ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Primary Carnitine Deficiency as a Treatable Cause of Heart Failure in Young Patients

Genç Hastalarda Tedavi Edilebilir Bir Kalp Yetersizliği Nedeni Olarak Primer Karnitin Eksikliği

ABSTRACT

Non-ischemic dilated cardiomyopathy is the most common subgroup of heart failure in young adults. Several metabolic defects could be the underlying etiology in these young heart failure patients. However, most cases are considered idiopathic. Primary carnitine deficiency is an overlooked inherited metabolic disease causing cardiomyopathy in these patients. Oral carnitine replacement therapy could prevent primary carnitine deficiency patients from progressing to advanced heart failure and life-threatening arrhythmias. In this case report, we present an index primary carnitine deficiency case and his brother's diagnosis and successful treatment period to draw attention to primary carnitine deficiency as a treatable cause of heart failure in young adults.

Keywords: Cardiomyopathy, carnitine deficiency, heart failure, rare disease

ÖZET

İskemik olmayan kardiyomiyopati genç erişkinlerde kalp yetersizliğinin en sık karşılaşılan alt grubudur. Olguların çoğunda etiyoloji tespit edilemez ve idiyopatik olarak sınıflandırılır. Halbuki, birincil karnitin eksikliği, oral karnitin replasmanı ile tedavi edilebilmesine rağmen, ayırıcı tanıda akla gelmediği için sıklıkla atlanmaktadır. Birincil karnitin eksikliği hastalarında ileri kalp yetersizliğine ilerleme ve hayatı tehdit eden aritmiler karnitin replasmanı ile önlenebilir. Bu olgu sunumu ile birincil karnitin eksikliği tanısı alan indeks vaka ve kardeşinin tanı alma ve tedavi süreci ile tedavi edilebilir bir kalp yetersizliği nedeni olan birincil karnitin eksikliğine dikkat çekmek ve farkındalık sağlamak istedik.

Anahtar Kelimeler: Kalp yetersizliği, kardiyomiyopati, karnitin eksikliği, nadir hastalık

CASE REPORT
OLGU SUNUMU

Meral Kayıkçıoğlu, M.D.[1]
Benay Özbay, M.D.[2]
Burcu Yağmur, M.D.[1]
Ebru Canda, M.D.[3]
Selen Bayraktaroğlu, M.D.[4]
Evrim Şimşek, M.D.[1]
Sema Kalkan Uçar, M.D.[3]

[1]*Department of Cardiology, Ege University Faculty of Medicine, İzmir, Turkey*
2Department of Cardiology, Başakşehir Çam and Sakura State Hospital, İstanbul, Turkey
3Department of Pediatric Metabolic Disorders, Ege University Faculty of Medicine, İzmir, Turkey
4Department of Radiology, Ege University Faculty of Medicine, İzmir, Turkey

Corresponding author:
Meral Kayıkçıoğlu
✉ meral.kayikcioglu@gmail.com

Received: December 23, 2021
Accepted: March 16, 2022

Cite this article as: Kayıkçıoğlu M, Özbay B, Yağmur B, et al. Primary carnitine deficiency as a treatable cause of heart failure in young patients. *Turk Kardiyol Dern Ars.* 2022;50(7):535-539.

DOI:10.5543/tkda.2022.21319

Carnitine is essential for the transfer of long-chain fatty acids from the cytosol to mitochondria for subsequent β-oxidation, especially in the heart muscle.[1] Primary carnitine deficiency (PCD) may result in acute metabolic decompensation such as hepatic encephalopathy, hypoketotic hypoglycemia, sudden infant death early in life, and cardiomyopathy (CMP) in later onset.[2] If carnitine replacement is performed with early diagnosis, patients can live a normal life on continuous treatment.[3] Primary carnitine deficiency is not included in the neonatal screening program in most countries. However, PCD is the second most frequent fatty acid oxidation disorder ranging from 1/40 000 to 1/120 000 among newborns around the world.[4] Primary carnitine deficiency is inherited autosomal recessively, and carnitine transporter organic cation transporter-2 (OCTN-2), encoded by *SLC22A5* (solute carrier family 22), defect causes the disease.[5] Due to recessive inheritance, PCD is more common in societies where consanguineous marriages are common or where there is a closed gene pool like Faroe Islands.[6] Limited newborn and childhood case reports have been published from Turkey.[7,8] Herein, we present 2 adult siblings with dilated CMP to draw attention to carnitine deficiency as a rare but treatable cause of heart failure.

Case Reports

Table 1 displays the clinical characteristics of 2 siblings with carnitine deficiency and dilated CMP. Both cases were referred from the pediatric metabolic disease unit to our adult cardiology outpatient clinic as they reached the age of 18 years. Both were

asymptomatic with functional class I effort capacity on carnitine therapy during the initial evaluation in our clinic. Figure 1 depicts the electrograms, Figure 2 echocardiography images, and Figure 3 the cardiac magnetic resonance images (MRI) at this initial work-up in their first visit to our adult cardiology department. Though 2 brothers had proven dilated CMP with echocardiography, both were active basketball players in the school team. Both brothers gave informed consent for reporting their information about their cardiac disease in a medical journal.

Case 1: The index patient was admitted to the hospital for the first time at the age of 6 years due to weakness and general illness. He was the first child of a consanguineous (first-degree cousin marriage) family. At the age of 7 years, he was referred to a pediatric metabolism clinic with the symptoms of heart failure. On his physical examination, sinus bradycardia and hepatomegaly with normal motor-mental development were detected. An echocardiogram revealed dilated CMP with a left ventricular ejection fraction (LVEF) of 40%. On examination for juvenile dilated CMP, tandem mass spectrometry analyses have depicted low free-carnitine levels under carnitine therapy (1.38 µmol/L normal range: 7-80 µmol/L). Also, acyl arnitine levels were low as follows: C_2 carnitine: 2.19 µmol/L (N: 9-80 µmol/L), C_3 carnitine: 0.25 µmol/L (0.6-7 µmol/L), and C_{16} carnitine: 0.03 µmol/L (0.5-8 µmol/L). Due to the suspicion of carnitine transport deficiency, carnitine uptake (with 5 µmol carnitine) in fibroblast analyses was performed, and low transport was detected as 0.03 pmol/min mg (control: 1.01 ± 0.26 pmol/min mg). Organic cation transporter-2 (*SLC22A5*) gene analyses showed homozygous c.506G>A(p. R169Q) mutation. He was diagnosed as having carnitine transport deficiency. Oral carnitine treatment was continued with the dose of 4 g/day and during follow-up, he was treated with 6 g/day oral carnitine. He was completely asymptomatic on carnitine therapy during our follow-up. We also added an angiotensin-converting enzyme inhibitor (ramipril 5 mg) and a beta-blocking agent (metoprolol 50 mg) as conventional heart failure treatment. However, 1 year later, he was admitted with typical severe exertional to resting dyspnea with functional capacity of class 2-3. The symptoms got initiated 2 months after he had stopped the carnitine supplementation. He was put again on oral carnitine therapy and immediately in a few days symptoms resolved and for the last 3 years, he is completely asymptomatic on carnitine therapy.

Case 2: Carnitine transport deficiency was also detected at the age of 11 during the family screening. At the time of diagnosis, his ECG and echocardiographic evaluation were within normal limits. Cranial MRI evaluation was normal. Tandem mass spectrometry analyses showed a low free-carnitine level: 0.74 µmol/L (N: 7-80 µmol/L). Also, acylcarnitine levels were low as follows:

ABBREVIATIONS

CMP	Cardiomyopathy
LGE	Late gadolinium enhancement
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance images
OCTN-2	Organic cation transporter-2
PCD	Primary carnitine deficiency
SLC22A5	Solute carrier family 22

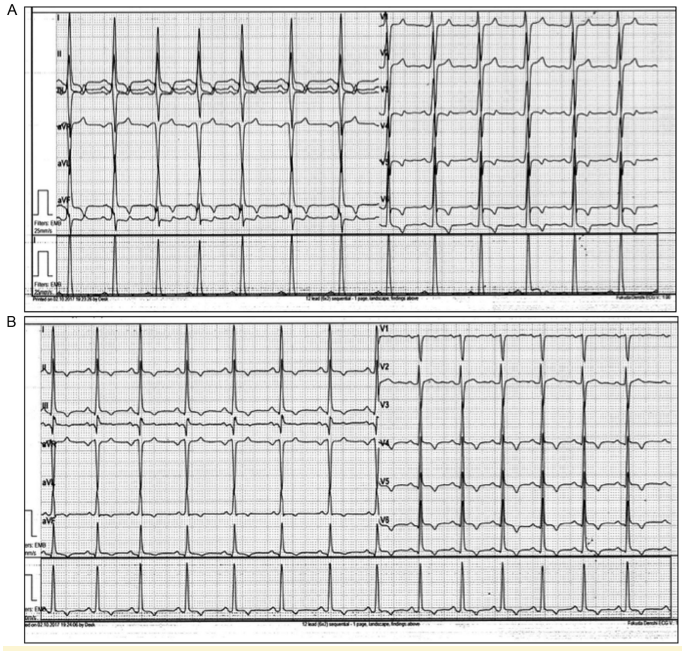

Figure 1. ECG images of case 1 (A) and case 2 (B). Left ventricular hypertrophy and left axis could be seen in both ECGs. ECG, electrocardiogram.

C2 carnitine: 3.93 µmol/L (N: 9-80 µmol/L), C3 carnitine: 0.11 µmol/L (0.6-7 µmol/L), and C16 carnitine: 0.02 µmol/L (0.5-8). Carnitine uptake (with 5 µmol carnitine) in fibroblast analyses showed low transport of 0.03 pmol/min mg (control: 1.01 ± 0.26). Organic cation transporter-2 (*SLC22A5*) gene analyses showed homozygous c.506G>A(p. R169Q) mutation. He was treated with oral carnitine (4 g/day) and up-titrated to a dose of 6 g/day. During the follow-up in our adult cardiology unit, he was admitted with syncope after he has stopped the

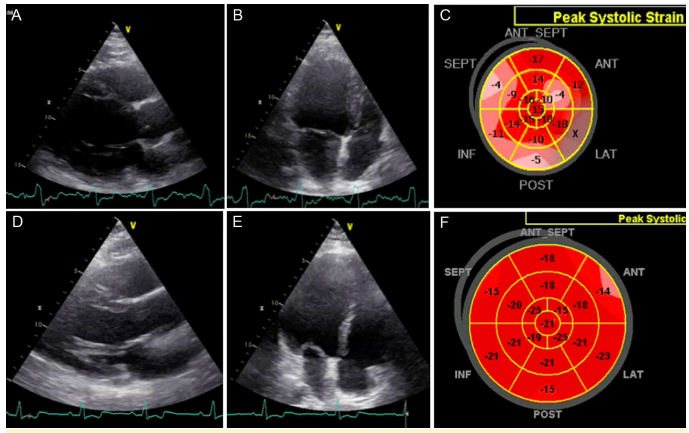

Figure 2. Echocardiography (A-B) and strain echocardiography Bull's eye (C) images of case 1 and echocardiography (D-E) and strain echocardiography Bull's eye (F) images of case 2. Left ventricular hypertrophy with global hypokinesis and decreased GLS could be seen in A-C. Left ventricular hypertrophy with normal ejection fraction and within normal limits GLS could be seen in D-F (A and D: parasternal long axis view, B and E: apical 4-chamber view) (Video 1-2-3-4). GLS, global longitudinal strain.

Table 1. Clinical Characteristics of the Patients with Carnitine Deficiency

	Sibling 1	Sibling 2
Age (years)	30	23
Age onset of PCD disease (years)	7	11
Age at the diagnosis of HF (years)	7	NA
Gender	Male	Male
Body mass index (kg/m^2)	30	32
Presenting symptoms on admission during childhood	Weakness	None
Prior medical history	Heart failure was diagnosed	Diagnosed by screening test
Exercise intolerance on admission	Yes	No
Heart Failure	Yes	No
Physical examination	Normal	Normal
ECG on treatment		
Rhythm	Sinus	Sinus
Axis	16°	26°
Sokolow–Lyon index	3.99	3.14
Cornell index	3.08	1.94
QT/QTc (Bazzet formula) (ms)	395/452	350/417
Echocardiography		
Left ventricular EF (%)	40	66
Left ventricular ESV (mL)	154	59
Left ventricular EDV (mL)	254	173
IVS (mm)	12	10.5
PW (mm)	10	9
Septal/Lateral E' (cm/s)	10/14	11/10
GLS (strain echocardiography)	−12.6	−19.5
Holter ECG findings	Supraventricular ectopy (0.008%)	Supraventricular ectopy (0.009%)
Cardiac MRI findings	Global hypokinesia	Normal
	No LGE	No LGE
Laboratory		
SGOT/SGPT (U/L)	23/38	18/26
CK (mg/dL)	51	51
HDL (mg/dL)	47	33
LDL (mg/dL)	139	112
Triglycerides (mg/dL)	114	115
Creatinine (mg/dL)	1	0.8
Hemoglobin/ hematocrits (g/dL)	14.8/41.7	14.5/40.4
NT-proBNP (pg/mL)	14.43	< 5
TSH (μIU/mL)	2.35	0.904
Carnitine uptake (pmol/min mg) in OCTN	0.03	0.01
Genetic mutation analysis	Homozygous for OCTN2 (*SLC22A5*)	Homozygous for OCTN2 (*SLC22A5*)

All measurements belong to the first evaluation of the cases in adult cardiology unit otherwise mentioned.
PCD, primary carnitine deficiency; HF, heart failure; LV, left ventricle; ESV, end systolic volume; EDV, end diastolic volume; IVS, Inter ventricular septum; PW, posterior wall; GLS, global longitudinal strain; ECG, electrocardiography; MRI, magnetic resonance imaging; SGOT, serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; CK, creatinine kinase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NT-proBNP, N terminal peptide-pro brain natriuretic peptide; TSH, thyroid-stimulating hormone; OCTN2, organic cation transporter-2; SLC22A5, solute carrier family 22.

carnitine therapy for 2-3 months. After commencing the oral carnitine replacement, he became completely asymptomatic. The poor compliance with carnitine treatment was the major reason for the clinical deterioration of both brothers. And with long conversations, their awareness of the importance of carnitine supplementation for their cardiovascular health and well-being increased. Holter ECG recordings are within normal limits with no life-threatening arrhythmia episodes on carnitine therapy. Therefore, no additional therapy for CMP was considered.

Discussion

Fatty acids and carbohydrates are recognized as key sources of energy for the heart.[9] L-Carnitine and carnitine acyltransferases participate in the oxidation of fatty acids by transporting acyl groups between cell organelles and into the mitochondrial matrix, where β-oxidation occurs. In addition, L-carnitine enhances non-oxidative glucose metabolism and improves slightly glucose tolerance. The sources of L-carnitine in humans are both endogenously synthesized and are present in ingested food such as dairy and meat.[10]

Primary carnitine deficiency is an inherited metabolic disease of carnitine transportation with a wide variety of clinical manifestations with respect to the age of onset, organ involvement, and severity of symptoms. However, PCD symptoms are typically characterized by episodes of hypoketotic hypoglycemia, hepatomegaly, elevated transaminases, and hyperammonemia in infants; skeletal myopathy, elevated creatine kinase, and cardiomyopathy in childhood; or cardiomyopathy, arrhythmias, or fatigability in adulthood.[5] The most common symptom is fatigue and weakness like in our cases, and in those diagnosed in late childhood, it is often diagnosed during exploring the etiology of CMP or rhabdomyolysis. Some patients may remain asymptomatic throughout life. Both sexes are equally affected. Low plasma free-carnitine levels (usually <5 μM) is used as a diagnostic tool for PCD. In most cases, carnitine transporter OCTN-2, encoded

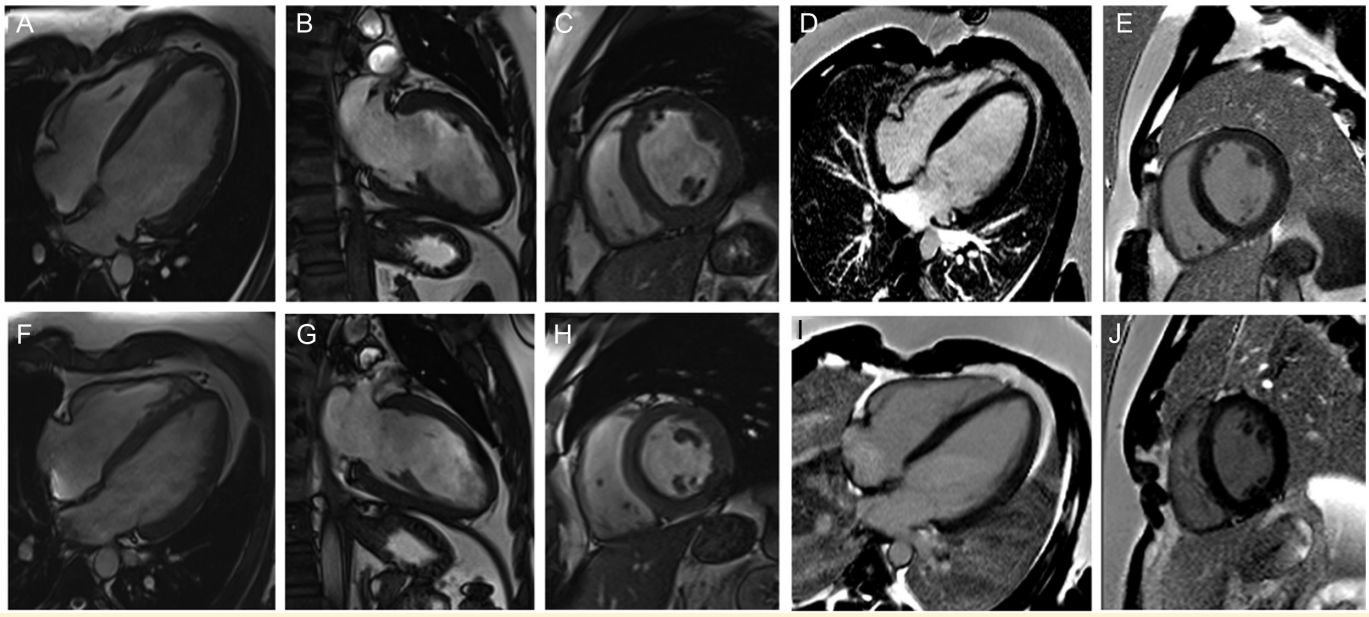

Figure 3. Cardiac MRI images of the cases. (A-E) cardiac MRI images of case 1 showing global hypokinesis with no LGE. (F-J) cardiac MRI images of case 2 are within normal limits with no LGE (Video 5-6-7-8-9). MRI, magnetic resonance imaging; LGE, late gadolinium enhancement.

by *SLC22A5* (solute carrier family 22), defects lead to PCD. The diagnosis is definitively confirmed by molecular testing of the *SLC22A5* gene or by studying carnitine transport in fibroblasts (<20% of normal controls) as in our cases.[11]

Primary carnitine deficiency patient's myocardium demonstrates massive lipid accumulation and fibrosis associated with clinical dilated CMP.[12] However, a few hypertrophic CMP cases have been described.[13] It is reported that daily 100-400 mg/kg carnitine replacement could resolve symptoms and improve LVEF in these patients. Fu et al[14] reported the rapid reversal of left ventricular systolic dysfunction with 1 month of carnitine therapy in a series of 6 children with PCD. The opposite is also true, a short-term non-adherence to therapy may lead to rapid deterioration of cardiac functions as in our cases. Similarly, 2 adult female patients, aged 23 and 24 years, were reported to have clinical deterioration with cessation of treatment and then prompt recovery with carnitine replacement.[13-15] Our case 2 has experienced syncope due to arrhythmia probably associated with a 2-3-month interruption of the carnitine replacement. Similarly, Tomlinson et al's[15] adult case (24-year-old female) has developed syncope with an interval of 3 months treatment cessation. Arrhythmic events could be lethal in untreated PCD. Some treatment-naïve cases may present with syncope and arrhythmia on admission. Cardiomyopathy is the major cause of arrhythmia in these patients. However, PCD could trigger arrhythmia without CMP.[13] It has been shown that the accumulation of long-chain fatty acids in the cytosol of mitochondria could cause arrhythmia in animal studies.[16] Oral carnitine replacement could decrease the non-sustained ventricular tachycardia episodes on Holter ECG.[5]

Our cases together with the previous 2 adult cases in the literature, denoting the fast deterioration with cessation of therapy, emphasize the importance of adherence to carnitine therapy in PCD.[13-15] Therefore, PCD patients and their families should be educated about the life-threatening consequences of cessation of essential carnitine therapy.

Our cases have further important contributions to the current literature on several aspects. These cases provide evidence for the long-term effective treatment of PCD with carnitine. With regular carnitine replacement, patients could remain asymptomatic with a very good functional class such as active participating in sports like basketball as in our cases. The second brother is also a good example to emphasize the importance of family screening as he has received the PCD diagnosis during family genetic screening before developing overt heart failure. To the best of knowledge, our 2 cases are the first adult PCD cases reported in Turkey. Rare inherited metabolic diseases leading to CMP are highly prevalent due to high consanguinity and closed gene pool in rural areas in Turkey. However, all PCD cases from Turkey have been published in newborn and childhood period which probably denote the lack of awareness of adult cardiologists on PCD as a cause of CMP. Moreover, the mutation of 506G>A (p. R169Q) mutation we detected in both brothers is a novel mutation in the *SLC22A5* gene. Another important aspect of our PCD patients is that they provide further evidence for the prevention of myocardial fibrosis with early diagnosis and life-long carnitine replacement therapy. There are very limited reports of myocardial fibrosis assessed by late gadolinium enhancement (LGE) of cardiac MRI. One of these previous adult cases who had had first diagnosed with nonischemic CMP at the age of 10 years had only been intermittently compliant with her carnitine supplement regimen probably leading to patchy LGE in cardiac MRI.[13] Our second case had no LGE in cardiac MRI and strain echocardiographic evaluations were within normal limits; therefore, intracardiac defibrillator implantation was not considered. However, index case had moderately decreased ejection fraction, thus impaired global longitudinal strain was measured

even had no LGE in cardiac MRI. Of note, our cases constitute the first presentation of strain echocardiographic data of PCD in the literature. However, the lack of evaluation with strain imaging and further imaging data during the deterioration period when both brothers have interrupted carnitine replacement is the major limitation of our case presentation. We could not retrieve the archive records from that period due to technical problems. In addition, discontinuing carnitine treatment and monitoring patients would not be ethical. Nevertheless, our cases clearly demonstrate that oral carnitine replacement is essential for patients with PCD. With life-long simple inexpensive oral carnitine supplementation, there would be no need for advanced heart failure treatment options, such as cardiac devices and heart transplantation in patients with PCD. Moreover, carnitine treatment has been shown to improve clinical symptoms and cardiac functions and decrease serum brain natriuretic peptide levels.[17] However, the hypothesis of carnitine treatment as conventional therapy in heart failure is still not clarified, and large randomized controlled trials are warranted.

Conclusion

Primary carnitine deficiency as an inherited metabolic disease should be kept in mind as a treatable cause of heart failure in young adults, particularly in countries with high consanguinity. As an inexpensive, readily available oral treatment, carnitine replacement not only ameliorates heart failure symptoms and complications including lethal arrhythmias but also protects these patients from unnecessary use of expensive treatments and heart transplantation. Besides, the hypothesis of carnitine therapy as an effective adjuvant agent in conventional treatment of heart failure is still not clarified.

*Supplementary video files associated with this article can be found in the online version of the journal.

Informed Consent: Written informed consent was obtained from the patients/patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Data Collection and/or Processing – M.K., E.C., E.Ş., S.K.U.; Analysis and/or Interpretation – B.Y., S.B.; Literature Review – B.Ö.; Writing – M.K., B.Ö., B.Y., E.C., S.B., E.Ş., S.K.U.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This study received no funding.

References

1. Longo N. Primary carnitine deficiency and newborn screening for disorders of the carnitine cycle. *Ann Nutr Metab*. 2016;68(suppl 3):5-9. [CrossRef]
2. Scaglia F, Wang Y, Longo N. Functional characterization of the carnitine transporter defective in primary carnitine deficiency. *Arch Biochem Biophys*. 1999;364(1):99-106. [CrossRef]
3. Fu L, Huang M, Chen S. Primary carnitine deficiency and cardiomyopathy. *Korean Circ J*. 2013;43(12):785-792. [CrossRef]
4. Wilcken B, Wiley V, Sim KG, Carpenter K. Carnitine transporter defect diagnosed by newborn screening with electrospray tandem mass spectrometry. *J Pediatr*. 2001;138(4):581-584. [CrossRef]
5. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. *Orphanet J Rare Dis*. 2012;7:68. [CrossRef]
6. Steuerwald U, Lund AM, Rasmussen J, Janzen N, Hougaard DM, Longo N. Neonatal screening for primary carnitine deficiency: lessons learned from the Faroe Islands. *Int J Neonat Screening*. 2017;3(1):1. [CrossRef]
7. Kilic M, Ozgül RK, Coşkun T, et al. Identification of mutations and evaluation of cardiomyopathy in Turkish patients with primary carnitine deficiency. *JIMD Rep*. 2012;3:17-23. [CrossRef]
8. Yilmaz BS, Kor D, Mungan NO, Erdem S, Ceylaner S. Primary systemic carnitine deficiency: a Turkish case with a novel homozygous SLC22A5 mutation and 14 years follow-up. *J Pediatr Endocrinol Metab*. 2015;28(9-10):1179-1181. [CrossRef]
9. Lopaschuk GD, Ussher JR. Evolving concepts of myocardial energy metabolism: more than just fats and carbohydrates. *Circ Res*. American Heart Association. 2016;119(11):1173-1176. [CrossRef].
10. Adeva-Andany MM, Calvo-Castro I, Fernández-Fernández C, Donapetry-García C, Pedre-Piñeiro AM. Significance of l-carnitine for human health. *IUBMB Life*. 2017;69(8):578-594. [CrossRef].
11. Longo N, Frigeni M, Pasquali M. Carnitine transport and fatty acid oxidation. *Biochim Biophys Acta*. 2016;1863(10):2422-2435. [CrossRef].
12. Kyhl K, Róin T, Lund A, et al. Cardiac function and incidence of unexplained myocardial scarring in patients with primary carnitine deficiency - a cardiac magnetic resonance study [sci rep:13909]. *Sci Rep*. 2019;9(1):13909. [CrossRef].
13. Ascunce RR, Nayar AC, Phoon CKL, Srichai MB. Cardiac magnetic resonance findings in a case of carnitine deficiency. *Tex Heart Inst J*. 2013;40(1):104-105.
14. Fu L, Huang M, Chen S. Primary carnitine deficiency and cardiomyopathy. *Korean Circ J*. 2013;43(12):785-792. [CrossRef]
15. Tomlinson S, Atherton J, Prasad S. Primary carnitine deficiency: a rare, reversible metabolic cardiomyopathy. *Case Rep Cardiol*. 2018;2018:3232105. [CrossRef]
16. Ferro F, Ouillé A, Tran TA, et al. Long-chain acylcarnitines regulate the hERG channel. *PLoS One*. Public Library of Science. 2012;7(7):e41686. [CrossRef]
17. Song X, Qu H, Yang Z, Rong J, Cai W, Zhou H. Efficacy and safety of L-carnitine treatment for chronic heart failure: a meta-analysis of randomized controlled trials. *BioMed Res Int*. 2017;2017:6274854. [CrossRef]