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Short Communication

Recurrent rhabdomyolysis caused by palmitoyltransferase II (CPT-2) deficiency but complete normal acylcarnitine profile: A patient presentation and review of the literature

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ABSTRACT

Recurrent rhabdomyolysis, marked by skeletal muscle breakdown, can stem from various causes, including genetic disorders. We detail a patient of a 22-year-old male with carnitine palmitoyltransferase II (CPT-2) deficiency manifesting recurrent rhabdomyolysis despite normal acylcarnitine profiles. Whole-genome sequencing identified two *CPT2* gene variants: c.338C > T and c.482G > A, confirming the diagnosis. We conducted a case report and a comprehensive literature review encompassing 262 articles related to CPT-2 deficiency available on PubMed. The review detailed 245 cases across various forms, including lethal neonatal, severe infantile hepatocardiomuscular, and myopathic forms. The study highlighted the variability and complexity of CPT-2 deficiency phenotypes, emphasizing correlations between variants and phenotypes as well as gender distribution. Although the CPT-2 deficiency genotype does not entirely predict phenotype severity, it remains informative for most patients, assisting in assessing the severity linked to each genetic variant. The results of our study offer crucial insights into evaluating the severity associated with individual genetic variants. Notably, our patient displayed normal acylcarnitine profiles between illness episodes, indicating possible profile abnormalities only during active disease states.

We propose the collection of additional blood samples for acylcarnitine analysis during episodes of rhabdomyolysis without delay in all patients presenting with rhabdomyolysis of unknown cause as a crucial diagnostic strategy. This approach may unveil unexpected underlying diseases, enabling early and accurate diagnoses.

1. Introduction

Rhabdomyolysis is a medical condition characterized by the rapid breakdown of injured skeletal muscle tissue. This process results in the release of intracellular muscle components such as myoglobin, creatine kinase (CK), aldolase, and lactate dehydrogenase (LDH), along with electrolytes, into the bloodstream and surrounding tissues [1]. While direct traumatic injury is a common cause of rhabdomyolysis, it can also stem from various factors, including drugs, toxins, infections, muscle ischemia, electrolyte/metabolic disorders, genetics, exertion, prolonged bed rest, and temperature-related conditions such as neuroleptic malignant syndrome (NMS) and malignant hyperthermia (MH) [2,3].

Carnitine palmitoyltransferase II (CPT-2) deficiency is an autosomal recessive disease (OMIM #600650). In this report, we present a patient of recurrent rhabdomyolysis attributed to a rare abnormality in fatty acid metabolism known as carnitine palmitoyltransferase II (CPT-2) deficiency. It is noteworthy that the patient displayed normal results in multiple blood acylcarnitine and urinary organic acid analyses during periods between illness episodes. Ultimately, whole-genome sequencing revealed the presence of two *CPT2* gene variants. This article serves as a crucial reminder not to dismiss the possibility of CPT-2 deficiency based solely on normal acylcarnitine and urinary organic acid analyses. Furthermore, we conducted a comprehensive review and analysis of literature related to CPT-2 deficiency to enhance our understanding of

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this condition, as detailed in this report.

2. Materials and methods

2.1. Subject

The medical chart was thoroughly reviewed. A 22-year-old male patient first presented with rhabdomyolysis at the age of 15 after a strenuous afternoon of playing basketball. He initially experienced malaise and myalgias, especially in his lower extremities, which progressed to generalized weakness and dark-colored urine. Initial laboratory investigations revealed significantly elevated serum levels of creatine kinase (CK), lactic dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), with values of 43,500 IU/L, 1443 IU/L, 573 IU/L, and 83 IU/L, respectively. A diagnosis of rhabdomyolysis was made, and the patient received emergency hydration therapy, leading to a rapid recovery. He was discharged with normal muscle power and renal function after five days of hospitalization.

One year later, the patient experienced a second episode of rhabdomyolysis at the age of 16 during a severe upper respiratory infection marked by high fever, chills, and a sore throat. During this period, he complained of myalgia, particularly in his bilateral lower limbs. Laboratory data showed elevated serum CK (25,770 IU/L), AST (1250 IU/L), and ALT (280 IU/L) levels. Urgent therapy was administered, and the patient showed rapid improvement after emergency hydration therapy.

Due to recurrent rhabdomyolysis, the patient was referred to our genetic clinics to investigate the possibility of inherited myopathies and metabolic disorders. Initial laboratory metabolic investigations, including serum lactate levels, acylcarnitine profiling, and urinary organic acid analysis, among others, all yielded results within normal ranges. However, despite the recommendation for whole exome sequencing, the parents hesitated to do.

It is important to note that some fatty acid oxidation disorders may present normal metabolic profiles when the patient is not in acute metabolic decompensation. Therefore, the possibility of fatty acid oxidation disorders could not be ruled out for this patient [4].

In light of this uncertainty, we recommended specific management strategies, including avoiding fasting and supplementing with additional sugar during periods of exercise and illness. Subsequently, the patient underwent regular follow-up appointments at our clinics. Over the course of these visits, we conducted a total of six acylcarnitine profile (Table 1) and several organic acid analyses. All acylcarnitine profiles consistently showed normal results, and no dicarboxylic acids were detected in the urinary organic acid analyses. Given the relatively high prevalence of late-onset multiple acyl-CoA dehydrogenase deficiency (MADD) in Taiwan [5,6], we conducted genetic testing for two hotspot variants, c.250 G > A and 419C > T variants of the *ETFDH* gene, both of which yielded normal results.

Nevertheless, in 2023, at the age of 22, he contracted a COVID-19 infection, resulting in a third episode of rhabdomyolysis with a peak CK level of 17,305 IU/L. The parents finally agreed to undergo whole-genome sequencing examination, which revealed that this patient carried two *CPT2* gene variants: one pathogenic variant, c.338C > T (p. Ser113Leu), inherited from the mother, and one novel variant, c.482G > A (p. Arg161Gln), inherited from the father. Consequently, a diagnosis of carnitine palmitoyltransferase II deficiency was made.

2.2. Method

We conducted a comprehensive literature review of all publications related to carnitine palmitoyltransferase 2 deficiency available on PubMed. This review involved an extensive search using keywords as follows: “CPT2 deficiency,” OR “CPT 2 deficiency” OR “CPTII deficiency” OR “CPT II deficiency” OR“Carnitine palmitoyltransferase 2 deficiency” OR “Carnitine palmitoyltransferase II deficiency”. Subsequently, we meticulously reviewed and analyzed the papers identified through this search, with a particular focus on parameters including gender, age of disease onset, and the correlation between genotypes and phenotypes.

3. Results and literatures review

A search using this method yielded a total of 262 articles, with 99 of them pertaining to patient case reports (Supplemental Table S1). Within these 99 articles, a total of 245 cases of patients with CPT-2 deficiency were documented. Among them, 21 cases were classified as the lethal neonatal form, 32 as the severe infantile hepatocardiomuscular form, and 192 as the myopathic form.

The distribution among these patients revealed the following ratios: for the lethal neonatal form, 15 males to 6 females; for the severe infantile hepatocardiomuscular form, 21 males to 10 females (one unknown gender); and for the myopathic form, 125 males to 67 females.

Among the 21 patients diagnosed with the lethal neonatal form, a

Table 1
Results of six acylcarnitine profiles with (C16 + C18:1)/C2 and C12/C0 ratios for the patient across different time points.

	Acylcarnitine and Free Carnitine (C0) Levels														Acylcarnitine Ratios	
	C0 8.5 < C0 < 70	C2 2 < C2 < 100	C3 <4.00	C4 <0.7	C6 <0.5	C8 <0.5	C10 <0.5	C12 <1.5	C14:1 <0.65	C14 <0.75	C16-OH <0.25	C18 <2.3	C18:1 <2.00	C16 <5.60	(C16 + C18:1)/C2 <0.857	C12/C0 <0.008
2016/06/14	28.140	4.000	0.660	0.145	0.025	0.035	0.070	0.035	0.035	0.040	0.005	0.365	0.355	0.525	0.220	0.001
2016/07/27	32.600	4.070	0.725	0.175	0.060	0.020	0.040	0.040	0.020	0.050	0.010	0.365	0.365	0.620	0.242	0.001
2017/04/12	32.180	6.150	0.835	0.230	0.085	0.030	0.045	0.045	0.030	0.055	0.005	0.450	0.410	0.545	0.155	0.001
2017/07/05	40.820	7.225	1.010	0.180	0.060	0.120	0.215	0.110	0.120	0.105	0.010	0.675	0.830	0.940	0.245	0.003
2020/07/18	20.380	7.980	0.700	0.200	0.050	0.070	0.060	0.040	0.070	0.050	0.010	0.410	0.560	0.440	0.125	0.002
2023/07/30	30.084	4.002	0.480	0.111	0.023	0.042	0.075	0.020	0.042	0.030	0.010	0.516	0.612	0.557	0.292	0.001

total of 18 variants were identified. Among these patients, 11 individuals exhibited homozygous variants across 8 distinct alleles, while the remaining 10 patients displayed compound heterozygosity for some of these variants (Table 2). As a general rule in autosomal recessive metabolic diseases, the severe phenotype often arises from the presence of two severe variants simultaneously. Thus, all 22 variants identified in these patients are tentatively categorized as belonging to the most severe form of variants within the *CPT2* gene, given the correspondingly severe phenotype associated with CPT-2 deficiency, notably the lethal neonatal form.

Among the 32 patients with the severe infantile hepatocardiomuscular form, a total of 27 variants were identified. Of these, 13 individuals displayed homozygous variants in 9 distinct alleles, while the remaining 14 patients exhibited compound heterozygosity for some of these variants (Table 3). Given the severe phenotypes associated with the severe infantile hepatocardiomuscular form, we classified these variants as belonging to the severe form variants of the *CPT2* gene. Of the 27 variants identified in the severe infantile hepatocardiomuscular form, the F383Y and V368I variants individually accounted for 15.6 %, totaling 31.2 % of the variant alleles in patients of this type.

Among the 192 patients diagnosed with the myopathic form, a total of 67 variants were identified. Within this group, 88 individuals exhibited homozygous variants in 7 distinct alleles (Table 4), while the remaining 108 patients showed compound heterozygosity involving some of these variants. For the *CPT2* gene in patients with a mild form, a variant can be anticipated as a mild form variant when present in a homozygous state. Specifically, 6 variants—S113L, Q46A, P50H, E174K, I502T, and R247W—were exclusively detected in a homozygous state among patients diagnosed with the myopathic form. Consequently, these 6 variants could be projected as mild form variants of the *CPT2* gene. However, homozygous R631C and F383Y variants were found in both the myopathic form and the severe infantile hepatocardiomuscular form. This finding suggests that clinical severity cannot be judged solely based on genotype, as various modifier factors may influence the severity of phenotypes.

Furthermore, predicting the severity of uncertain variants in compound heterozygous myopathic form patients poses a challenge [7]. This complexity arises due to the potential for a mild form variant to result in a mild form phenotype when occurring alongside either another mild form or a severe form variant. Therefore, determining the severity of both variants becomes challenging, especially when the individual severity of each variant is unknown. An uncertain variant can only be considered a mild form variant when it coincides with known severe variants in patients who display characteristics of the mild form. In our study, among 108 compound heterozygous patients, only 3 uncertain variants were observed alongside a severe-type variant. The S112F, R560W, and Y479C variants exhibit significant potential to be categorized as mild-form variants (Table 5). Among the variants identified in the myopathic form, the S113L variant stands out as a hotspot variant, accounting for approximately 64 % of the variant alleles in patients of this type.

Table 2
CPT2 variants in lethal neonatal form.

Allele 1	Allele 2	Total	M	F
Homozygous				
E641fs	E641fs	1	0	1
R124X	R124X	1	1	0
L178_I186delinsF	L178_I186delinsF	1	1	0
L224del	L224del	1	1	0
P227L	P227L	3	2	1
D328G	D328G	2	1	1
Q413fs	Q413fs	1	1	0
F602Lfs*20	F602Lfs*20	1	1	0
Compound heterozygous				
Q413fs	F448L	3	2	1
895-896insGGGCAGAGCT	G174L	1	0	1
del1737C	G520A	2	1	1
P55R	P595fs	1	1	0
Q413fs	109AGC > GCAGC	1	1	0
R296Q	L178_I186delinsF	1	1	0
R579X	G520A	1	1	0

Express the genotype of the lethal neonatal form and the number of patients.

Table 3
CPT2 variants in the severe infantile hepatocardiomuscular form.

Allele 1	Allele 2	Total	M	F
Homozygous				
I54S	I54S	1	1	0
Y120C	Y120C	1	?	?
R151W	R151W	1	0	1
F383Y	F383Y	2	1	1
R503C	R503C	1	0	1
P504L	P504L	2	1	1
Y628S	Y628S	2	2	0
R631C	R631C	1	1	0
L644S	L644S	1	1	0
Compound heterozygous				
F352C	V368I (homozygous)	5	4	1
D213G	L358R	2	2	0
F383Y	R151Q	1	1	0
F383Y	R161W	1	1	0
F383Y	V605L	1	1	0
F383Y	E174K	1	0	1
F383Y	R296X	1	0	1
L178_I186delinsF	R151Q	1	1	0
p.I332Hfs*2	P571T	1	0	1
P50H	K457X	1	0	1
S122F	F352C	1	1	0
Q413fs	P50H	1	1	0
R296Q	R631C	1	1	0
V368I	R631C	1	1	0

Express the genotype of Severe infantile hepatocardiomuscular form and the number of patients.

Table 4
Homozygous CPT2 Variants Associated with the Myopathic Form.

Allele 1	Allele 2	Total	M	F
Homozygous				
Q46A	Q46A	1	1	0
P50H	P50H	1	1	0
S113L	S113L	79	46	33
E174K	E174K	1	1	0
R247W	R247W	1	1	0
F383Y	F383Y	1	0	1
I502T	I502T	1	0	1
R631C	R631C	4	4	0

Express the genotype of the Myopathic form and the number of patients. The F383Y variant has also been observed in the severe infantile hepatocardiomuscular form.

Table 5
Suspected mild-form variants associated with the known severe variants that causes the myopathic form of CPT2 deficiency.

Allele 1 (known severe)	Allele 2 (suspected mild)
P504L	S122F
V605L	R560W
748-749delAA	Y479C

The column for Allele 1 lists three known severe pathogenic variants of the CPT2 gene (Table 3). In contrast, the column for Allele 2 lists three CPT2 variants with unknown severity. However, the presence of compound heterozygosity with severe variants in these three cases—resulting in clinical symptoms of the myopathic form-strongly suggests that the variants S112F, R560W, and Y479C are mild-form variants of the CPT2 gene.

4. Discussion

CPT-2 deficiency is a rare genetic disorder affecting long-chain fatty acid oxidation, presenting in three clinical forms: the lethal neonatal form (OMIM 608836), severe infantile hepatocardiomuscular form (OMIM 600649), and myopathic form (OMIM 255110) [8,9]. The lethal neonatal form emerges within days of birth and is characterized by recurrent episodes of liver failure accompanied by hypoketotic hypoglycemia, cardiomyopathy, seizures, and coma. This condition is often accompanied by facial abnormalities and structural malformations such as cystic renal dysplasia or neuronal migration defects [10,11]. The severe infantile hepatocardiomuscular form often manifests within the first year, characterized by occurrences of liver failure, seizures, hypoketotic hypoglycemia, and peripheral myopathy, frequently triggered by stress, fasting, or infection [10,12]. Moreover, the myopathic form, typically emerging between the first to sixth decade of life, is characterized by recurrent myalgia and myoglobinuria, usually triggered by prolonged exercise, fasting, cold exposure, or infection. Notably, it presents without apparent signs of myopathy during periods between attacks [10,13]. However, the phenotypes associated with CPT-2 deficiency could manifest as a spectrum, making it challenging at times to precisely classify patients into distinct types. There may be some overlap between different groups, blurring clear-cut distinctions among them.

Additionally, the onset of CPT-2 deficiencies (possibly except for the lethal neonatal form) often requires triggering factors, such as prolonged fasting or infection. Moreover, unknown genetic modifying factors may also exist, complicating the expression of CPT-2 deficiency phenotypes. This complexity occasionally results in the same homozygous genotype being categorized differently. For example, two common variants, F631C and F383Y, are typically associated with the severe infantile hepatocardiomuscular form, interestingly, two patients with homozygous F631C or F383Y have been reported to manifest the myopathic form [14,15].

When predicting the severity of CPT-2 deficiency phenotypes, CPT-2 enzyme activity has previously been utilized as an auxiliary method. According to prior reports, CPT-2 activity in fibroblasts ranged from 15 % to 26 % of normal controls in the myopathic form and from 4 % to 10 % in the severe infantile hepatocardiomuscular form [16]. However, despite these findings, several reports have highlighted that CPT-2 activity in fibroblasts is not always consistently reliable for predicting the severity of CPT II phenotypes [15,17]. Measuring CPT-II enzyme activity through skin biopsy has become less common in modern clinical practice due to the invasive nature of the procedure and the need for specialized expertise in both performing the test and interpreting its results. Such analyses are now typically limited to specialized metabolic centers or reference laboratories, as they are not feasible in most general clinical settings. Recently, a novel non-invasive approach, fluxomic assays, has been developed as an alternative for assessing CPT-II enzyme activity. This method involves blood sampling and measures the conversion rates of stable isotope-labeled fatty acids, offering a functional diagnosis of CPT-II deficiency. In cases where genetic results and blood acylcarnitine profiles are inconclusive, fluxomic assays can provide valuable diagnostic insights and may also correlate with disease severity [18,19]. However, access to this advanced method is currently limited to a select few specialized metabolic centers worldwide.

While comprehending the potential impact of the aforementioned factors on evaluating the severity of genetic variants in patients, our study offers a thorough and detailed classification of genes corresponding to each phenotype [20]. Although the genotype of CPT-2 deficiency might not completely and accurately predict the severity of the phenotype in some unusual cases, most of the time, it still provides useful information to predict the severity of the phenotype in the majority of patients. Therefore, the findings of this study continue to offer crucial insights into assessing the severity associated with each genetic variant. Particularly for patients identified through newborn screening, understanding the potential severity of the patient's genotype before the onset of the disease can facilitate the implementation of more meticulous prevention and treatment strategies, especially for potentially more severe phenotypes.

In fact, the diagnosis of CPT-2 deficiency in most patients is accomplished through tandem mass spectrometry. Spectra obtained from CPT II deficiency often display distinctive elevations of C16:0 and C18:1 acylcarnitines, while acetylcarnitine C2 does not show elevated levels [21,22]. The phenotypes associated with CPT-2 deficiency could manifest as a spectrum, making it challenging at times to precisely classify patients into distinct types. There may be some overlap between different groups, blurring clear-cut distinctions among them. Throughout the entire course, our patient was never found to have an abnormal acylcarnitine profile. This might be attributed to the fact that all six blood sampling instances occurred during the interictal periods when the patient was not experiencing disease episodes. Several reports also mentioned the inability to detect abnormal acylcarnitine profiles in their patients [23–25]. However, carnitine deficiency secondary to fatty acid oxidation defects should be considered a potential factor, as it can impair the formation of long-chain acylcarnitines and lead to false-negative results. Although our patient did not exhibit low levels of free carnitine or acetylcarnitine, the possibility that carnitine deficiency could contribute to the absence of abnormal acylcarnitine findings should not be overlooked. Therefore, it is crucial to carefully monitor free carnitine (C0) levels in the acylcarnitine profile and evaluate the C16:0 + C18:1)/C2 or C12:0/C0 ratio to account for potential errors in interpreting the acylcarnitine profile [26].

We believe that for some mild CPT-2 deficiency patients, their abnormal acylcarnitine profile can only be detected during active disease episodes. This prompted us to consider obtaining an additional blood sample for acylcarnitine analysis in patients experiencing rhabdomyolysis. This approach may help uncover unexpected underlying diseases. Not only can this lead to an early and accurate diagnosis for the patient, but it can also prevent a series of subsequent complicated and expensive examinations.

In our literature review, we observed that CPT-2 deficiency is reported at least twice as frequently in males compared to females. This disparity raises questions regarding the underlying reasons for the higher prevalence in male patients, particularly given that CPT-2 deficiency is an autosomal recessive condition. One possible explanation is that differences in the metabolic rate of fatty acid oxidation between the sexes could potentially influence symptom presentation. Another consideration is that males may be more likely to engage in higher levels of physical activity, which could increase the occurrence of rhabdomyolysis. These potential factors warrant further investigation to improve our understanding of their roles in the observed sex-based differences in CPT-2 deficiency prevalence.

5. Conclusion

We detail a patient of a 22-year-old male with CPT-2 deficiency manifesting recurrent rhabdomyolysis despite normal acylcarnitine profiles and conduct a comprehensive literature review available on PubMed. We recommend the prompt collection of additional blood samples (in plasma, serum, or dried blood spots) during episodes of rhabdomyolysis for acylcarnitine analysis in all patients with rhabdomyolysis of unknown cause. This approach aims to improve the identification of diagnostic methods for CPT-2 deficiency, particularly in cases where acylcarnitine profiles may appear normal during interictal periods. Furthermore, our research provides characteristics of CPT-2 deficiency and emphasizes correlations between variants and phenotypes, offering valuable insights into the evaluation of the severity linked to individual genetic variants.

Ethical statement

All procedures performed in studies involving human participants

were in accordance with the ethical standards of the Taipei Veterans General Hospital Institutional Review Board. The Taipei Veterans General Hospital Institutional Review Board approved the study (2021–10-001CC). Informed consent was obtained from the subject.

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CRediT authorship contribution statement

Chih-Hsuan Lu: Writing – original draft, Formal analysis, Data curation. **Chia-Feng Yang:** Writing – review & editing, Supervision, Funding acquisition. **Yun-Ru Chen:** Methodology, Formal analysis. **Yann-Jang Chen:** Supervision, Methodology, Investigation, Conceptualization. **Yung-Hsiu Lu:** Methodology, Formal analysis, Data curation. **Dau-Ming Niu:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to eliminate possible grammatical or spelling errors. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

Data availability

Due to considerations of patient privacy and confidentiality, the datasets produced and examined in the present study are not publicly accessible. Anonymized data can be provided by the corresponding author upon reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101151.

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