Patient report

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Primary systemic carnitine deficiency: a Turkish case with a novel homozygous *SLC22A5* mutation and 14 years follow-up

Abstract: Systemic primary carnitine deficiency is an autosomal recessive disorder caused by the deficiency of carnitine transporter. Main features are cardiomyopathy, myopathy and hypoglycemic encephalopathy. We report a Turkish case with a novel *SLC22A5* gene mutation presented with a pure cardiac phenotype. During the 14-year follow-up study, cardiac functions were remained within a normal range with oral L-carnitine supplementation.

Keywords: cardiomyopathy; carnitine deficiency; novel mutation.

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Introduction

Systemic primary carnitine deficiency (CDSP, OMIM #212140) is an autosomal recessive disorder of fatty acid oxidation caused by mutations in the *SLC22A5* gene, which encodes the high-affinity carnitine transporter, OCTNII, expressed in the muscle, heart, kidney, lymphoblasts, and fibroblasts (1). Carnitine has an important role in the transfer of long-chain fatty acids across the inner mitochondrial membrane. Deficiency of the OCTNII protein increases renal wasting of carnitine, resulting in low serum levels and diminished hepatic uptake of carnitine by passive diffusion (2). Once low serum carnitine levels are indicated in the diagnosis, the molecular analysis of the *SLC22A5* gene is essential (3). Early diagnosis can provide marked clinical outcomes (4).

Here, we report a 17-year-old boy who first presented at 3 years of age with dilated cardiomyopathy. The diagnosis of CDSP is confirmed with the detection of a novel mutation in the *SLC22A5* gene. During the 14-year follow-up study, significant improvements in the cardiac functions due to oral carnitine supplementation were observed.

Case report

A 17-year-old boy presented at 3 years of age with an acute episode of lethargy, somnolance, vomiting, feeding disturbances, and moderate respiratory insufficiency following an upper airway infection. He was the first child of a Turkish-origin consanguineous couple. He had normal birth history and normal physical and mental development. The family history was unremarkable.

Physical examination showed clear breathing sounds, and there was no heart murmur. The liver was palpable 4–5 cm below the right costal margin. Full neurological examination, including the muscle strength and reflexes, were totally normal. There were no episodes of hypoketotic hypoglycemia. Acute metabolic decompensation was not observed.

The main manifestations were cardiac insufficiencies. Chest radiography revealed cardiomegaly with cardio-thoracic ratio of 64%. Electrocardiography showed left ventricular hypertrophy. Echocardiogram showed a markedly dilated left ventricle with reduced systolic function (fractional shortening, FS: 25%, reference range 29%–37%) with myocardial thickening and thickening of the trabecular and mitral valve papillary muscles and mild mitral regurgitation.

Laboratory results showed normal levels of serum aspartate aminotransferase, 33 U/L; alanine aminotransferase, 30 U/L and creatine kinase (CK), 62 U/L. Viral

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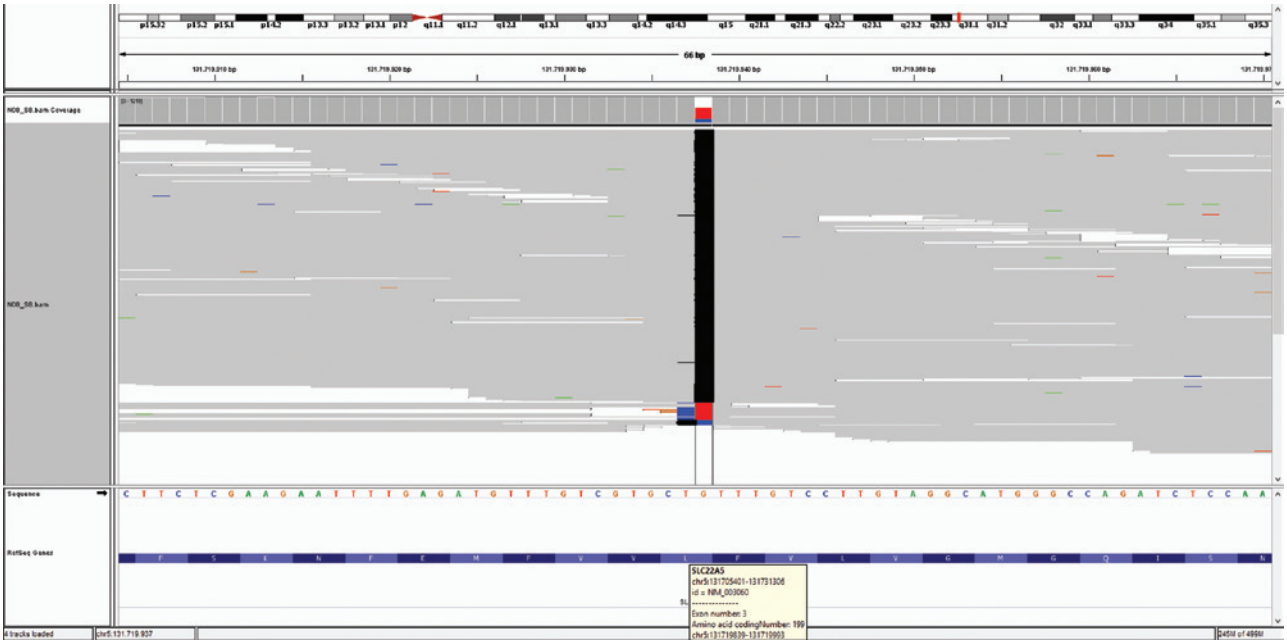

Figure 1: Direct sequencing of the *SLC22A5* gene in the patient revealed homozygous mutations: p.F200Lfs*4(c.597_597delG).

serology, blood lactate, plasma amino acids, and urine organic acids were all normal. In acylcarnitine analysis, plasma free and total carnitine levels were <0.01 mg/dL (reference ranges were 0.45–0.95 and 0.40–0.85, respectively). Low free carnitine (C0, the marker of primary carnitine deficiency), C2 acetylcarnitine, C3 propionylcarnitine, and C16 palmitoylcarnitine levels were detected in a dried blood spot of the newborn screening test.

These results were diagnostic for primary systemic carnitine deficiency. Genetic analysis for the *SLC22A5* gene was performed by next generation sequencing (Miseq-Illumina, San Diego, CA, USA). Sequence analyses of all coding regions and exon-intron boundaries were done and a homozygote novel mutation p.F200Lfs*4 (c.597_597delG) was determined (Figure 1). In silico evaluation with Mutation Taster predicted this variant as a disease causing mutation. As this was a frameshift mutation that caused an early stop codon, it was most probably a damaging variation. Parents were heterozygotes for the same mutation. Screening of 200 healthy persons for this variant was done and no one had this mutation.

After confirmation of the diagnosis, he was placed on treatment with L-carnitine supplements (50–100 mg/kg/day, p.o.) plus digoxin, diuretics, and vasodilators. Carnitine treatment was interrupted several times because of the high cost of this treatment.

In this 14-year follow-up study, echocardiography was performed every 3–6 months. Carnitine levels could not be measured regularly since the previous year because of technical limitations. Nevertheless, the treatment resulted in significant improvement in the cardiac functions (Table 1). On May 2008, while the patient was not under treatment, left ventricular ejection fraction was significantly reduced after an episode of severe gastroenteritis. Carnitine supplementation was restarted with a dose of 100 mg/kg/day and rapid improvement in the cardiac functions were seen.

Serum free and total carnitine monitarisation could have been done since 2013, and a slight increase has been provided both in free and total carnitine levels. Urinary carnitine measurement could not be performed in our laboratory, but it is expected to be increased with treatment.

Discussion

Primary systemic carnitine deficiency is a lethal autosomal recessive condition caused by defects in the OCTNII carnitine transporter. Cardiac insufficiency and dilated cardiomyopathy might be the presenting sign either in early or late childhood. The key to the diagnosis is the measurement of plasma carnitine levels. If possible, increased urinary carnitine excretion should be identified. The confirmation of the diagnosis should be done with the mutation analysis of the *SLC22A5* gene.

High doses of oral carnitine supplementation (100–400 mg/kg/day) could provide significant improvement in the cardiac functions and serve as a life-saving treatment

Table 1: Echocardiographic findings of the follow-up.

Date	LVEF, %	LVED, mm	LVES, mm	IVSd, mm	LVPWd, mm	EFS, %	OCD, mg/kg/day
10.10.2000	50	49	36			25	N/U
14.11.2001	68	36	25	5	6	31	N/U
23.10.2002	64	43	28	6.5	7	34	N/U
20.09.2004	71	50	29	6.6	6.6	41	50
29.05.2006	61	46	31	9		33	50
28.03.2007	61	53	35	9		33	50
27.05.2008	25	68	60	8		12	N/U
01.09.2008	60	50	34	9	11	32	77
16.06.2009	58	54	37	9	9	31	66
14.09.2010	67	51	30	10	9.6	37	62
06.09.2011	63	54	35	9.6	10	35	52
15.05.2012	70	50	48	11	10	40	48
20.08.2013	62	59	39	10	10	34	75
23.06.2014	72	63	36	9.5	10	42	69

LVEF, left ventricular ejection fraction; LVED, left ventricle end-diastolic diameter; LVES, left ventricle end-systolic diameter; IVSd, interventricular septum diameter; LVPWd, left ventricular posterior wall diameter; EFS, endocardial fractional shortening; OCD, oral carnitine dose; N/U, not used.

in the process. Here we would like to emphasize the importance of continous carnitine supplementation. After the initial acute improvement in the cardiac functions, the echocardiographic parameters were all within normal range in this follow-up, apart from the period without carnitine supplementation. Fasting, infections and other metabolic stress conditions may rapidly cause worsening of the symptoms. Acute episode of gastroenteritis caused severe deterioration of the cardiac functions without carnitine supplementation. Significant recovery was observed with the readminstration of the carnitine treatment.

A large number of heterogeneous mutations have been reported in the *SLC22A5* gene. In the literature, no correlation between the types of mutation and cardiomyopathy and no genotype-phenotype relationship was found (5). A new homozygous frameshift mutation of p.F200Lfs*4(c.597_597delG) was identified in this patient. This mutation caused only cardiac phenotype, and neither CK elevation nor clinical myopathy were developed.

Although carnitine supplementation leads to an increase in the serum carnitine levels, free carnitine levels may not reach the normal range. Increased urinary carnitine levels in the primary systemic carnitine deficiency increases further with the oral carnitine supplementation (6). Even though we could not detect the urinary carnitine levels, mild increase in the serum carnitine levels were observed with oral carnitine supplementation.

In conclusion, primary systemic carnitine deficiency is a treatable disorder of fatty acid oxidation. In case of early diagnosis and early initiation of the treatment, favorable outcomes could be achieved.

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