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CLINICAL BRIEF

Dilated Cardiomyopathy as the Only Clinical Manifestation of Carnitine Transporter Deficiency

Kyriaki Papadopoulou-Legbelou[1] · **Maria Gogou**[1,2] · **Vaia Dokousli**[1] · **Maria Eboriadou**[1] · **Athanasios Evangeliou**[1]

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Abstract The authors present a case of carnitine transporter deficiency, which was unmasked after an episode of respiratory distress resistant to treatment with bronchodilators. Chest radiograph showed cardiomegaly; electrocardiogram showed left ventricular hypertrophy and echocardiography revealed dilated cardiomyopathy. Heart failure therapy was initiated and metabolic screening was requested, as family history was indicative of inborn errors of metabolism. Very low levels of free carnitine and carnitine esters in blood were found and genetic testing confirmed the diagnosis of carnitine transporter deficiency. After oral supplementation with L-carnitine, symptoms gradually ameliorated and heart function had fully recovered. Sequence analysis in the *SLC22A5* gene revealed the missense mutation c.1319C > T (p.Th440Met) in homozygous state. Homozygous c.1319C > T (p.Th440Met) mutation has not been associated with a pure cardiac phenotype before.

Keywords Carnitine transporter deficiency · *SLC22A5* gene · Dilated cardiomyopathy · Childhood

Introduction

Carnitine transporter deficiency represents a rare disorder of long-chain fatty acids oxidation. Its prevalence ranges from 1:20,000 to 1:120,000 births, highly depending on ethnicity [1].

✉ Maria Gogou
mariaangogou@gmail.com

[1] 4th Department of Pediatrics, School of Medicine, Aristotle University of Thessaloniki, General Hospital Papageorgiou, Thessaloniki, Greece

[2] Dimitriou Nika 44, 60 100, Katerini, Greece

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The disease is inherited in an autosomal recessive way and is caused by mutations in the *SLC22A5* gene on chromosome 5q23.3. Deficiency of this transporter leads to low carnitine levels in plasma, urinary carnitine wasting and impaired fatty acids transfer into the mitochondria. The clinical phenotype can include hypoketotic hypoglycemia, hepatic encephalopathy, skeletal myopathy (muscle weakness or hypotonia) and cardiomyopathy [2]. Until now no "genotype-phenotype correlation" has been described with regards to this disease.

The authors present a case of carnitine transporter deficiency with cardiomyopathy as exclusive phenotype, caused by homozygous c.1319C > T (p.Th440Met) missense mutation.

Case Report

A 3-y-old girl presented to the Emergency Department due to respiratory distress. Symptoms had begun 7 d before. On admission physical examination revealed respiratory distress, wheezing and crepitant rales on the bases of lungs. Vital signs were within normal ranges.

The girl was the 4th child of non-consanguineous parents and was delivered through normal labor on 39th wk of an uneventful gestation. The 1st child of the family died at the age of 18 mo after a febrile illness with prominent hepatomegaly. Two paternal sisters had also died in infancy of obscure causes.

Common laboratory tests were normal (including creatine phosphokinase, SGOT, SGPT values), while arterial blood gas analysis demonstrated a mild metabolic acidosis (pH = 7.34, serum bicarbonate = 13.8 mEq/L). The chest radiograph revealed cardiomegaly and electrocardiogram showed peaked T waves and left ventricular hypertrophy (Fig. 1). Echocardiography revealed dilated cardiomyopathy (increased dimensions of the left ventricle, low ejection fraction) and heart failure therapy was initiated.

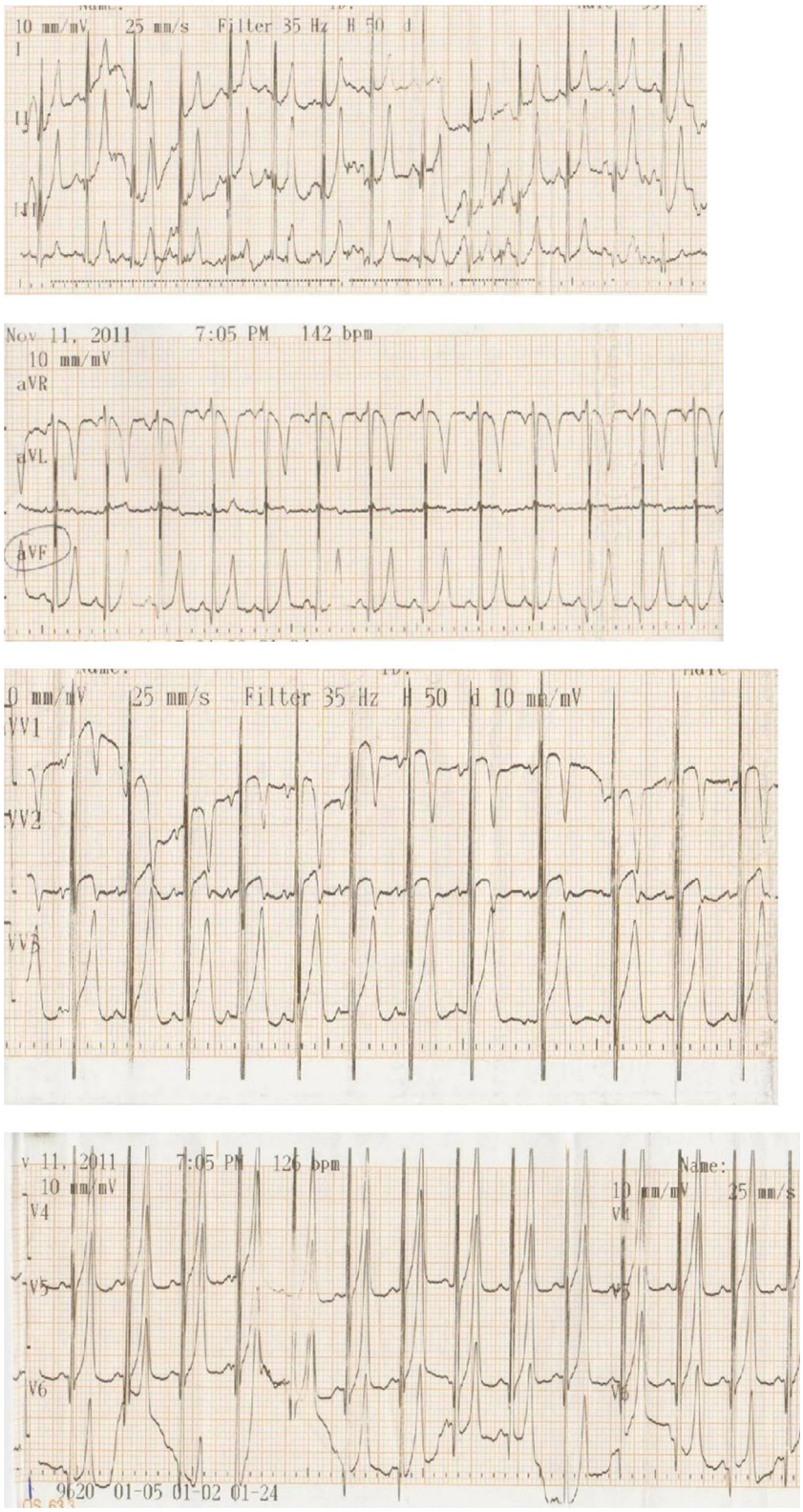

Fig. 1 A 12-lead electrocardiogram on admission revealed peaked T waves and left ventricular hypertrophy (R voltage in V6: 40 mm, upper limits for age: 24 mm, S voltage in V1: 20 mm, upper limits for age 27 mm)

In the view of metabolic acidosis along with a family history of unexplained infantile deaths, a metabolic screening was requested. Levels of free carnitine and carnitine esters in blood were low (free carnitine: 0.82 μmol/L, normal values: 5–75 μmol/L), while urinary organic acids profile demonstrated increased concentrations of branched chain amino acids, lactic acid and ketone bodies. These findings were consistent with carnitine deficiency and administration of L-carnitine

was initiated (150 mg/kg/d per os in 3 doses). Sequence analysis in *SLC22A5* gene revealed the missense mutation c.1319C > T (p.Th440Met) in homozygous state.

Ten days after L-carnitine initiation systolic function got improved, one month later electrocardiographic abnormalities disappeared and serum carnitine levels have been within normal range since then.

The girl was discharged home with digoxin, furosemide, spironolactone, carvedilol and L-carnitine. One year later heart failure therapy had been stopped, as heart function had fully recovered and the girl continued to receive lifelong treatment with L-carnitine.

Discussion

Inborn errors of metabolism account for 5 % of cardiomyopathies in pediatric age group and 15 % of those are due to known causes [3]. Primary carnitine deficiency has a broad clinical spectrum including cardiomyopathy in childhood with average age of presentation at 2–4 y [3, 4]. The incidence of dilated cardiomyopathy (DCM) seems to be higher than hypertrophic cardiomyopathy in these children, but a mild degree of ventricular hypertrophy in some patients with DCM has also been reported [3].

As family history of unexplained deaths in infancy was present in index case, an inherited metabolic disorder was highly suspected. Diagnosis was initially based on free carnitine and carnitine esters levels in plasma and was confirmed by genetic testing.

According to literature, mutation c.1319C > T(p.Th440Met) has been revealed in heterozygous state in few subjects with carnitine deficiency, in unaffected infants with abnormal newborn screening, as well as in asymptomatic mothers of these infants [5]. Moreover, previous genome sequence studies have identified certain mutations in *SLC225A* gene associated with an exclusive cardiac phenotype [5–7]. However, these cases included heterozygous or compound heterozygous mutations and the majority of them have been revealed after newborn screening. In this way, mutations assessed have not been associated with any particular symptom or clinical phenotype. The index case brings out a new correlation; of c.1319C > T mutation in homozygous state with a pure cardiac phenotype.

In conclusion, although DCM is usually "idiopathic" in childhood, definable causes can be identified. A thorough family history may be a clue to the diagnosis of a treatable metabolic error. Genetic sequencing along with an accurate phenotyping of patients can contribute to a better understanding of genotype-phenotype correlation and expressivity of the disease [7]. This can provide the opportunity for more appropriate therapeutic interventions. For instance, cardiac function in patients with carnitine transporter deficiency responds poorly to conventional therapy. However, continued treatment with oral L-carnitine supplements (as in index case) can alter the natural course of the disease [8].

On the other hand, as a diagnostic work-up based on all available tests in children with DCM may be unaffordable for some parts of the world [9], clinicians should primarily focus on investigations that can be translated into specific management strategies (*e.g.*, identification of treatable errors of metabolism).

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Contributions KP-L was involved in data collection, in the analysis of the case and supervised the writing of the manuscript. MG was involved in data collection, in the analysis of the case and in the writing of the manuscript. VD was involved in the data collection and in the writing of the manuscript. ME and AE were involved in the analysis of the case and critically reviewed the manuscript. AE will act as guarantor for the paper.

Compliance with Ethical Standards

Conflict of Interest None.

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References

1. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. Orphanet J Rare Dis. 2012;7:68.
2. Wilcken B, Wiley V, Sim KG, Carpenter K. Carnitine transporter defect diagnosed by newborn screening with electrospray tandem mass spectrometry. J Pediatr. 2001;138:581–4.
3. Fu L, Huang M, Chen S. Primary carnitine deficiency and cardiomyopathy. Korean Circ J. 2013;43:785–92.
4. El-Hattab AW, Scaglia F. Disorders of carnitine biosynthesis and transport. Mol Genet Metab. 2015;116:107–12.
5. Li F-Y, El-Hattab AW, Bawle EV, et al. Molecular spectrum of SLC22A5 (OCTN2) gene mutations detected in 143 subjects evaluated for systemic carnitine deficiency. Hum Mutat. 2010;31:1632–51.
6. Yamak A, Bitar F, Karam P, Nemer G. Exclusive cardiac dysfunction in familial primary carnitine deficiency cases: a genotype-phenotype correlation. Clin Genet. 2007;72:59–62.
7. Shibbani K, Fahed AC, Al-Shaar L, et al. Primary carnitine deficiency: novel mutations and insights into the cardiac phenotype. Clin Genet. 2014;85:127–37.
8. Wang SS, Rao J, Li YF, Zhang ZW, Zeng GH. Primary carnitine deficiency cardiomyopathy. Int J Cardiol. 2014;174:171–3.
9. Kumar RK. A practical approach for the diagnosis and management of DCM. Indian J Pediatr. 2002;69:341–50.