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Successful orthotopic heart transplantation in CPTII deficiency

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Abstract

Carnitine palmitoyl transferase II (CPT II) catalyzes the release of activated long-chain fatty acids from acylcarnitines into mitochondria for subsequent fatty acid oxidation. Depending on residual enzyme activity, deficiency of this enzyme leads to a spectrum of symptoms from early onset hypoglycemia, hyperammonemia, cardiomyopathy and death to onset of recurrent rhabdomyolysis in adolescents and young adults. We present a case of successful orthotopic heart transplantation in a patient with severe infantile onset cardiomyopathy due to CPT II deficiency identified through newborn screening. Excellent cardiac function is preserved 12 years post-transplantation; however, the patient has developed intermittent episodes of hyperammonemia and rhabdomyolysis later in childhood and early adolescence readily resolved with intravenous glucose. Successful heart transplant in this patient demonstrates the feasibility of this management option in patients with even severe forms of long chain fatty acid oxidation disorders.

Keywords

Carnitine palmitoyl transferase deficiency; CPT2 deficiency; Fatty acid oxidation disorder; Cardiomyopathy; Heart transplantation

1. Introduction

Carnitine palmitoyl-transferase II (CPT II) deficiency (OMIM 600650) is an autosomal recessive inborn error of metabolism due to mutations in the *CPT2* gene with variable presentation [1,2]. CPT II is part of the carnitine cycle responsible for importing long chain substrates from the cytoplasm into mitochondria for fatty acid oxidation [3]. It catalyzes the release of a long-chain acyl-CoA from carnitine, releasing the activated acyl-CoAs into the mitochondria with exchange of the carnitine moiety back to the cytoplasm. Deficiency of this enzyme leads to accumulation of long-chain acylcarnitines in blood, free carnitine depletion, and impaired fatty acid oxidation [4]. Patients can present in the neonatal period with fatal energy deficiency (neonatal lethal form); in infancy with cardiomyopathy, hyperammonemia, and/or hypoketotic hypoglycemia (hepatocardiomuscular form); or later in childhood or adulthood with recurrent rhabdomyolysis and exercise intolerance (milder

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Declaration of Competing Interest

None.

muscular form) [1,2,4]; The pathophysiology of the heart failure is of uncertain etiology, but may relate to the heart's dependency on fatty acid oxidation for up to 80% of energy. While there is clinical variability depending on the specific enzyme defect, if cardiomyopathy develops it can be either dilated or hypertrophic [5]. We report a case of successful orthotopic heart transplantation in a girl with severe infantile onset dilated cardiomyopathy secondary to CPT II deficiency.

2. Case report

The patient was born at 36 weeks gestation, after a pregnancy complicated by intrauterine demise of a twin. Family history was unremarkable. She was admitted for 3 days after birth for respiratory distress, with a glucose nadir 62. Newborn screen identified elevated C16 carnitine level in a dried blood spot (28.07 μmol/L; normal < 0.9), and the diagnosis was confirmed by DNA analysis, which showed a c.533/534 T insertion and a c.534–558 (25BP) deletion [p.L178F with N179-I186del) on one *CPT2* allele and c.425G>A [p.R151Q] on the other allele. Fibroblast enzyme activity was assayed in a CLIA certified laboratory at the Children's Hospital of Philadelphia, using the method of Bennett et al. [6], noting activity of 0.03 nmol palmitate/min/mg protein (normal 0.4–1.85). A western blot of extract from patient derived fibroblasts showed no identifiable CPT II protein (Fig. 1). She was initially prescribed a diet of Pregestamil, ProViMin and Polycose consisting of 22% of calories from fat, with 10% of calories coming from LCT, plus essential fatty acid and carnitine supplements.

In the first seven months of life she had multiple hospital admissions for intercurrent illnesses at other institutions. At age 7 months she presented with increased work of breathing, irritability, and decreased appetite. She was subsequently found to have new dilated cardiomyopathy (DCM), with dilated left ventricle (internal dimension 4.3 cm, z-score 7.7), ejection fraction (EF) of 30% (Fig. 2), and an elevated BNP of 1761 pg/mL (normal < 100 pg/mL). She also had carnitine deficiency (free carnitine 2 μmol/L, normal range 27–49), hypoglycemia 36 mg/dL (normal 70–99), hyperammonemia (159 μmol/L, normal < 12–38) and pancreatitis (lipase 311 IU/L, normal <200) with normal CK (185 IU/L, normal 20–170) (Table 1). During a lengthy hospitalization, gastrostomy tube was placed, night feedings were initiated, and she was ultimately discharged on bumetanide, captopril, digoxin. With medical management, her LV dilation improved to 3.4 cm (z-score 3.7) and ejection fraction of 39% (normal 55–75%) and fractional shortening of 20% (normal 28–45%). At age 10 months, she presented with an *E. coli* urinary tract infection and developed acute on chronic decompensated heart failure that was recognized clinically based on persistent tachycardia. Echocardiogram showed LV dilation at 4.6 cm (z-score 10.3), and fractional shortening of 7%. She also had pancreatitis (lipase 246 IU/L), mild hyperammonemia (51 μmol/L) hypoglycemia (57 mg/dL), and elevated CK (2190 IU/L) (Table 1).

At age 12 months she developed a blocked gastrostomy tube and presented with glucose of 17 mg/dL. Examination at this time noted normal skeletal strength and tone, with normal motor development but mild language delays. Over the next year she remained clinically stable from a cardiovascular perspective with a prescribed diet containing 30% of calories

from fat (75% of fat from MCT) and carnitine 20 mg/kg/d, largely by gastrostomy due to oral aversion.

At age 24 months she presented with fever and lethargy, due to presumed septic shock. She required intubation for ARDS and ionotropic support for hypotension. Labs revealed ammonia 56 μmol/L, CK 405 IU/L, and normal lipase and glucose (Table 1). Following that admission she was discharged on 24-h continuous enteral feedings. Triheptanoin therapy was initiated in a research trial at 25 months of age with reported improvement in stamina and decreased hepatomegaly, but persistent cardiomyopathy [7,8]. At age 27 months she developed a respiratory syncytial virus infection (peak ammonia 60 μmol/L, peak CK 1208 IU/L) which led to a prolonged hospital admission requiring continuous intravenous inotropic support. Due to her inability to be weaned from inotropes in the setting of severely depressed cardiac function she underwent an orthotopic heart transplantation at age 30 months. Following transplantation her treatment included triheptanoin at 1.5–2 g/kg, long chain fat restriction to 20% of calories, carnitine (20 mg/kg/d), and immunosuppression with tacrolimus and sirolimus.

These same medical treatments were prescribed over the ensuing years through her current age of 14 years. During this time, she has had excellent cardiac function despite occasional admissions for vomiting and diarrhea with asymptomatic hyperammonemia (35–157 μmol/L) and normal CK and glucose levels. Plasma glutamine was within normal limits during all hyperammonemic episodes, and all episodes responded rapidly to intravenous glucose. At age 10 years she presented with symptomatic hyperammonemia (312 μmol/L) and elevated CK (9910 IU/L), requiring hemodialysis (Table 1). On this admission she developed a focus of increased T2 signal in the left thalamus that is stable on latest follow-up. Over the next 4 years she has had a flurry of brief admissions for vomiting and diarrhea with asymptomatic hyperammonemia resolving rapidly with glucose, and psychological concerns have become apparent (Table 1). A few of the admissions had significant hyperammonemia with some alteration in mental status and elevated CK, but all resolved quickly with intravenous glucose without dialysis or use of ammonia scavengers (Table 1). Now age 14 years, she has normal cognition and does not report exercise intolerance, although she is not particularly active. She is non-adherent with triheptanoin, dietary or carnitine therapy and has had psychological concerns including attempting to lose weight for social reasons even though her BMI is 22 (75%ile). Baseline plasma ammonia remains mildly elevated (31–99 μmol/L), and plasma C16 levels range from 3.4–8.3 μmol/L (normal < 0.52). From a cardiovascular perspective she has done well with normal graft function, normal hemodynamics, no evident coronary allograft vasculopathy, and no arrhythmias at 12 years after transplantation.

3. Discussion

Successful cardiac transplantation has been previously described in a case of mitochondrial trifunctional protein deficiency [9]. To our knowledge, this is the first reported case of cardiac transplantation in a CPT II deficient patient. First, cardiac function remains excellent in this patient 12 years post transplantation, demonstrating that the localized energy production in the transplanted heart can provide sufficient energy to sustain cardiac

function. Second, systemic toxicity of long-chain acylcarnitines is cited as a possible reason for the development of cardiac arrhythmias in patients with long chain fatty acid oxidation defects [10,11]. This patient has not developed cardiac arrhythmias, in spite of extremely elevated long-chain acylcarnitine levels, suggesting lack of a direct cardiotoxic effect.

Not surprisingly, enzyme activity in the transplanted heart has not been sufficient to restore bioenergetic homeostasis to the rest of the body. Hypoglycemia and hyperammonemia with normal glutamine are common in patients with long-chain fatty acid deficiencies, thought to be due to depletion of key TCA cycle intermediates and coenzyme A. The anaplerotic medication triheptanoin has been shown to reduce episodes of hypoglycemia, and reverse hyperammonemia, especially in patients with carnitine-acylcarnitine translocase deficiency, the step immediately preceding CPT II in the carnitine cycle [12]. Unfortunately, the patient became non-adherent with triheptanoin therapy as an adolescent, and developed episodes of hyperammonemia and/or rhabdomyolysis typical of those episodes in most patients with long-chain fatty acid oxidation disorders as they reach adolescence and young adulthood.

The potential role of local inflammation merits consideration relative to symptoms in this patient post-transplant. We have recently published evidence for an atypical inflammatory response in patients with VLCAD deficiency, regardless of clinical status or treatment with triheptanoin [13]. Indeed, the response is exaggerated in patients when in metabolic crisis. The etiology of this phenomenon is unknown, though accumulation of abnormal long-chain complex lipids from excess fatty acid oxidation intermediates has been proposed. The role of such inflammation in the development of cardiomyopathy long-chain fatty acid oxidation defects is unexplored, though the long-term viability of the transplanted heart in this patient suggests that it may not be an issue. Of note, in human patients with diabetes, cardiomyopathy is associated with increased lipid oxidation, intramyocardial triglyceride accumulation, and reduced glucose utilization, and also a local rise in cytokines in cardiac cells and the activation of the proinflammatory transcription factor nuclear factor (NF)-κB, among other inflammatory and metabolic changes [14]. Thus, additional studies on this phenomenon are necessary to resolve its effect on cardiac function in CPT II deficiency, as well as all other long-chain fatty acid oxidation disorders.

4. Conclusion

Cardiac transplantation is a viable option for patients with CPTII deficiency and refractory cardiomyopathy, with preservation of normal cardiac function and no arrhythmias for more than a decade after transplant, despite poor adherence with metabolic therapy over the last several years.

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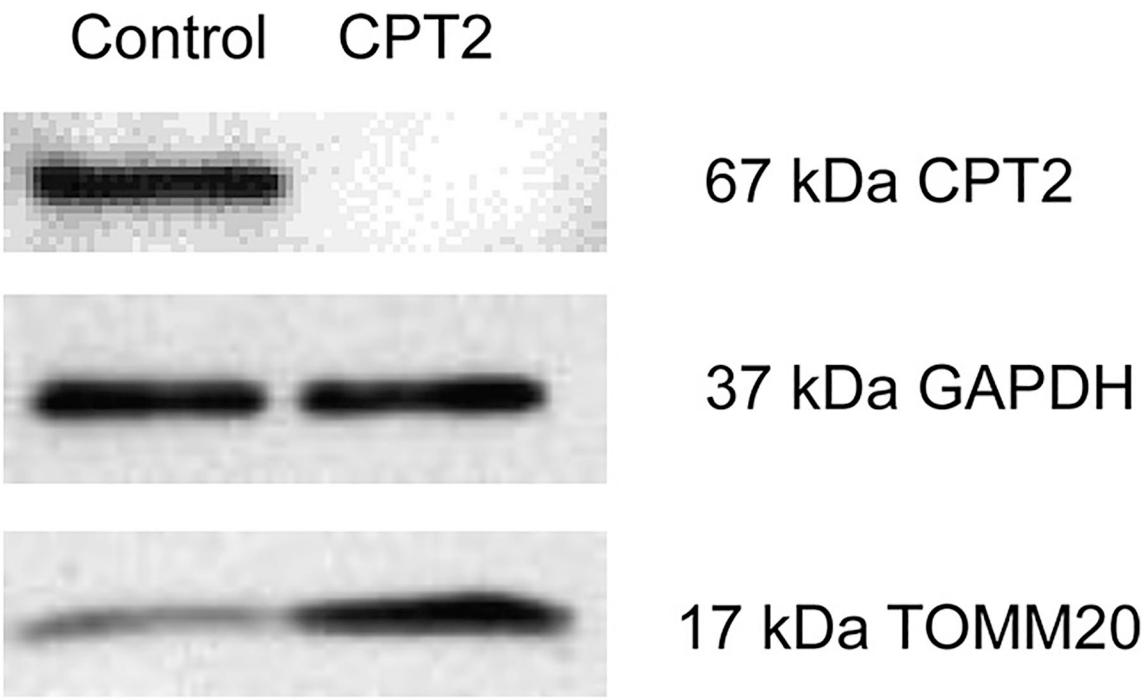

Fig. 1.

Western blot of control and patient fibroblast extracts. 25 μg of protein was loaded into each well of a 4–15% SDS-PAGE gel, and transferred to a nitrocellulose membrane after electrophoresis. Antibodies used for blotting were CPT2 (1:1000, Abcam), GAPDH (1:25,000, Abcam), and TOMM20 (1:5000, Abcam).

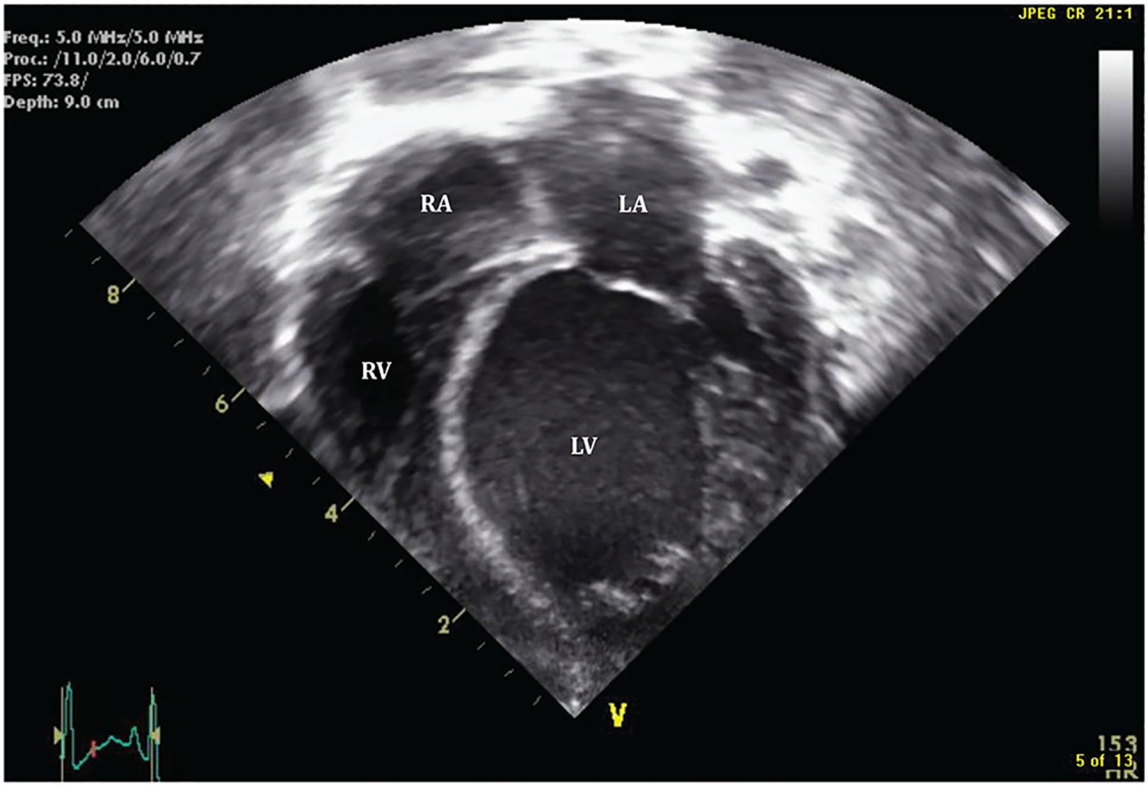

Fig. 2.

Transthoracic echocardiograph, apical 4 chamber view demonstrating a dilated left ventricle. At 7 months old the patient presented with increased work of breathing, irritability, and decreased appetite. On this initial echocardiographic evaluation she was found to have a severely dilated left ventricle and severely depressed systolic wall motion. RA, right atrium, RV, right ventricle, LA, left atrium, LV left ventricle.

Table 1

Clinically significant hospital admissions.

Age	Length of admission (days)	EF (50–70%)	Glucose nadir (70–99 mg/dL)	Peak NH3 (12–38 μmol/L)	Peak CK (20–170 IU/L)	C16 (<0.52 nmol/mL)	Free Carnitine Nadir (24–63 μmol/L)	Peak Amylase/Lipase (<90/<200 IU/L)
7 mos	28	30%	36	159	185	-	2	−/311
10 mos	22	36%	57	51	2190	-	3	−/246
24 mos	5	30%	44	56	405	15.84	-	33/−
26 mos	19	29%	66	9	403	-	22	130/37
28 mos	88	22%	68	60	1208	-	-	285/493
30 mos	*a*	31% (on inotropes)	148	24	54	-	-	70/54
10 yr	9	60%	103	312 (required dialysis)	9910	2.1	10	−/32
10 yr	2	-	88	90	1024	-	33	−/28
10 yr	3	60%	116	374	193	-	-	-
13 yrs	1	62%	61	213	103	3.49	5	50/55
13 yrs	6	-	89	285	8137	5.99	-	58/68
14 yrs	3	61%	75	144	77	4.14	-	-
14 yrs	5	60%	86	207	478	8.13	6	43/44

[a]At transplant (during 88 day admission).

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