Pediatr Cardiol 16:76–78, 1995

Pediatric Cardiology

Reversible Cardiomyopathy Due to Carnitine Deficiency from Renal Tubular Wasting

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Abstract. The clinical course of a 4-month-old male infant with a dilated cardiomyopathy secondary to renal tubular losses of carnitine is outlined. He was admitted to the hospital with severe congestive heart failure. An echocardiogram demonstrated normal anatomy. The left ventricular shortening fraction measured 10%. A comprehensive cardiomyopathy evaluation was initiated.

The total plasma carnitine level was only 25 μmol/ml, but the urine carnitine measured 434 nm/mg of creatinine. He was begun on oral L-carnitine and weaned from mechanical ventilation and inotropic support 10 days later. Two years later he remains asymptomatic with normal left ventricular function.

Key words: Carnitine deficiency—Cardiomyopathy—Renal wasting

L-Carnitine is an essential cofactor responsible for the transfer of long-chain fatty acids across the mitochondrial membrane to undergo β-oxidation. The proper functioning of this mechanism is important because free fatty acids make up 60% of the myocardial energy substrate. Since the initial report by Tripp in 1981 [4] describing a family with carnitine deficiency that presented as endocardial fibroelastosis, there have been several reports linking carnitine deficiency to cardiomyopathy [1–6]. Our report describes the clinical course of a 4-month-old infant who manifested a severe dilated cardiomyopathy secondary to apparent renal tubular losses of carnitine.

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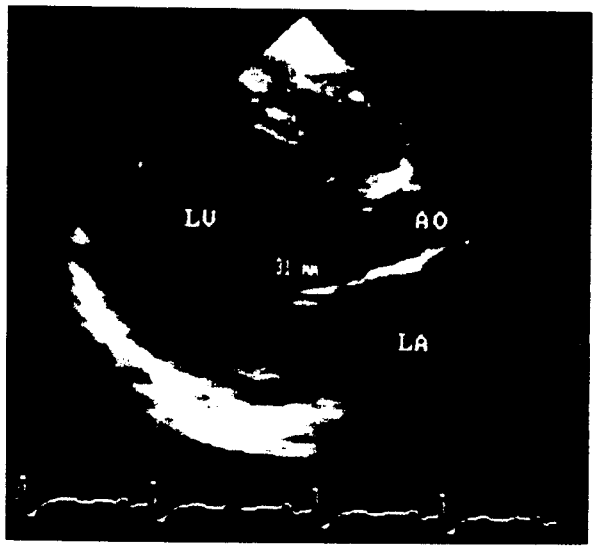

Fig. 1. Parasternal long-axis two-dimensional echocardiographic view demonstrating a dilated left ventricle (*LV*). The left ventricular end-diastolic dimension measured 31 mm at presentation. AO, aorta; LA, left atrium.

Case Report

The patient was born at 28 weeks' gestation (age-adjusted 4-week-old) after placental abruption. Apgar scores were 6 and 7. He had mild hyaline membrane disease and received surfactant. He did remarkably well and required no further supplemental oxygen after day 5 of life. He was fed enterally with Special Care Enfamil. His neonatal course was uncomplicated, and he was discharged from the newborn nursery in good condition at 1 month of age. He grew and developed normally over the next 3 months and was completely asymptomatic.

Five days before admission to the hospital, he developed tachypnea and fatigue with feedings. There was no history of fever, vomiting, or diarrhea. The family history was negative. He developed respiratory distress and severe congestive heart failure and was admitted to the intensive care unit. Physical exam-

Table 1. Patient carnitine assays

Time of assay	Plasma (μmol/ml)				Urine (nm/mg CR/24 h)		
	Total	Free	LCAC	SCAC	Total	Free	Acyl-C
Before therapy	25	28	6	1	434	48	386
Two weeks	94	65	25	4	19,000	14,000	5,000
Four weeks	99	69	26	4	10,465	9,270	1,195
Twelve weeks	123	105	15	4	8,118	5,824	2,294
Normal	46 ± 10	37 ± 8	6 ± 4	4 ± 2	125 ± 75	51 ± 40	44 ± 40

Acyl-C, acylcarnitine; LCAC, long-chain acylcarnitine; SCAC, short-chain acylcarnitine; CR, creatinine.

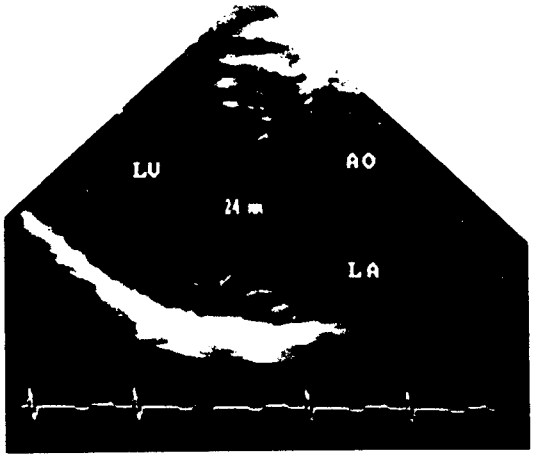

Fig. 2. Parasternal long-axis two-dimensional echocardiographic view demonstrating a decrease in the left ventricular end-systolic dimension to 24 mm 10 days after institution of carnitine therapy. LV, left ventricle; AO, aorta; LA, left atrium.

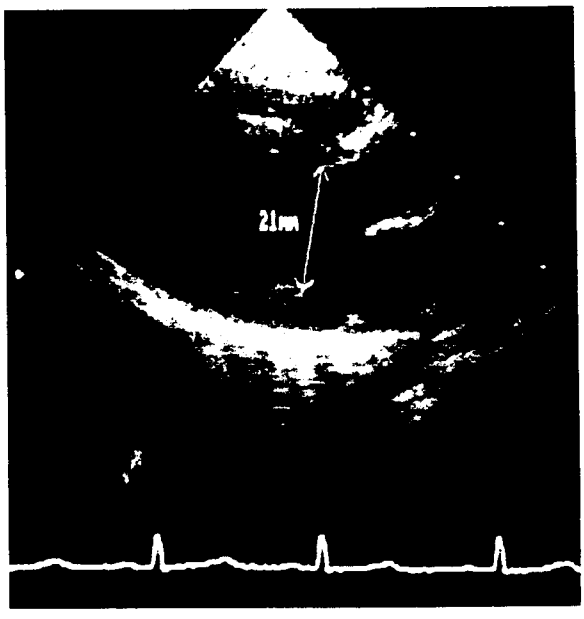

Fig. 3. Parasternal long-axis two-dimensional echocardiographic view demonstrating normal left ventricular dimensions 6 months after presentation.

ination revealed basilar rales, a loud gallop, a murmur of mitral regurgitation, and hepatomegaly. The neuromuscular examination was normal. A chest radiograph demonstrated moderate cardiomegaly and pulmonary edema. An electrocardiogram (ECG) showed left ventricular hypertrophy with strain pattern. No Q waves were noted in leads I or AVL. An echocardiogram demonstrated normal intracardiac anatomy, with no evidence of aortic stenosis or coarctation. The coronary artery anatomy was normal. The left ventricular end-systolic dimension measured 31 mm (>210% of predicted normal). The left ventricular shortening fraction measured 10% in the presence of severe mitral regurgitation (Fig. 1). The patient was mechanically ventilated, and dobutamine was begun.

A cardiomyopathy workup was initiated. Viral cultures and titers for enterovirus were negative. The thyroid hormone was normal. The creatine phosphokinase (CPK) and aldolase enzymes were normal. Three days after admission, the patient developed episodes of pallor and bradycardia, and amrinone was administered.

Cardiac catheterization revealed a cardiac index of 2.5 L/min/m^2. The pulmonary artery pressure measured 31/10 mmHg with a mean of 16 mmHg. The mean wedge pressure measured 10 mmHg, and the left ventricular end-diastolic volume measured 125%. The end-systolic volume measured 180% of normal, yielding an ejection fraction of 63% of predicted. The left coronary artery was clearly demonstrated to arise from the ascending aorta in the usual position. Because of the patient's size and poor left ventricular function, an endomyocardial biopsy was not performed.

On the eighth hospital day, the plasma and urine carnitine results became available from the Duke University Medical Center. The total plasma carnitine level measured 25 μmol/L (normal 46 ± 10 μmol/L), and the urine total carnitine measured 434 nm/mg of creatinine (normal mean 125 ± 75 nm/mg) (Table 1). No organic aciduria (Duke/CMH labs) or renal Fanconi defect was identified. The mother's carnitine levels were normal. The patient was begun on oral L-carnitine, with a loading dose of 200 mg/kg/day divided every 6 hours for 2 days, followed by 100 mg/kg/day divided every 6 hours. Ten days after replacement carnitine therapy, the left ventricular end-systolic dimension measured 24 mm in diameter, and the left ventricular shortening fraction was 14% (Fig. 2). The patient was weaned from mechan-

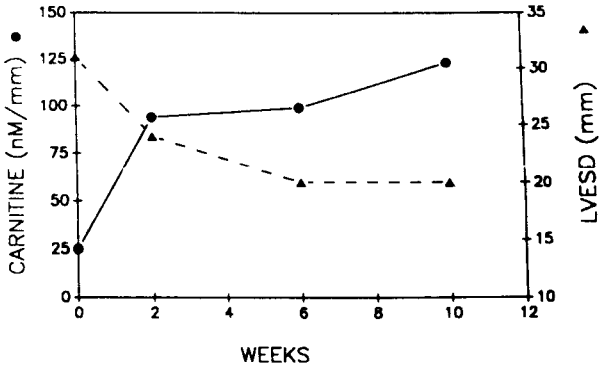

Fig. 4. Decrease in the left ventricular end-systolic dimension (LVESD) in response to carnitine administration.

ical ventilation and to oral decongestive therapy with digoxin, furosemide, and captopril 10 days after the institution of carnitine.

Two years after the onset of congestive heart failure the patient remains asymptomatic, with clinical, ECG, and echocardiographic evidence of normal left ventricular function (Fig. 3). The improvement in left ventricular systolic function following carnitine administration is demonstrated in Figure 4. The plasma carnitine level remains ≥50 μmol/ml while the patient is receiving supplemental carnitine.

Discussion

Carnitine is an essential cofactor responsible for the metabolism of fatty acids, the dominant energy substrate of the heart. Carnitine is synthesized from lysine and methionine in the liver and kidney and is present in the diet. It is not metabolized but is excreted by the kidneys. Primary carnitine deficiency exists as systemic and myopathic forms. Patients with the systemic form are characterized by having low plasma levels of carnitine and typically present with acute encephalopathy, hepatic dysfunction, or heart failure early during the first year of life. The myopathic form is characterized by a variable degree of muscle weakness but normal plasma carnitine levels. Secondary carnitine deficiency has been reported [6]. Secondary carnitine deficiency may be related to a variety of defects including genetic defects of intermediary metabolism, especially those associated with an organic aciduria. Additionally, carnitine deficiency has been demonstrated in patients with chronic renal or liver failure and in neonates receiving chronic total parenteral nutrition. Our patient demonstrated a cardiomyopathy secondary to the renal tubular loss of carnitine. Carnitine deficiency resulting from renal tubular loss has been previously reported by Engel et al., but none of their patients had a cardiomyopathy [1]. There was no evidence of hypoglycemia or encephalopathy seen with organic acidurias of medium chain acyl-CoA-dehydrogenase deficiency [5].

The response of the myocardium to oral L-carnitine treatment in this patient was dramatic. As shown in Table 1, the total plasma carnitine level rose fourfold while on therapy. This patient demonstrates the importance of evaluating carnitine deficiency, one of the few treatable etiologies, in all patients with cardiomyopathy. The evaluation should include careful measurement of both plasma and urine carnitine levels. Additionally, skeletal muscle biopsy and endomyocardial biopsy should be considered for histologic confirmation of the characteristic lipid vacuolation [6].

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