A Rare Presentation of Carnitine Palmitoyltransferase II (CPT-2) Deficiency With Normal Acylcarnitine Profile in a 10-Year-Old Boy With Muscle Weakness and Bilateral Hearing Loss

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Abstract

Carnitine palmitoyltransferase II (CPT-2) deficiency is a rare and autosomal recessive disorder of long-chain fatty acids oxidation. Here, we reported a 10-year-old boy with bilateral hearing loss and a myopathic form of CPT II deficiency, which was confirmed by a molecular genetic test. He was admitted to our hospital with unexplained headaches, vomiting, and fever. Furthermore, he developed seizures, muscle weakness, neck stiffness and pain, mild respiratory distress, and an icteric appearance. The laboratory test results also showed severely elevated lactate dehydrogenase levels (LDH) and creatine phosphokinase (CPK) levels. He also had an icteric appearance with unexplained indirect hyperbilirubinemia. Further examinations revealed a normal heart and liver without any neurological disorders. Muscle pathological examination reported normal pathology without neuromuscular and mitochondrial disorders and storage diseases. Finally, molecular test analysis with next-generation sequencing (NGS) revealed CPT-II deficiency fatty acid oxidation disorder. Furthermore, we identified a homozygous pathogenic variant in the ADGRV1 gene, c.15736C>T p. (Arg5246*), which suggests the Usher syndrome type 2C and the reason for sensorineural hearing loss in this case. Our finding indicates that CPT-II can be associated with multiple symptoms and clinical features. Therefore, evaluation of CPT-II deficiency with molecular test analysis may be helpful in cases with unexplained icteric appearance, muscle weakness, and rhabdomyolysis.

Keywords: Carnitine palmitoyltransferase II deficiency; Next-generation sequencing; Muscle weakness; Usher syndrome; Rhabdomyolysis
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Introduction

Carnitine palmitoyltransferase II (CPT-II) deficiency is a rare autosomal recessive disorder that is caused by mutations in the CPT-II gene (1). This enzyme plays a significant role in the transfer of long-chain fatty acids from cytosol to the mitochondrial matrix, where they are metabolized through β-oxidation (2). Therefore, patients with CPT-II deficiency are unable to metabolize long-chain fatty acids. This is also associated with lipid accumulation, hypoketotic hypoglycemia, and energy depletion during fasting or exercise in patients (3). Myopathic phenotype is the most frequent and milder phenotype of CPT-II deficiency (4). This disease can be associated with multiple features and clinical findings, such as hypoketotic hypoglycemia, cardiomyopathy, liver and kidney failure, seizures, muscle weakness, myalgia, myoglobinuria, or rhabdomyolysis (4).

In this report, we explained a 10-year-old boy with the presentation of bilateral hearing loss and rhabdomyolysis. Initially, all patient's symptoms, including rhabdomyolysis and hearing loss, were thought to be due to disease and a pathogenic mutation, and most likely a mitochondrial disorder. In further evaluation, the whole-exome sequencing results showed a homozygous pathogenic variant in the ADGRV1 gene, c.15736C>T p. (Arg5246*), suggesting the Usher syndrome type 2C and the reason for sensorineural hearing loss. Additionally, a homozygous pathogenic variant was identified in the CPT2 gene, c.338C>T p. (Ser113Leu) causing a rare presentation of the myopathic form of CPT II deficiency.

Case presentation

A 10-year-old boy was admitted to the pediatric intensive care unit in Rasul Akram hospital with chief complaints of fever, headache, and vomiting for two days. Before admission to our hospital, he had received co-amoxiclav antibiotics, diphenhydramine, and dexamethasone ampule due to the possibility of sinusitis under examination by a general physician. In addition to the continuation of symptoms, he developed severe neck pain, which caused his admission to our hospital. The patient's biography revealed the use of non-pasteurized dairy and contaminated water. He was the fourth child of the family (IV/IV) from parents with consanguineous marriage. His older sister had died due to abdominal pain, vomiting, and the possibility of diabetic ketoacidosis when she was five years old. Our patient was born through the normal vaginal delivery method and had normal developmental milestones. His birth weight was 3.2 kg. He had complete vaccination history without a history of seizures. However, he had some complications, like muscle pain after exercises in his history. Currently, he was using a hearing aid due to bilateral hearing loss, which was identified when he was one year old. On physical examination, he was alert but seemed ill and icteric. His vital signs were normal. His sclera was icteric. He had a postnasal and mucopurulent discharge. His pupils were midsize and light-sensitive without papilledema. He also had neck stiffness without kerning and Budzinski signs. Tachypnea and mild respiratory distress were observed (respiratory rate: 50/min and positive nasal flaring). The heart was normal, but the abdomen was soft with generalized tenderness under abdominal examination. Furthermore, he had no organomegaly. On muscle examinations, there was tenderness in the proximal extremities, neck, and paraspinal muscles, as well as a decrease in the proximal muscle force of upper and lower extremities (4/5) but not in the distal

muscle force (5/5). Deep tendon reflexes of upper and lower limbs were normal (2+) and symmetric.

A complete blood count (CBC) and biochemical test analysis were provided. The level of muscle enzymes was measured to rule out the possibility of myositis. Chest X-ray was performed due to mild respiratory distress, which revealed a slight bilateral pleural effusion (PE). Because of his fever, headache, neck pain, and rigidity, a lumbar puncture (LP) was performed due to the possibility of meningitis. However, the cerebrospinal fluid (CSF) analysis was normal. The CBC test result showed an increased number of white blood cells (13400; neutrophil: 90% and lymphocyte: 10%), leukocytosis, CRP: 96, Hb: 11, and ESR: 14 (Table 1). After ensuring the normal function of the kidneys (Cr: 0.7), antibiotic therapy was initiated with cefotaxime. Because of icteric appearance (bilirubin: T:2.2 and D:0.5), increased liver enzymes [aspartate aminotransferase (AST): 732; alanine aminotransferase (ALT): 161] and a history of the use of non-pasteurized dairy and contaminated water, specific tests [hepatitis B surface antigen (Hbs Ag), hepatitis C virus antibody (HCV Ab), hepatitis A virus antibody (HAV Ab), wright test, coombs wright test, Widal test, and 2-mercaptoethanol Brucella agglutination test (2ME)] were performed to rule out the possibility of infectious diseases caused by viral hepatitis, salmonella, and brucellosis. All test results were normal. Levels of muscle enzymes were significantly increased [creatine phosphokinase (CPK): 63365 and lactate dehydrogenase (LDH): 5178] (Table 1). The patient was then admitted to the PICU and fully hydrated because of severe rhabdomyolysis, which was associated with respiratory problems and respiratory distress. To rule out the possibility of mitochondrial and metabolic myopathies, metabolic tests analysis, such as the serum lactate, plasma acylcarnitine profile, tandem mass spectrometric (MS/MS) in plasma, and urinary organic acids was performed and showed normal results. Abdominal and pelvic ultrasound showed increased corticomedullary differentiation and parenchymal echogenicity in both kidneys. Additionally, an accumulation of free fluid was found in the pelvis and the whole abdominal cavity. The test results of antinuclear antibodies (ANA), Anti-ds-DNA, P-ANCA, C-ANCA, rheumatoid factor (RF), complement 3 (C3), C4, Anti-Ro (SSA), and Anti-La (SSB) were normal to rule out the possibility of rheumatological, autoimmune, dermatomyositis, and polymyositis. The thyroid function test results [thyroid-stimulating hormone (TSH) and T4 were normal (Table 1). Due to free fluid in the abdomen and pleural effusion, a cardiac consultation was provided to evaluate the pericardial effusion and cardiovascular involvement. The result was normal, and there was no pericardial effusion. Electromyography (EMG) showed mild and early polymyopathy with some evidence of spontaneous muscle fiber activity (+1 fibrillation) without myotonic discharge.

On the fifth day after admission, due to increased CPK up to 100000 U/l and cola-colored urine, which suggested myoglobinuria, intravenous immunoglobulin (IVIG) therapy (1 gr/kg/day for two days) was initiated for the possibility of polymyositis. Urine intake and output chart and then serum therapy were performed. The uric acid level was checked following rhabdomyolysis to rule out hyperuricemia. Due to hyperuricemia (uric acid: 8.5), treatment with Rasburicase was started. On the 10th day after admission, the patient developed severe nausea and vomiting along with headache,

severe abdominal pain, and tenderness. To rule out the acute abdomen, an abdominal X-ray in supine and upright positions was performed. Furthermore, emergency sonography was provided and revealed the accumulation of free fluid in subhepatic, diaphragmatic, and inter-loop spaces. The acute abdomen was ruled out by surgery consultation. At that time, the patient developed a seizure with blindness for two minutes, which was followed by an upward gaze and loss of consciousness for about two minutes. He experienced another seizure with eye gaze and turning of the head and eyes to the right side. He was treated with phenytoin due to focal seizures with impaired awareness. The other stimulator factors for seizure, like electrolyte disturbance, were also considered in a normal range.

The brain computed tomography scan (CTS) and magnetic resonance imaging (MRI) revealed normal results. An electroencephalogram (EEG) test was also provided, which showed a normal result. Because of suspicion of vasculitis and rheumatologic diseases, the ophthalmic examination was performed and revealed normal results. Eventually, due to the pleural effusion and free fluid in the abdomen, the central nervous system (CNS) involvement (seizure), and myopathy with the possibility of autoimmune diseases and after a negative test result for purified protein derivative (PPD), the patient was treated with a high dose of methylprednisolone at 20 mg/kg/day for five consecutive days. Symptoms were improved, and then headache, vomiting, and abdominal pain were cured. Laboratory test results showed an improvement in the liver [Cr: 0.7; AST: 43, and ALT: 92] and muscle (CPK: 258 U/l and LDH: 21000U/l) enzymes (Table 1).

A muscle biopsy was provided to rule out the possibility of metabolic and mitochondrial myopathies, especially glutaric aciduria type II and glycogen storage disease types V and VII. The pathological muscle examination reported normal pathology without evidence of any neuromuscular, metabolic, or mitochondrial disorders. Although viral myositis is a post-infection disorder, we ruled out some viral infections, like viral hepatitis, by tests. Eventually, whole-exome sequencing with the next-generation sequencing (NGS) method was performed to consider any possible mutations. The results showed a homozygous pathogenic variant in the ADGRV1 gene, c.15736C>T p. (Arg5246*), suggesting the Usher syndrome type 2C and the reason for sensorineural hearing loss in this case. Additionally, a homozygous pathogenic variant was identified in the CPT2 gene, c.338C>T p. (Ser113Leu). Both mutations were confirmed with Sanger sequencing.

Table 1. The biochemical test results of the patient

	Initial Results	Day 5	Day 10	Day 18
CBC				
WBC(×1000/mm3)	13.4	10.24	12.3	17.39
RBC (Mill/mm3)	4.76	4.21	3.67	3.64
Neutrophil(%)	90%	Norm	-	-
Lymphocyte(%)	10%	Norm	-	-
Hct (%)	39.9	33.4	30	30
M.C.V (fL)	83.8	Norm	Norm	82.4
M.C.H (pg)	30	Norm	Norm	28.8
M.C.H.C (%)	35.8	Norm	Norm	35
Plt (×1000/mm3)	201	Norm	374	423
Hb (g/dl)	14.3	11.8	10.6	10.5
RDW (%)	13.1	9.2	-	9.7
Biochemical tests				
ESR (mm/h)	11	8	-	12
CRP	96	12	12	12
Blood sugar (mg/dl)	120			60
Cr (mg/dl)	0.7	3.9	1.5	0.7
AST (IU/l)	732	520	105	43
ALT (IU/l)	161	594	192	92
Total Bili (mg/dl)	2.2	0.7	0.4	-
Direct Bili (mg/dl)	0.5	0.2	0.2	-
CPK (IU/l)	63365	>100000	2740	258
LDH-p (IU/l)	2133	4737	3679	21000
Uric acid (mg/dl)	1	1	3.4	-
ALK-p (IU/l)	608	275	-	280

	Initial Results	Day 5	Day 10	Day 18
Albumin (g/dl)	3.9	-	2.9	
BUN (mg/dl)	8	43	15	16
Inorganic P (mg/dl)	5.3	-	-	3.4
Serum Mg (mg/dl)	2.5	2.4	2.6	2.2
Serum Na (mEq/L)	140	135	140	137
Serum K (mEq/L)	3.9	4.3	3.9	3.6
Serum Ca (mg/dl)	8.5	8.8	9.3	8.8
Lipase (IU/L)	155.56	-	155.56	162.15
Infectious disease test				
CSF analysis	Normal	-		-
HbsAg	Normal	-		-
HCV Ab	Normal	-		-
HAV Ab	Normal	-		-
2ME	Normal	-		-
Rheumatological tests				
Anti-ds-DNA	Normal	-		-
P-ANCA	Normal	-		-
C-ANCA	Normal	-		-
RF	Normal	-		-
Immunological tests				
C3, C4	Normal	-		-
Anti-Ro	Normal	-		-
Anti-La	Normal	-		-
Metabolic tests				
Ammonia	Normal	-	-	-

	Initial Results	Day 5	Day 10	Day 18
Lactate	Normal	-	-	-
Acylcarnitine profile	Normal	-	-	-
HPLC	Normal	-	-	-
MS/MS	Normal	-	-	-

Discussion

CPT-II deficiency is an inherited autosomal recessive disorder, and the early diagnosis of the disease is important because it is almost invariably fatal, especially in neonates (5). This disease may be associated with different clinical phenotypes, such as acute muscle weakness, muscle pain, myoglobinuria, increased fat intake, ketotic hypoglycemia, and emotional distress (6, 7). Because of myoglobinuria, the urine may be brown. Seizures, hepatomegaly, nephromegaly, hypoglycemia, metabolic acidosis, respiratory distress, cardiomegaly with cardiomyopathy, increased serum aminotransferase and ammonia, and decreased serum carnitine are the other clinical and laboratory findings reported in previous studies (3, 8, 9). Some studies have reported increased serum creatinine and blood urea nitrogen levels and acute renal failure in these cases (10, 11). Muscle injury may be identified under electromyography in some cases (12). Currently, the tandem mass spectrometric (MS/MS) measurement of serum acylcarnitine is a valuable screening test for identifying fatty acid oxidation defects in neonates (13). However, molecular genetic tests are necessary for a definitive diagnosis of CPT-II deficiency.

Here, we reported a 10-year-old boy with Usher syndrome and a myopathic form of CPT II deficiency, which was confirmed under genetic test analysis. To the best of our knowledge, this is the first case of Usher syndrome with CPT II deficiency. Our case not only had muscle weakness, neck stiffness, and pain, but also he developed seizures, headaches, and mild respiratory distress. He was admitted with complaints of headache and fever. Similarly, Kabbouche et al. (1) reported migraine headaches in two adolescent cases with CPT-II deficiency. The laboratory test analysis showed that our case had increased levels of the liver (AST and ALT) and muscle (LDH and CPK) enzymes. He had cola-colored urine due to myoglobinuria. Our case also had an icterus appearance and hyperbilirubinemia. Similarly, Malik et al. (13) reported a three-day-old female child with CPT-II deficiency, icterus, and conjugated hyperbilirubinemia. However, the underlying mechanism of hyperbilirubinemia in our case is not clear.

Although some studies have recommended MS/MS measurement of serum acylcarnitine for the diagnosis of the disease, this test result was normal for our case. Therefore, this indicated that genetic testing or measurement of enzyme activity is essential to make a definite diagnosis of CPT-II deficiency. Recent studies have reported various mutations in at least one copy of S113L, P50H, or Q413fs-F448L genes (14). After genetic test analysis and whole-genome sequencing, we found that our case had a homozygous pathogenic variant in the CPT-II gene, c.338C>T p. (Ser113Leu).

Furthermore, he had a homozygous pathogenic variant in the ADGRV1 gene, which was related to the Usher syndrome and the reason for his sensorineural hearing loss. Similarly, Gempel et al. (15) reported a six-year-old girl with CPT-II deficiency who presented with acute muscle weakness, pain, and inability to walk. Further genetic test analysis showed that this case was homozygous for the S113L (338C>T) mutation, which is usually associated with the adult form of the disease. More recently, Avila-Smirnow et al. (2) reported a heterozygous mutation of p.Ser113Leu in a boy and a girl with CPT-II deficiency. They also found an increased level of CK in both cases. The p.Ser113Leu variant is considered the most frequent (60%) mutation in white populations. However, this is not obvious whether there is a relationship between Usher syndrome and CPT-II deficiency, which was observed in our case. Treatment of the disease usually contains diet modifications with a high carbohydrate and low-fat diet, glucose infusions, avoiding extended fasting, frequent meals, avoiding prolonged exercise, sufficient hydration during rhabdomyolysis, and myoglobinuria to prevent renal failure (13).

These data have suggested that CPT-II can be associated with various symptoms and clinical features. Variation in the disease severity and the number of clinical features is likely because of different mutations in the CPT-II gene. Therefore, further studies are necessary to evaluate the relationship between genotype and phenotype. Our patient was born from parents with consanguineous marriage; however, no evidence of similar conditions was reported in his family. Since consanguineous marriage is common in Iran, there may be a relationship between the incidence of CPT-II deficiency and consanguineous marriage. Therefore, further considerations are required to evaluate the correlation, and premarital genetic counseling and education may be helpful.

In Conclusion

CPT-II deficiency is a lipid metabolism disorder inherited in an autosomal recessive manner. We reported a ten-year-old boy with a myopathic form of CPT II deficiency despite a normal muscle biopsy and serum acylcarnitine profile, which was confirmed under NGS analysis. Therefore, evaluation of CPT-II deficiency with molecular test analysis may be helpful in suspected cases despite normal muscle biopsy and serum acylcarnitine profile.

Written informed consent was obtained from the parents of the patient for the publication of this case report.

Author's Contribution

VM and RA analyzed and interpreted the patient data regarding the neurologic disease. GS and TL performed a follow-up of the patient and were major contributors in writing the manuscript. All of the authors read and approved the final manuscript.

Acknowledgment

Written informed consent was obtained from the parents of the patient for the publication of this case report

Conflict of interest

The authors declare no conflict of interest in preparing this case presentation.

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