

Late Diagnosis of Adult-Onset Carnitine Palmitoyltransferase II Deficiency in a 63-Year-Old Man Presenting with Recurrent Rhabdomyolysis: A Case Report

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Case Report

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Abstract

Carnitine palmitoyltransferase II (CPT II) deficiency is one of the most common disorders of long-chain fatty acid oxidation presenting in adulthood and is characterized by recurrent episodes of rhabdomyolysis, myalgia, and transient muscle weakness. Because the clinical manifestations are episodic and neurological examination and electromyography findings are often normal during asymptomatic periods, diagnosis is frequently delayed. Herein, we report the case of a 63-year-old man who had been followed since 2011 for persistent creatine kinase elevation and recurrent episodes of rhabdomyolysis. Although he had initially been diagnosed with myositis, persistent creatine kinase elevation, recurrent attacks, and normal neurological findings between episodes prompted further evaluation for a metabolic myopathy. Comprehensive genetic testing identified a homozygous CPT2 c.338C > T (p.Ser113Leu) variant, confirming the diagnosis of adult-onset CPT II deficiency. Following the diagnosis, the patient received dietary counseling and was advised to avoid prolonged fasting, strenuous exercise, and other known precipitating factors. This case highlights that CPT II deficiency should be considered in adults presenting with recurrent rhabdomyolysis and persistent creatine kinase elevation, regardless of age, and emphasizes the importance of early molecular genetic testing to establish the diagnosis, prevent unnecessary investigations, and facilitate appropriate management.

Introduction

Carnitine palmitoyltransferase II (CPT II) deficiency is a rare inherited metabolic disorder that impairs the body's ability to effectively utilize long-chain fatty acids (LCFAs) for energy production (1). Fatty acids are a vital energy source for cardiac, hepatic, and skeletal muscle tissues, particularly during periods of fasting, between meals, febrile illness, low glucose availability, and increased or high energy demand such as exercise (2). Under these conditions, the body increases the mobilization of triglycerides into free fatty acids, which subsequently undergo mitochondrial beta-oxidation to generate adenosine triphosphate (ATP) (3). However, long-chain fatty acids cannot passively cross the mitochondrial membrane and require an integrated enzymatic "carnitine shuttle" system that facilitates their transport into the mitochondrial matrix (4, 5). This system consists of CPT1 located on the outer mitochondrial membrane, CPT2 located on the inner mitochondrial membrane, and carnitine-acylcarnitine translocase (1). The CPT II enzyme converts long-chain acylcarnitines back into acyl-CoA and free carnitine, thereby enabling beta-oxidation to proceed. CPT II deficiency is an autosomal recessive disorder classified among long-chain fatty acid oxidation disorders (6).

The clinical presentation of CPT II deficiency is highly heterogeneous and is classified into three major phenotypes according to mutation type: the lethal neonatal form, the severe infantile hepatocardiomyopathic form, and the adult-onset myopathic form. The neonatal form is the most severe phenotype and is characterized by seizures, liver failure, cerebral malformations, cardiomyopathy, and death shortly after birth. The infantile form usually presents in early childhood with multisystem involvement, hypoketotic hypoglycemia, and early death. The adult-onset myopathic form is the most common phenotype and typically manifests during adolescence or adulthood, with recurrent myalgia,

muscle weakness, and muscle stiffness as its main clinical features. In this form, CPT2 enzyme activity is less than 30% of normal, whereas enzyme activity is below 10% in the neonatal and infantile forms (3). More than 75% of reported cases are male, indicating a clear male predominance in muscle CPT II deficiency. However, it remains unclear whether this predominance is related to sex-based differences in exercise activity, an X-linked modifier gene, or hormonal factors such as estrogen, which appears to act as a regulator of CPT (1).

Attacks are commonly triggered by metabolic stressors such as physical activity, fasting, infection, emotional stress, or extreme temperatures. These triggers lead to energy depletion in myocytes, followed by recurrent episodes of rhabdomyolysis. During rhabdomyolysis, myoglobin released into the bloodstream as a result of muscle fiber breakdown causes dark-colored urine, or myoglobinuria, in approximately 75% of cases (6). Interestingly, most patients do not show signs of myopathy between attacks, and serum creatine kinase and carnitine levels often remain within normal limits. The greatest diagnostic challenge in CPT II deficiency is that clinical symptoms are nonspecific and often present with an unclear clinical picture. Genetic diagnosis is critically important for disease management and diagnostic confirmation. Single-gene testing or multigene panel testing is considered the gold standard for excluding other inherited disorders and confirming the diagnosis (3). Genetic confirmation enables patients to modify their lifestyle, including avoidance of strenuous exercise and prolonged fasting and adoption of a low-fat, high-carbohydrate diet, thereby helping to prevent future attacks and complications (7).

Case Presentation

A 63-year-old man was admitted to the emergency department with diffuse muscle pain, weakness, and dark-colored urine. His medical history revealed that he had been followed with a diagnosis of myopathy since 2011 and had been evaluated and treated at several centers for recurrent episodes of creatine kinase elevation and rhabdomyolysis. His most recent episode of rhabdomyolysis had occurred approximately one year before the current admission.

The patient had no history of diabetes mellitus, hypertension, coronary artery disease, or chronic kidney disease. He was not taking any regular medication. There was no history of statin use, alcohol consumption, toxic exposure, or trauma. His family history was negative for myositis, muscular dystrophy, or known hereditary muscle disease, and there was no parental consanguinity.

On physical examination, his vital signs were stable. Cardiovascular and respiratory system examinations were unremarkable. Neurological examination showed full muscle strength, normoactive deep tendon reflexes, and normal sensory findings. Dark-colored urine was noted. On detailed questioning, the patient reported recurrent episodes of diffuse myalgia, transient muscle weakness, and occasional shortness of breath over the years.

Laboratory Findings

Biochemical tests obtained at admission showed the following results: AST, 165 U/L; ALT, 51 U/L; LDH, 317 IU/L; CK, 6292 U/L; and CK-MB, 124 U/L. Autoimmune serological testing was negative, including anti-dsDNA, anti-Scl-70, anti-Sm, anti-Sm/RNP, anti-SSA/Ro, anti-SSB/La, anti-CCP, anti-Jo-1, and antinuclear antibody testing. The autoimmune serology panel results are summarized in Table 1.

Table 1
Autoimmune Serology Panel Results

Tests	Results
Anti-dsDNA	Negative
Anti-Scl-70 (immunoblot)	Negative
Anti-Sm (immunoblot)	Negative
Anti-Sm/RNP (immunoblot)	Negative
Anti-SSA (Ro) (immunoblot)	Negative
Anti-SSB (La) immunoblot)	Negative
Anti-CCP	Negative
Anti-Jo-1 (immunoblot)	Negative
Antinuclear antibody (ANA, IFA)	Negative

Intravenous fluid therapy was initiated, and CK levels were monitored. The patient’s urine color gradually became lighter, and his muscle pain improved. Review of his available medical records dating back to 2011 demonstrated variable elevations in CK and CK-MB levels at different time points. Hepatitis B and hepatitis C serologies were negative. Because of persistent creatine kinase elevation and a history of recurrent rhabdomyolysis, metabolic myopathy was considered in the differential diagnosis.

Imaging Findings

Abdominal ultrasonography showed a liver size of 165 mm, consistent with mild hepatomegaly. The hepatic parenchymal echogenicity was homogeneous, and no focal lesion was detected. Hepatosplenomegaly and bilateral renal cysts were also reported. Contrast-enhanced thigh magnetic resonance imaging demonstrated diffuse edematous changes in the pelvic floor muscle groups. These findings were interpreted as compatible with myopathy or stage 1 muscle injury.

Electrophysiological Examination

Nerve conduction studies were normal. Needle electromyography performed in the right lower and left upper extremities showed no evidence of myopathic or neurogenic pathology in the examined muscles.

Muscle Biopsy

The patient had previously undergone a muscle biopsy from the upper extremity at an external center, which had reportedly been interpreted as “myositis.” However, the detailed histopathological report could not be obtained.

Differential Diagnosis and Further Evaluation

Although the patient had a history of oral aphthae and diffuse myalgia, there was no rash, arthritis, or organ involvement suggestive of systemic autoimmune disease. No pathological findings had been detected in biopsy specimens obtained during a previous endoscopic retrograde cholangiopancreatography procedure. Given the recurrent episodes of rhabdomyolysis, long-standing CK elevation, normal electromyography findings, and normal neurological examination between attacks, metabolic myopathy became the leading diagnostic consideration.

Accordingly, a comprehensive myopathy panel, including CPT2 gene analysis, was planned by the Department of Medical Genetics. In parallel, because a possible fatty acid oxidation disorder was suspected, the patient was consulted with the pediatric metabolism team, and an appropriate dietary program for suspected CPT deficiency was arranged.

Genetic Examination

A comprehensive muscular dystrophy/myopathy panel performed for suspected metabolic myopathy identified a homozygous CPT2 c.338C > T (p.Ser113Leu) variant.

Genetic Testing Method

DNA was isolated from the patient’s sample. Genes included in the “Comprehensive Muscular Dystrophy/Myopathy Panel” within the GeneMind CES kit were filtered and analyzed using the GeneMind SurfSeq5000 platform. BAM and VCF files were generated from the raw data using bioinformatic software tools. For pathogenicity classification of single-nucleotide variants in the VCF file, the SEQ analysis platform, VarSome, ClinVar, OMIM, PubMed, in silico prediction tools, and population databases were used. The GRCh38/hg38 reference genome was used for analysis. The molecular genetic analysis result is presented in Table 2.

Table 2
CPT2 Result From Molecular Genetic Analysis

Gene and Variant	Zygosity	Pathogenicity Assessment	OMIM-Associated Clinical Condition
CPT2 c.338C > T p.Ser113Leu	Homozygous	(PP3, PP5, PS3, PP2, PM2)	OMIM: *600650

Interpretation

The patient was found to have a homozygous CPT2 gene [NM_000098.3] c.338C > T (p.Ser113Leu) variant. This variant is classified as a variant of uncertain significance by the Genomize SEQ analysis platform, pathogenic by the Franklin pathogenicity prediction tool, pathogenic according to VarSome Verdict, and pathogenic/likely pathogenic in ClinVar. The frequency of this variant in gnomAD exome datasets is 0.00171. According to OMIM, potentially pathogenic variants in the CPT2 gene are associated with encephalopathy, acute infection-induced, 4, susceptibility to; myopathic, stress-induced CPT II deficiency with autosomal dominant-recessive inheritance; and infantile CPT II deficiency and lethal neonatal CPT II deficiency with autosomal recessive inheritance (OMIM *600650).

When evaluated together with the patient's long-standing recurrent rhabdomyolysis episodes, persistent hyperCKemia, exercise intolerance, and clinical features suggestive of metabolic myopathy, the molecular genetic findings confirmed the diagnosis of adult-onset carnitine palmitoyltransferase II (CPT II) deficiency. Following the genetic diagnosis, the patient was reassessed by the pediatric metabolism and dietetics teams. A nutritional program appropriate for fatty acid oxidation disorder was arranged, and the patient was advised to avoid prolonged fasting, strenuous exercise, and other triggering factors that may increase the risk of rhabdomyolysis.

Discussion

Carnitine palmitoyltransferase II (CPT II) deficiency is a rare autosomal recessive metabolic disorder that affects fatty acid β -oxidation as a result of disruption of the carnitine shuttle system, which is responsible for transporting long-chain fatty acids into mitochondria. Its clinical spectrum ranges from the lethal neonatal form to the adult-onset myopathic form. The adult myopathic form is the most common phenotype and is characterized by recurrent episodes of rhabdomyolysis, myalgia, exercise intolerance, and myoglobinuria (8).

In the case reported by Seferi et al. (3), the presence of recurrent myalgia and myoglobinuria episodes beginning in childhood in the patient's brother, together with a similar clinical picture triggered by intense physical activity, provided a strong family history suggestive of hereditary metabolic myopathy. Therefore, a genetic etiology was considered early in that case. In contrast, the absence of a positive

family history in our patient made it more difficult to initially suspect hereditary metabolic disorders such as CPT II deficiency and was one of the factors contributing to the diagnostic delay.

Although our patient had characteristic clinical features of adult-onset myopathic CPT II deficiency, the diagnosis was notable because it was established at an advanced age. In the literature, symptoms in adult-onset CPT II deficiency are reported to begin most commonly during adolescence or early adulthood, whereas the diagnosis is usually made in the third or fourth decade of life. The diagnosis was established at 40 years of age in the case reported by Lease et al. (9), at 33 years of age in the case reported by Seferi et al. (3), and at 38 years of age in the case reported by Castillo et al. (6). Similarly, the 49-year-old patient reported by Akar et al. (10) represents an example of late-diagnosed adult-onset disease. In contrast, our patient had been followed for more than a decade because of recurrent rhabdomyolysis episodes and persistent CK elevation, but the definitive diagnosis was reached only after molecular genetic testing performed at the age of 63 years. This finding demonstrates that CPT II deficiency may become clinically evident at an advanced age or may remain undiagnosed for many years. Our case also emphasizes that CPT II deficiency should be considered in the differential diagnosis of adult patients with unexplained recurrent rhabdomyolysis, chronic creatine kinase elevation, and normal neurological examination findings, regardless of age.

Our patient had recurrent muscle pain, episodes of dark-colored urine, and marked CK elevation over many years. Similarly, Lease et al. (9) reported a rhabdomyolysis episode following influenza infection, Seferi et al. (3) presented a severe rhabdomyolysis case complicated by acute kidney injury after intense physical activity, and Castillo et al. (6) described severe rhabdomyolysis and acute kidney injury after marathon training. The common feature of these cases is that symptoms occurred after conditions causing metabolic stress. Although no clear triggering factor could be identified in our patient, the presence of recurrent attacks over several years supports an underlying persistent disorder of energy metabolism.

In the case reported by Lease et al. (9), a high-titer positive antinuclear antibody result initially suggested the possibility of inflammatory myopathy and led to rheumatological evaluation. However, further investigations ultimately established the diagnosis of metabolic myopathy. In contrast, ANA was negative in our patient, and no serological marker supporting autoimmune myopathy was detected. The absence of additional laboratory clues that could guide the diagnosis made etiological evaluation more challenging and further increased the importance of molecular genetic testing in reaching the diagnosis of metabolic myopathy.

In our patient, the previous interpretation of a muscle biopsy performed at an external center as “myositis” contributed to the diagnostic delay. This finding is consistent with the observation by Akar et al. (10) that biopsies obtained during acute rhabdomyolysis may show necrosis and secondary inflammatory changes that can mimic inflammatory myopathy. Therefore, the biopsy result in our patient may have been misinterpreted as primary myositis, whereas it more likely reflected secondary inflammatory changes related to rhabdomyolysis. Normal EMG findings should also not exclude

metabolic myopathy, because EMG may be normal or may show only mild myopathic changes in CPT II deficiency (3).

Diekman et al. (11) performed muscle magnetic resonance imaging in 20 patients with long-chain fatty acid oxidation disorders and identified increased signal intensity on short tau inversion recovery and T1-weighted sequences, reflecting increased lipid accumulation and inflammation. The authors reported that these imaging findings may be useful in the evaluation of long-chain fatty acid oxidation disorders, although STIR and T1-weighted signal changes may be less prominent in patients with CPT II deficiency than in those with other fatty acid oxidation disorders. In our patient, contrast-enhanced thigh magnetic resonance imaging demonstrated diffuse edematous changes in the pelvic floor muscle groups, and these findings were interpreted as compatible with stage 1 muscle injury or myopathy. Although the imaging findings were nonspecific, they were considered an important supportive finding when evaluated together with the patient's recurrent rhabdomyolysis episodes, persistent CK elevation, and suspected metabolic myopathy.

In the present case, the definitive diagnosis was established by identifying a homozygous CPT2 c.338C > T (p.Ser113Leu) variant on a comprehensive myopathy panel. The p.Ser113Leu variant is one of the commonly reported pathogenic variants in adult-onset myopathic CPT II deficiency. In the literature, the diagnosis is also generally confirmed by genetic analysis. Lease et al. (9) reported a 40-year-old patient with a homozygous CPT2 mutation, whereas Seferi et al. (3) identified a pathogenic variant affecting the CPT2 gene in a 33-year-old patient. Castillo et al. (6) described a different variant, c.1342T > C/p.Phe448Leu, while Akar et al. (10), similar to our case, reported a homozygous c.338C > T (p.Ser113Leu) variant in a 49-year-old patient. Therefore, the present case is consistent with genetically confirmed cases of adult-onset myopathic CPT II deficiency.

The most important contribution of this case to the literature is that it demonstrates that CPT II deficiency may remain undiagnosed even until advanced age. It also shows that metabolic myopathies should be considered in patients who have been followed for many years with a diagnosis of "myositis," have normal EMG findings, and present with persistent CK elevation. In adult patients with recurrent rhabdomyolysis episodes, unexplained CK elevation, and normal neurological examination findings between attacks, CPT II deficiency should be evaluated early in the differential diagnosis, and molecular genetic testing should be performed without delay.

Conclusion

Metabolic myopathies should be considered in the differential diagnosis of patients with long-standing CK elevation and recurrent rhabdomyolysis episodes. Normal EMG and neurological examination findings do not exclude CPT II deficiency. In such cases, early genetic testing may reduce unnecessary invasive procedures and allow initiation of appropriate metabolic treatment.

Declarations

Ethics and consent to participate: This case report was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was not required for this single-patient case report according to the institutional policy.

Consent for publication: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon reasonable request.

Availability of data and materials: The datasets generated and/or analyzed during the current study are not publicly available because they contain information that could compromise patient privacy. De-identified data are available from the corresponding author upon reasonable request.

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