



# International Journal of Pediatrics and Neonatology

ISSN Print: 2664-8350  
ISSN Online: 2664-8369  
Impact Factor: RJIF 5.26  
IJPN 2024; 6(2): 24-26  
[www.pediatricsjournal.net](http://www.pediatricsjournal.net)  
Received: 12-05-2024  
Accepted: 17-06-2024

**Marisa Pereira**  
Serviço de Cardiologia  
Pediátrica, UAG da Mulher e da  
Criança, Centro Hospitalar  
Universitário de São João, Porto,  
Portugal

**Regina Silva**  
Serviço de Pediatria, UAG da  
Mulher e da Criança, Centro  
Hospitalar Universitário de São  
João, Porto, Portugal

**Teresa Campos**  
Centro de Referência de Doenças  
Hereditárias do Metabolismo,  
UAG da Mulher e da Criança,  
Centro Hospitalar Universitário  
de São João, Porto, Portugal

**Carla Vasconcelos**  
Centro de Referência de Doenças  
Hereditárias do Metabolismo,  
UAG da Mulher e da Criança,  
Centro Hospitalar Universitário  
de São João, Porto, Portugal

**Laura Vilarinho**  
Unidade de Rastreio Neonatal,  
Metabolismo e Genética,  
Departamento de Genética  
Humana, Instituto Nacional de  
Saúde Dr. Ricardo Jorge, Porto,  
Portugal

**Esmeralda Rodrigues**  
Centro de Referência de Doenças  
Hereditárias do Metabolismo,  
UAG da Mulher e da Criança,  
Centro Hospitalar Universitário  
de São João, Porto, Portugal

**Elisa Leão Teles**  
Centro de Referência de Doenças  
Hereditárias do Metabolismo,  
UAG da Mulher e da Criança,  
Centro Hospitalar Universitário  
de São João, Porto, Portugal

**Corresponding Author:**  
**Marisa Pereira**  
Serviço de Cardiologia  
Pediátrica, UAG da Mulher e da  
Criança, Centro Hospitalar  
Universitário de São João, Porto,  
Portugal

## Rhabdomyolysis in childhood: A case of carnitine palmitoyltransferase deficiency type II

**Marisa Pereira, Regina Silva, Teresa Campos, Carla Vasconcelos, Laura Vilarinho, Esmeralda Rodrigues and Elisa Leão Teles**

**DOI:** <https://doi.org/10.33545/26648350.2024.v6.i2a.77>

### Abstract

The conditions known as fatty acid oxidation disorders (FAODs) are a cluster of genetic disorders inherited in an autosomal recessive manner and associated with substantial morbidity and mortality. However, they are generally considered promising candidates for newborn screening (NBS) programs. Carnitine palmitoyltransferase (CPT) II deficiency ranks among the prevalent types of disorders affecting muscle fatty acid metabolism. This condition has been categorized clinically into three phenotypes, with the myopathic form being the most prevalent manifestation of CPT II deficiency. Here we report a case of rhabdomyolysis due to a muscle form of CPT II deficiency in an infant with normal NBS results.

We conclude that CPT II deficiency should be suspected in cases of significant rhabdomyolysis episodes, even when NBS results are normal. Additionally, if the acylcarnitine profile during the rhabdomyolysis crisis remains normal but clinical suspicion persists, genetic studies must be conducted.

**Keywords:** Rhabdomyolysis, fatty acid oxidation disorders, carnitine-palmitoyltransferase deficiency type ii

### Introduction

The conditions known as fatty acid oxidation disorders (FAODs) are a cluster of genetic disorders inherited in an autosomal recessive manner and associated with substantial morbidity and mortality, but early diagnosis and early initiation of treatment are improving outcomes <sup>[1]</sup>. On the whole, FAODs are considered suitable candidates for newborn screening (NBS) due to the fact that most affected children typically present as healthy during this period. Catastrophic symptoms can often be averted through regular feeding, adherence to a tailored nutritional regimen, and proactive measures such as avoiding decompensation by increasing energy intake or administering high doses of glucose intravenously during illness episodes <sup>[2]</sup>.

Carnitine palmitoyltransferase (CPT) II deficiency ranks among the prevalent types of disorders affecting muscle fatty acid metabolism <sup>[3, 4]</sup>. CPT II functions as an enzyme firmly anchored to the inner membrane of the mitochondria. The transportation of long-chain fatty acids into the mitochondria involves a series of steps: they are first converted into acylcarnitines of matching chain length by the successive actions of acyl-CoA synthetase, CPT I, and carnitine-acylcarnitine translocase. Subsequently, CPT II catalyzes the conversion of these long-chain acyl-carnitines back into acyl-CoA, thus providing substrates for the  $\beta$ -oxidation system <sup>[2]</sup>.

CPT II deficiency is clinically categorized into three distinct phenotypes: (1) a muscular form characterized by recurrent episodes of rhabdomyolysis typically appearing in adolescence or later; (2) a severe infantile form, manifesting with symptoms such as hypoglycemia, Reye-like encephalopathy, and in severe cases, cardiopulmonary arrest, primarily occurring during infancy and early childhood; and (3) a fatal neonatal form linked with cardiomyopathy <sup>[2, 3, 4]</sup>. The myopathic form of CPT II deficiency represents the most common variant of the condition. Approximately sixty percent of individuals experience symptom onset during early childhood, as opposed to adolescence or adulthood.

Clinical manifestations typically include episodes of muscle weakness, myalgia, pain, and rhabdomyolysis, sometimes accompanied by renal failure. Triggers for these symptoms may include prolonged physical activity, fasting, fever, or exposure to cold temperatures. Additionally, in 90% of cases, the S113L point mutation has been identified on the CPT2 gene<sup>[3, 4]</sup>.

While most FAODs can be identified through newborn screening (NBS), significant variations exist among screening programs across different countries. DNA testing is widely regarded as the standard method for confirming diagnoses and can offer valuable insights into genotype/phenotype correlations<sup>[1, 3]</sup>.

Although in our country newborns are routinely screened for fatty acid oxidation defects, some cases of long chain fatty acids oxidation defects may be missed on NBS. Here we report a case of rhabdomyolysis due to a muscle form of CPT II deficiency in an infant with normal NBS results.

### Case report

A previously healthy 8-month-old girl was referred to our emergency department with liver cytolysis. Three days before admission, she developed a fever and refused food, and two days later, dark-colored urine was noted. Initially evaluated at another hospital, laboratory tests revealed elevated transaminases and proteinuria in urine analysis. She is the first daughter of non-consanguineous healthy parents, and there is no family history of musculoskeletal, renal, liver, or metabolic disorders. Her neonatal period was uneventful, without episodes of hypoglycemia, and normal newborn screening (NBS) results. Throughout the months, she exhibited normal growth and psychomotor development. During the physical examination, the patient showed no dysmorphic features, and no other abnormal signs were found. Blood tests confirmed elevated cytolysis markers (aspartate aminotransferase 3762 U/L, alanine aminotransferase 1040 U/L, lactic dehydrogenase 5528 U/L), with normal coagulation, but also elevated levels of creatine kinase (74914 U/L) and serum myoglobin (2477 ng/mL), supporting the hypothesis of transaminase elevation secondary to rhabdomyolysis. Urine analysis revealed normal color and only slight proteinuria, without blood or myoglobinuria. Hyperhydration was initiated, resulting in progressive clinical and analytical improvement.

For etiological evaluation, an acylcarnitine profile of dried blood spot (DBS) was initially performed, showing normal results. Subsequently, a genetic panel encompassing genes associated with rhabdomyolysis was conducted, revealing the pathogenic variant c.338C>T (p.Ser113Leu) in homozygosity in the *CPT2* gene, associated with the myopathic form of CPT II deficiency. Following this diagnosis, the acylcarnitine profile analysis was repeated in plasma, demonstrating a slight increase in C16 and C18 acylcarnitines.

Initiation of a controlled lipid diet, avoidance of fasting, supplementation with MCT oil, and adoption of a stress management protocol led to a favorable outcome.

### Discussion

FAODs can be identified by examining their distinctive acylcarnitine profiles and levels of free carnitine. In the case of CPT II deficiency, there is typically a significant increase in C16 and C18 acylcarnitines<sup>[5]</sup>. When conducting NBS for CPT II deficiency, the most reliable indicator is often an

elevated (C16+C18:1)/C2 ratio. However, it's worth noting that in this particular FAOD, the acylcarnitine profile may appear normal under regular conditions and only become abnormal during crisis episodes. Additionally, analyzing dried blood spots may be less sensitive compared to plasma assessment.

In this case, the acylcarnitine profile in DBS was normal in newborn screening and in the rhabdomyolysis crisis. Later, at baseline, analysis of acylcarnitine in plasma showed only a slight increase of C16 and C18 acylcarnitines.

The myopathic variant of CPT II deficiency stands as the predominant condition impacting lipid metabolism within skeletal muscle, serving as the leading genetic cause of hereditary myoglobinuria<sup>[6]</sup>. Detecting all instances of the muscular variant of CPT II deficiency through newborn screening can pose a challenge.<sup>[2]</sup> The patient in question has been identified with the missense variant c.338C>T (p.Ser113Leu), which is the most common pathogenic mutation of *CPT2* reported among individuals of caucasian descent. This mutation is occasionally linked to a normal acylcarnitine profile in newborn screening<sup>[7]</sup>.

Therefore, in conclusion, CPT II deficiency should be suspected in cases of significant rhabdomyolysis, even if NBS results were normal. Although dried blood spot testing is easier to perform during a rhabdomyolysis crisis, we recommend that the acylcarnitine profile should also be assessed in plasma. If the results remain normal but clinical suspicion persists, genetic studies must be conducted, either through direct gene analysis or by testing a panel of multiple genes related to diseases that present with rhabdomyolysis.

### Acknowledgements

Not applicable.

### Financial support

No financial support.

### Competing interests

Nothing to disclose.

### Availability of data and material

The data that support the findings of this case report are available on the hospital repository, which is only available for its health professionals. Remember that all important information is mentioned in this report.

The data necessary to interpret and verify the information in this case report is available in the sources mentioned in the references.

### Ethics approval and consent to participate

This case report has the approval and consent of the parents of the child, who gave their consent to participate.

### Consent for publication

The publication of this case report has been approved by the parents of the child, who gave their consent to publish.

### Authors' contributions

#### All authors have contributed equally by

1. Drafting the work or substantively revising it.
2. Approving the submitted version.
3. Agreeing both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work,

even those in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

## References

1. Lawrence Merritt J, Norris M, Kanungo S. Fatty acid oxidation disorders. *Ann Transl. Med.* 2018;6(24):473.
2. Tajima G, Hara K, Yuasa M. Carnitine palmitoyltransferase II deficiency with a focus on newborn screening. *J Hum Genet.* 2019;64:87-98.
3. Lehmann D, Motlagh L, Robaa D, Zierz S. Muscle Carnitine Palmitoyltransferase II Deficiency: A Review of Enzymatic Controversy and Clinical Features. *Int. J Mol. Sci.* 2017;18:82.
4. Raj Joshi P, Deschauer M, Zierz S. Carnitine palmitoyltransferase II deficiency: Genotype-Phenotype analysis of 50 patients. *J Neurol. Sci.* 2014;338:107-111.
5. Sain-van der Velden M, Diekman E, Verhoeven-Duif N, *et al.* Differences between acylcarnitine profiles in plasma and bloodspots. *Mol. Genet Metab.* 2013;110:1-2.
6. Wieser T, Adam M, Mirzaa G, *et al.* Carnitine palmitoyltransferase II deficiency. In: Adam MP, Ardinger HH, Pagon RA, *et al.*, editors. *GeneReviews®*. Seattle (WA): University of Washington, Seattle; c1993-2024. [Updated 2019 Jan 3; cited 2024 Jul 2]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1513/>
7. Maguolo A, Rodella G, Dianin A, *et al.* Diagnosis, genetic characterization and clinical follow up of mitochondrial fatty acid oxidation disorders in the new era of expanded newborn screening: A single centre experience. *Mol. Genet Metab. Rep.* 2020;100632.

### How to Cite This Article

Pereira M, Silva R, Campos T, Vasconcelos C, Vilarinho L, Rodrigues E, *et al.* Rhabdomyolysis in childhood: A case of carnitine palmitoyltransferase deficiency type II. *International Journal of Pediatrics and Neonatology.* 2024;6(2):24-26.

### Creative Commons (CC) License

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non Commercial-Share Alike 4.0 International (CC BY-NC-SA 4.0) License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.