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# Case Report: Carnitine Palmitoyl Transferase II (CPT II) Deficiency

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## Abstract

Carnitine Palmitoyl Transferase II (CPTII) is a very important enzyme that helps with the oxidation of long-chain fatty acid to produce energy. Deficiency in CPTII will lead to energy deficiency in the case of fasting and the accumulation of the long chain fatty in the body. There are three types of CPT II deficiency, the myopathic form, the severe infantile hepatocardiomuscular form and the lethal neonatal form. They are all inherited as an autosomal recessive. Diagnosis of the CPTII are 1) tandem mass spectrometry (MS/MS) in adult form and 2) CPTII polymorphism (F352C), which is linked to reducing the activity of CPTII in infantile form [1]. Glucose is the primary management and medium-chain fatty acid is an alternative due to the bypass of the CPTII enzyme in the pathway. For the prevention of CPTII deficiency are to avoid long chain fatty acid (C12-fatty acid), fasting, prolonged exercise, known triggers, and certain medications such as anti-epileptics and general anesthesia. During the rhabdomyolysis and myoglobinuria attack, it is very important to maintain hydration to avoid acute renal failure. If, however, renal failure occurs, dialysis is recommended. We present a case of a 27-year-old African American woman with the significant past medical history of CPT II deficiency leading to recurrent rhabdomyolysis and myoglobinuria. Together with all the research studies from diagnosis to treatment of CPTII deficiency will help in clinical management of patients. And this case report will add to the existing case reports of patients who have CPTII deficiency in terms of how we diagnose, how we treat, and how we prevent symptoms from re-occurring.

## Keywords

Carnitine Palmitoyl Transferase II (CPTII), Mitochondria, Long Chain Fatty Acid, Medium Chain Fatty Acid, Carnitine, Carnitine Palmitoyl Transferase I

(CPTI), Acyl-Carnitine, Beta-Oxidation, Rhabdomyolysis, Myoglobinuria, Renal Failure, Hypoketotic Hypoglycemia

## 1. Introduction

The Carnitine Palmitoyl Transferase II (CPTII) deficiency is the disorder of long-chain fatty acid oxidation. There are three types of CPT II deficiency, the myopathic form (the least fatal), the severe infantile hepatocardiomuscular form and the lethal neonatal form. They are all inherited as an autosomal recessive. It is seen in adults with recurrent rhabdomyolysis episodes and myoglobinuria which leads to renal failure in some cases. It is usually triggered by infection, exercise, cold, fasting, stress, and sickness before myopathic symptoms occur. The infantile involves multiple organ systems including liver failure, cardiomyopathy, peripheral neuropathy and patients usually develop hypoketotic hypoglycemia with the 628S (1883A > C) as the most common mutation. Most patients die in their early childhood. The neonatal disease is the least common but the most fatal with a rare missense mutation, R296Q (907G>A) [2]. Patients often die within the first few years of life.

Below is the diagram that includes the pathway of long-chain fatty acids and how they get oxidized in the mitochondria (**Figure 1**). It also includes the role of CPTII.

In our body, the beta-oxidization process of long-chain fatty acid (C14-C18) takes place in the mitochondrial carnitine system. Mitochondrial is the powerhouse in producing ATPs. During glucose depletion, our body undergoes ketogenesis and uses long-chain fatty acids to produce energy.

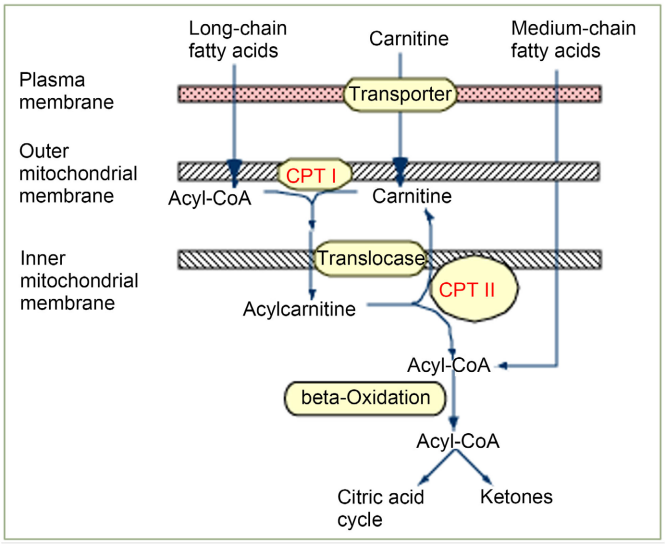


**Figure 1.** From Carnitine Palmitoyltransferase II Deficiency: Francesco Detomaso 1, Vito Pepe 1, Francesca Partipilo 1, Giuseppe Gernone 1. 1 UOSVD of Nephrology and Dialysis ASL Bari. Headquarters: Hospital. "St. Mary of the Angels" Putignano [3].

According to the diagram above, long-chain fatty acids (C14-C18) are activated at the cytosol to Acyl-CoA with the help of Acyl-CoA synthase. Acyl-CoA combined with Carnitine is transported from the cytosol into the outer mitochondrial membrane through a transporter and is converted to Acyl Carnitine with the help of CPT I enzyme and then translocated into the inner mitochondrial membrane. Acyl Carnitine has 2 roles, either recycling Carnitine back into the outer mitochondrial membrane or undergoing Acyl-CoA with the help of CPTII enzyme. Acyl-CoA undergoes beta-oxidation to produce byproducts to undergo citric acid cycle to produce energy and ketones. The lack of CPTII enzyme will result in a decrease in Acyl-CoA and beta-oxidation inside the mitochondrial matrix and will result in an increase in the free fatty acids in the cytosol.

## 2. Case Presentation

A 27 years old African American woman with significant past medical history of CPT II deficiency, rhabdomyolysis, anxiety and depression presented to the Mercy Hospital Emergency Department complaining of muscle pain and weakness. Patient reported that her muscle pain and weakness started a few days prior to hospitalization, mostly on her neck, back muscles, and calf muscles. Patient described the pain as crampy and sore, 7-8 in severity and localized to the neck, back muscles and calf muscles. Patient was diagnosed with CPT II deficiency since she was 12 years old and has been hospitalized 6 times due to rhabdomyolysis episodes and the last episode was 7 years ago. Patient reported that she had a sore throat a few days prior to her muscle weakness occurred which led her to the Mercy Emergency Department. She was sent home at the same day with a prescription of Bactrim for 5 days. After she went back home, she started to have difficulty moving her arms and legs. Her muscles started to feel sore and crampy which led her to come to the Emergency Department. Otherwise patient denied any fever, chills, headache, shortness of breath, abdominal pain urinary or bowel movement problems. Patient also denied any brown urine at that time. Patient reported of not smoking, drinking or using any illicit drugs. Patient was not on any home medications at the time besides the prescribed Bactrim that was given at the Emergency Department from her last admission. Upon arrival at the Emergency Department this time, her blood pressure was 137/66, her heart rate was 135, respiratory rate was 29, her temperature was 36.8 and her initial CK was 449. On physical examination, patient experienced pain and tenderness upon palpation on the neck, back and calf muscles. The rest of the physical examination showed normal heart sounds, normal lung sounds and normal bowel sounds. She was given IV fluid at the Emergency Department. Patient was admitted to the General Medicine Floor for the management of rhabdomyolysis.

Below is the summary of her CK levels and the amounts and types of fluids that were given during her entire hospital stay (**Figure 2**, **Figure 3**).

After she was transferred to the general medicine floor, there was a total of 4500 ml of normal saline was administered and her CK level was 9 K. On day 2,

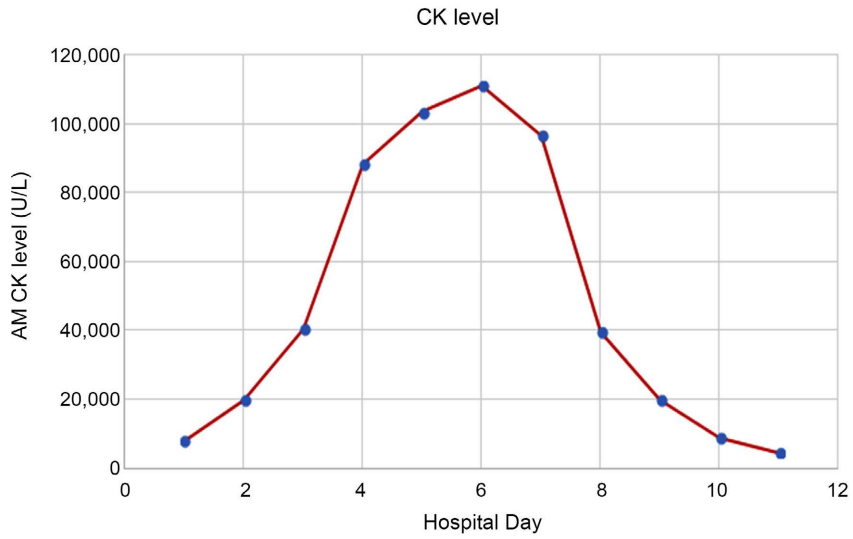


**Figure 2.** From Dr. Balpreet Kaur MD, Assistant Professor at Medical College of Wisconsin.

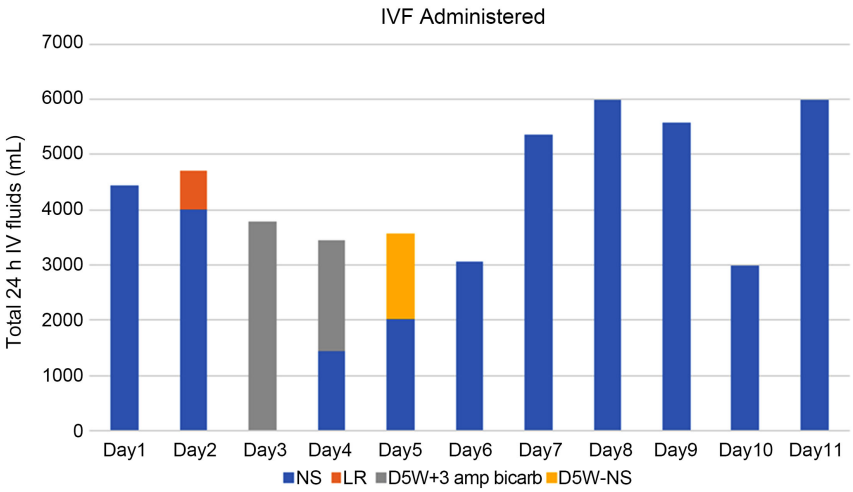


**Figure 3.** From Dr. Balpreet Kaur MD, Assistant Professor at Medical College of Wisconsin.

there a total of 4000 ml of normal saline and 700 ml of lactated ringer were administered and her CK level was 20 K. On day 3, a total of 3800 ml of D5W + 3 amp bicarb was administered and her CK level was 40 K. On day 4, a total of 1400 ml of normal saline and 2000 ml of D5W + 3 amp bicarb were administered and her CK level was 90 K. At this point, her CK was doubled in 1 day making the patient worried. She wanted to know what we did to her and preferred to transfer to Rush Hospital. We called Rush and explained to them about her situation. They confirmed to us that if the patient was transferred, they would still be provided the same treatment as it was done at Mercy Hospital. We informed the patient about the information that we got from Rush and she decided to stay at Mercy Hospital. On day 5, a total of 2000 ml of normal saline and 1500 ml of D5W-NS were administered and her CK level was 105 K. Her CK

level went up as high as 110 K on day 6 and that was when the nephrologist was consulted and they decided to discontinue D5W-NS and continue only with normal saline from now on until her CK started to decline to acceptable range. There was a total of 3000 ml of normal saline was administered that day. Nutritionist was also consulted and a diet low in fat and high in sugar was implemented. On day 7, her CK started to decline from 110 K to 98 K with a total of 5400 ml of normal saline was administered. On day 8, we had increased her normal saline to 6000 ml and her CK decreased dramatically to 40 K. On day 9, there was a total of 5500 ml of normal saline was administered and her CK decreased to 20 K. On day 10, there was a total of 3000 ml of normal saline was administered and her CK decreased to 9 K.

On day 11, we increased a total of 6000 ml of normal saline was given to the patient to ensure that her CK had gone down to an acceptable range before she could be discharged home. Her CK level declined to 1799 and the patient was discharged home that day. During her entire hospital stay, we monitored her CK levels, IVF, and any changes in her electrolytes cautiously. Luckily the patient did not develop any kidney problems, and did not experience changes in urinary color or any electrolyte abnormalities. Prior to discharge home, the patient was given information about changes in her diet and was scheduled as an outpatient follow-up with the neuromuscular specialist at the University of Illinois Chicago in December 2019.

Due to the rare nature of CPTII deficiency, there are not so many case reports available. However, there was a similar case available in the literature review in JStage, Journal of Internal Medicine. This is the very first case of CPTII deficiency in a Japanese patient who has Homozygous Point Mutation S113L. Below is the summary of the case report of the Japanese patient and the treatment that the patient received.

"Carnitine Palmitoyltransferase II (CPT II) deficiency is a rare inherited disorder related to recurrent episodes of rhabdomyolysis. The adult myopathic form of CPT II deficiency is relatively benign and difficult to diagnose. The point mutation S113L in CPT2 is very common in Caucasian patients, whereas F383Y is the most common mutation among Japanese patients. We herein present a case of CPT II deficiency in a Japanese patient homozygous for the missense mutation S113L. The patient showed a decreased frequency of rhabdomyolysis recurrence after the administration of a diet containing medium-chain triglyceride oil and supplementation with carnitine and bezafibrate [4]."

## 3. Discussion

The Carnitine Palmitoyl Transferase II (CPTII) deficiency is a rare disease, and the severity of the disease depends on the percentage of the CPT enzyme activity. There was a study "Allelic and Phenotypic Heterogeneity in 49 Italian Patients with Muscle Form of CPT-II deficiency" showed that if the CPT enzyme < 25%

increases the chance of muscle problems and CPT enzyme < 15% further increases muscle problem severity [5]. Out of the 15 mutations found, there were 2 homozygous missense mutations p.S113L and p.R631C that increase the severity of CPT II enzyme deficiency myopathic form [6]. There was also another study done on a Chinese patient found that the CPT II gene had 2 missense mutations p. H369Q and p. G497S that increase the risk of CPT II enzyme deficiency [7]. Based on these studies, we can say that each ethnicity does express different mutations but patients would experience similar episodes of CPT II deficiency myopathic form.

Presentation:

• Myopathic form: muscle pain in multiple trigger points, fatigue, abdominal pain, rhabdomyolysis, and myoglobinuria [8].

• Severe infantile hepatocardiomuscular form: liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia due to the liver not under ketogenesis during fasting or starvation. Fat accumulation in the liver due the inability to break down long-chain fatty acid causing hepatic steatosis [8].

• Lethal neonatal form: liver failure, cardiomyopathy, seizures, coma, cystic renal dysplasia, neuronal migration defects or brain dysgenesis [8].

Diagnoses of CPTII deficiency:

• In adult form: Tandem mass spectrometry (MS/MS) is a non-invasive and rapid method of detecting CPT II activity based on the stoichiometric of acylcarnitine [9]. With this mass spectrometry, the linear regression shows R = 0.8369. On the mass spec, it may show an increase in long chain (C16, C18:1) acylcarnitine with low C2 signal [2]. Labs may show increased excretion of long-chain dicarboxylic acids, increased levels of acylcarnitine and total blood carnitine levels are decreased.

• In infantile form: CPTII polymorphism (F352C) is linked to reducing the activity of CPTII [1].

Labs [8]:

• Increase CK levels

• Increase creatinine

• Increase BUN

• Hypoglycemia, hypoketonemia and hypoketonuria

•Aciduria

Treatment [2]:

• Glucose is the primary treatment

Note: During infection, IV glucose is recommended.

• Medium chain fatty acid is an alternative (due to the bypass of the CPTII enzyme)

• Avoiding long-chain fatty acid (C12-fatty acid), fasting, prolonged exercise, and known triggers

• Avoid medications such as valproic acid, general anesthesia, Ibuprofen, and diazepam

• Maintain hydration during rhabdomyolysis and myoglobinuria

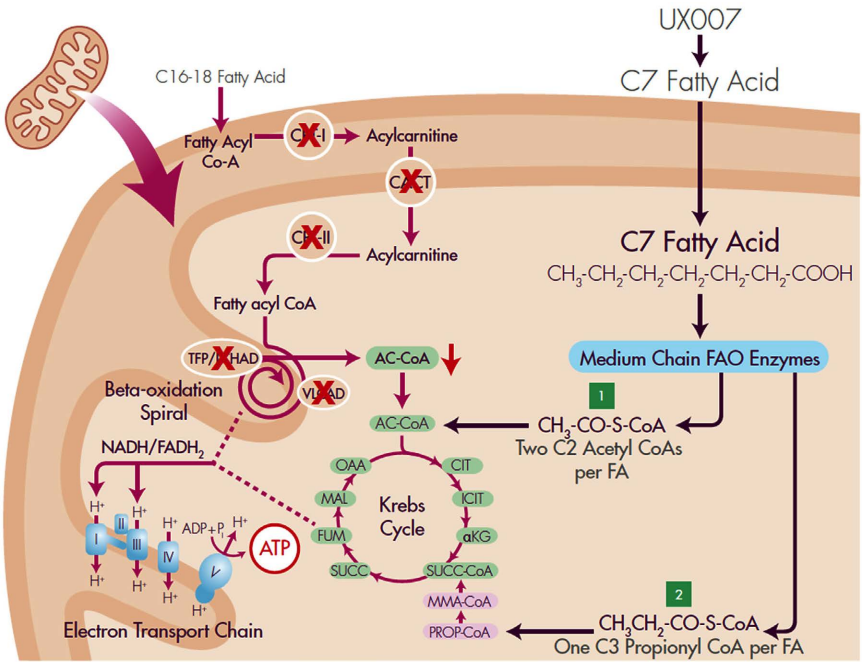


**Figure 4.** From Ultrageny, "UX007 For FAOD" [10].

• Dialysis when renal failure occurs

Treatment in pregnant women [2]:

• Analgesia

• Glucose

• Monitor CK level cautiously

Experiment treatment in rats [10]:

• Theophylline: increases cardiac and renal CPT acidity in rats.

• "UX007" which is an odd-fatty acid (C7) that can bypass the CPT I and CPT II enzymes and goes straight to the Krebs Cycle to replace any missing intermediates. UX007 also helps with the gluconeogenesis process. (**Figure 4**)

• Dojolvi (UX007/triheptanoin) is the first FDA approved drug to treat children and adults with long-chain fatty acid oxidation metabolism disease.

## 4. Conclusion

In this case report, we highlight the different types of Carnitine Palmitoyl Transferase II (CPTII) deficiency and the symptoms associated with each type accordingly. In myopathic form, CPTII deficiency presents with muscle pain in multiple trigger points, fatigue, abdominal pain, rhabdomyolysis, myoglobinuria, and renal failure in some cases. In severe infantile hepatocardiomuscular form: liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia due to Liver cannot undergo ketogenesis during fasting or starvation. Fat accumulation in the liver due to liver cannot breakdown long-chain fatty acid causing hepatic steatosis. In lethal neonatal form: liver failure, cardiomyopathy, seizures, coma, cystic renal dysplasia, neuronal migration defects or brain dysgenesis. It is very important to follow serum creatinine kinase (CK), BUN and creatinine levels as

we are concerned about the possibility of renal failure. Glucose is the primary management and medium-chain fatty acid is an alternative due to the bypass of the CPTII enzyme in the pathway. For the prevention are to avoid long chain fatty acid (C12-fatty acid), fasting, prolonged exercise, known triggers, and certain medications such as anti-epileptics and general anesthesia. During the rhabdomyolysis and myoglobinuria attack, it is very important to maintain hydration to avoid acute renal failure. If, however, renal failure occurs, dialysis is recommended. Due to the rare nature of this genetic disease, extensive research still needs to be done to come up with treatment management to prevent the recurrence of disease symptoms and possibly to cure the disease.

## Additional Information

### Human Subjects

Consent was obtained from all participants in this report.

### Payment/Services Info

The authors declare having no financial responsibility with any institution. The author did not receive any financial support for the submitted work.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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