Online publication ahead of print, AJMHS Vol 56, 2021

Rhabdomyolysis Due to Carnitine Palmitoyltransferase II Deficiency – a Common but Underrecognized Condition

Entela Greca[1*], Saimir Seferi[1], Anila Babameto[2], Ahmet Duraku[1], Bjeshkatore Selmani[1]

[1] Nephrology Department, "Mother Teresa" University Hospital, Tirana, Albania
[2] Genetic Department, "Mother Teresa" University Hospital, Tirana, Albania

Abstract

A young 33-year-old male goes to the emergency room with weakness, nausea, anuria, which started three days before admission. The symptoms appeared after a prolonged exercise. An acute kidney injury developed, and Hemodialysis treatment was needed. At the clinical presentation, he had a high plasma Creatine Kinase (CK) level and CK-MB level. The genetic testing confirmed the diagnosis of Inherited Rhabdomyolysis, a metabolic disorder of Carnitine Palmitoyl transferase II Deficiency.

Keywords: Carnitine Palmitoyltransferase II deficiency, Rhabdomyolisis, metabolic disorder, acute renal failure, genetic disorder

Address for correspondence: Entela Greca*, Nephrology Department, "Mother Teresa" University Hospital, Tirana, Albania. E-mail: entigreca@gmail.com

INTRODUCTION

Carnitine palmitoyltransferase II deficiency is an autosomal, recessively inherited genetic metabolic disorder that causes an amino acid change from Ser to Leu at position 113 (1). Carnitine palmitoyltransferase (CPT) catalyzes the transfer of long-fatty acids from the cytoplasm into mitochondria, where β-oxidation happens. The two forms of CPT are CPT I localized at the outer membrane of mitochondria and CPT II localized inside the mitochondria. If there is a defect of the CPT2 enzyme, long-chain fatty acid can not be transported into the mitochondria and can not be used as an energy source (1,2).

The three clinical presentations of CPT 2 deficiency described in the literature are:

- the *lethal neonatal* form that is lethal during the first months of life.
- the *infantile hepatic-cardiac-muscular* form is presented as severe attacks of hypoketotic hypoglycemia, associated with cardiac damage, which causes sudden death before the first year.
- the *myopathic* form characterizes by episodes of rhabdomyolysis triggered by intense exercise, drugs, or febrile episodes (3).

The most frequent pattern in clinical practice is the Myopathic form, and the symptomatology consists of recurrent attacks of rhabdomyolysis, presenting as myalgias, cramps, weakness, and myoglobinuria. Rhabdomyolysis may result in complications such as Acute Renal Failure and Respiratory Insufficiency (4).

CASE REPORT

A 33-year-old male patient was admitted to our hospital with muscle weakness, nausea, and anuria. The patient mentioned he had performed excessive physical activity three days before hospitalization and felt low back pain, muscle pain, and lightly brown-colored urine. He then experienced anuria for about two days before arriving at the emergency unit.

Six years ago, his older brother went through the same medical condition after a strenuous exercise.

Laboratory testing revealed high serum levels of CK64 180 U/L, CK-MB 1057 U/L, LDH 2890 U/L, AST 4017 U/L, ALT 1000 U/L, Creatinine 6.6 mg/dl, and Urea 169 mg/dl (Table 1). Kidney ultrasound showed normal kidneys in terms of size and structure. Other lab tests were within the normal range.

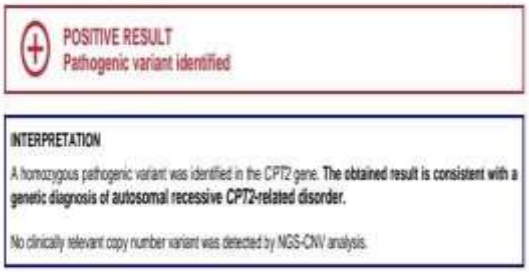
Table 1. Presentation of the laboratory findings during the patient hospitalization.

	First day	Last day	
CK	64180	62	U/L
CK MB	1057	35	U/L
LDH	2809	216	U/L
AST	407	97	U/L
ALT	1088	145	U/L

CREATININE	6.6	1.4	mg/dl
UREA	169	166	mg/dl
K	4.7	4.1	mmol/l
Ca	8	9	mg/dl
P	6.1	4	mg/l
WBC	10000	86000	/mm3
PLT	16300	25800	/mm3
TOTAL PROTEINE	7	8.5	g/dl
ALBUMINE	3.9	4.5	g/dl

The persistence of anuria and progressive decline of renal function were strong indicators to initiate dialysis treatment. The patient was treated with eight hemodialysis sessions until the improvement of the renal function.

Genetic testing (molecular analyses) for our patient and his brother confirmed Carnitine palmitoyl transferase II deficiency (Figure 1).


POSITIVE RESULT
Pathogenic variant identified

INTERPRETATION

A homozygous pathogenic variant was identified in the CPT2 gene. **The obtained result is consistent with a genetic diagnosis of autosomal recessive CPT2-related disorder.**

No clinically relevant copy number variant was detected by NGS-CNV analysis.


CENTOGENE

RESULT SUMMARY

GENE	VARIANT COORDINATES	AMINO ACID CHANGE	SNP IDENTIFIER	ZYGOSITY	IN SILICO PARAMETERS*	ALLELE FREQUENCIES**	TYPE AND CLASSIFICATION***
CPT2	NM_000098.2:c.338C>T	p.(Ser113Leu)	rs74315294	homozygous	PolyPhen: Probably damaging; Align-GVGD: C0; SIFT: Deleterious; MutationTaster: Disease causing; Conservation_int: high; Conservation_ext: high; 2/2 likely splice effect	gnomAD: 0.0014; ESP: 0.0014; 1000 G: 0.0000; CentoMD: 0.0012	Missense; Pathogenic (class 1)

Figure 1. Results of genetic testing

The CPT2 variant c.338C>T p. =(Ser113Leu) causes an amino acid change from Ser to Leu at position 113. The substitution is in close proximity to the highly conserved donor splice site of intron None.

Our patient was discharged from the hospital in good condition, with proper recommendations regarding his lifestyle to prevent similar episodes in the future.

DISCUSSION

Carnitine palmitoyltransferase II deficiency is the most common inherited disorder of mitochondrial long-chain fatty acid oxidation, characterized by attacks of myalgia and myoglobinuria.

The most common "classic" Myopathic form occurs in young adults and is characterized by recurrent episodes of rhabdomyolysis. The CPT2 defect prevents the transportation of long-fatty acids into mitochondria, as a result preventing the use as an energy source. The patient usually has muscle pain and weakness associated with the breakdown of muscle tissue. When the muscle

tissue breaks down, myoglobin is released. It is processed by the kidneys and released in the urine as myoglobinuria. This protein causes the redness of the urine. It can also damage the kidneys, in some cases leading to kidney failure (3,5).

In literature are described 300 cases. About 80% of the patients are males. It is linked to the X-chromosomal genes or hormonal factors (estrogen) that might regulate the CPT enzyme (6). The first description of this condition was made in 1973 by the brother's Di Mauro, and the mutation that is mainly found was p. (Ser113Leu) that causes an amino acid change from Ser to Leu at position 113. This variant has previously been described as disease-causing for Carnitine palmitoyl transferase II (CPT2) deficiency by Taroni (7).

For the diagnosis of CPT II deficiency is essential the muscle biopsy (to find reduced CPT enzyme activity in muscle) or molecular genetic testing to identify pathogenic variants of CPT2 (3).

It is characterized by recurrent episodes of rhabdomyolysis triggered by prolonged and intense exercise, drugs, fasting, or febrile illness. The treatment consists of a carbohydrate-rich diet and lifestyle changing.

We presented a patient with myalgia, fatigue, and dark urine (brown-colored), with Acute Liver Injury and Acute Kidney Injury requiring hemodialysis. Laboratory data suggested that it was due to rhabdomyolysis triggered by an intensive exercise. Six years ago, at University Hospital Center "Mother Theresa," his brother was admitted with the same medical history presentation. He also developed acute hepatic lesions, acute kidney injury and rhabdomyolysis. He was treated with supportive therapy and hemodialysis sessions. Genetic testing (molecular analyses) for our patient and his brother confirmed Carnitine palmitoyltransferase II deficiency. Our patient was discharged in good condition, without need for hemodialysis. We recommended a diet rich in carbohydrates, a low amount of fat and protein, eating often, and changing his lifestyle. He ought to stay away from habits that may trigger symptoms such as fasting, exposure to cold, stress, and intense exercise.

The same medical situation with the acute hepatic lesion, rhabdomyolysis, acute kidney injury requiring hemodialysis and then discharged in good condition was described by Nikola Gjorgjievski (8). Another case was described by M Valvukis (9), where a patient with CPT2 deficiency was presented with cardiomyopathy and rhabdomyolysis triggered by febrile episodes and intense physical work.

The patient was treated with supportive therapy and hemodialysis, and further was discharged in good condition with proper advice for a lifestyle modification.

In conclusion, we could say that Carnitine palmitoyltransferase II deficiency is an underdiagnosed cause of rhabdomyolysis. We should be vigilant to this defect if we have a patient presented with rhabdomyolysis and acute kidney injury. Recognition of CPT II deficiency

can prevent further episodes of acute kidney injury and other life-threatening conditions.

Acknowledgments: None declared.

Conflict of interest: None declared.

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