hyperCKaemia).⁹ In recurrent rhabdomyolysis, underlying disease can be found in 15 to 47% of patients.¹⁰ CPT-II deficiency was found to be the main aetiological factor in the majority of diagnoses. Normal histological or immunohistochemistry findings do not rule out inherited diseases. Prella *et al.* reported normal histology or histochemistry in muscle biopsies of patients with persistent hyperCKaemia, but reached a specific diagnosis in 12% of them by biochemical, immunohistochemical or genetic investigation (dystrophinopathy, partial CPT deficiency, malignant hyperthermia).¹¹ In our patient, we could not reach the diagnosis by histology and histochemistry. We identified CPT-II enzyme defect by biochemical investigation of the muscle tissue.

An intervention or preventive measures to avoid energy depletion can potentially prevent rhabdomyolysis. Preventions are either not doing exercise, or not augmenting the body metabolism (fever, anaesthesia). In our patient, all the rhabdomyolysis attacks occurred after prolonged exercise in hot and humid weather. Although he was asked not to engage in strenuous exercise, he kept on doing it on occasions. Intervention before energy depletion can consist of giving the necessary energy source with carbohydrates. This can be maintained by eating before exercise, but only intravenous glucose has been reported to be beneficial.¹²

In conclusion, patients with recurrent rhabdomyolysis should be further evaluated by means of muscle biopsies. Normal histology or histochemistry can be found in CPT-II deficient patients' muscle biopsies, hence the diagnostic steps, including acylcarnitine profile, need to be performed in suspected cases. Prolonged exercise must be avoided. If not, the patients must be fully rehydrated during exercise, or other conditions that elevate body metabolism, to prevent myoglobinuric acute renal failure.

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