Familial carnitine transporter defect: A treatable cause of cardiomyopathy in children

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Carnitine transporter defect is characterized by severely reduced transport of carnitine into skeletal muscle, fibroblasts, and renal tubules. All children with dilated cardiomyopathy or hypoglycemia and coma should be evaluated for this transporter defect because it is readily amenable to therapy that results in prolonged prevention of cardiac failure. This article details the cases of 3 children who have carnitine transporter defect, 2 of whom had severe dilated cardiomyopathy. Plasma and skeletal muscle carnitine levels were extremely low and both children were treated with oral L-carnitine, resulting in resolution of severe cardiomyopathy and prevention of recurrence or cardiac enlargement for more than 5 years. The third child had hypoglycemia and coma as presenting findings of the transporter defect and had mild left ventricular hypertrophy but no cardiac failure. The prognosis for long-term survival in pediatric dilated cardiomyopathy is poor. Children with carnitine transporter defect can have a different outcome if their underlying condition is detected early and treated medically.
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Dilated cardiomyopathy is a significant cause of death and morbidity in children and was responsible for 43,000 hospitalizations in 1990 alone. It has been estimated that the 2-year survival rate after diagnosis is only 50% to 60% despite the use of traditional therapies.[1] The causes of many cases of pediatric cardiomyopathy remain uncertain, but recent studies have suggested that a portion of these cases may be accompanied by carnitine deficiency or insufficiency.[2]

Carnitine is a small quaternary ammonium compound that facilitates the transport of long-chain fatty acids into mitochondria where β-oxidation occurs.[3] Deficiency of carnitine can result in variable clinical presentations, including metabolic encephalopathy, hypoglycemia, muscle weakness, and dilated cardiomyopathy with congestive heart failure. Primary deficiency of carnitine is caused by an inherited membrane transporter defect of carnitine, which causes impaired carnitine transport across membranes into tissues, resulting in low muscle carnitine levels.[4-7] Additionally, there is loss of carnitine in the urine because of impairment of the normal process of renal tubular reabsorption of carnitine. The renal carnitine loss leads to very low plasma carnitine levels. This membrane transporter defect is associated with progressive myocardial dysfunction, manifesting over time as dilated cardiomyopathy.

This article describes 3 children with carnitine transporter defect, 2 of whom had severe dilated cardiomyopathy. The 2 with cardiomyopathy are siblings and have been reported in brief describing the biochemical properties of their disease.[7,8] Oral L-carnitine supplementation resulted in a rapid increase in plasma carnitine levels, normalization of their cardiac function, and resolution of severe cardiomegaly in both children. Additionally, cardiac examination and function had been normal for more than 5 years with L-carnitine supplementation. The third child described in this report had hypoglycemia and coma with mild left ventricular hypertrophy and no overt heart failure.

Patient reports

Patient 1

A 6-and-a-half-year-old boy, who had a history of asthma, was admitted to the hospital for evaluation of cardiomegaly and congestive heart failure. Two years previously, a chest radiograph revealed that his heart size was at the upper limits of normal (Figure 1, *A*). During the 6 weeks before admission, he had increasing fatigue and dyspnea. A chest radiograph showed severe cardiomegaly (Figure 1, *B*). There was no family history of cardiac disease or sudden death, and the parents were not consanguineous. The mother is German and the father is of northern European descent.

On examination, patient 1 had tachypnea and tachycardia with weak pulses in all extremities. Blood pressure was 80/60 mm Hg. The heart sounds were distant, and a grade 2/6 systolic murmur of mitral regurgitation

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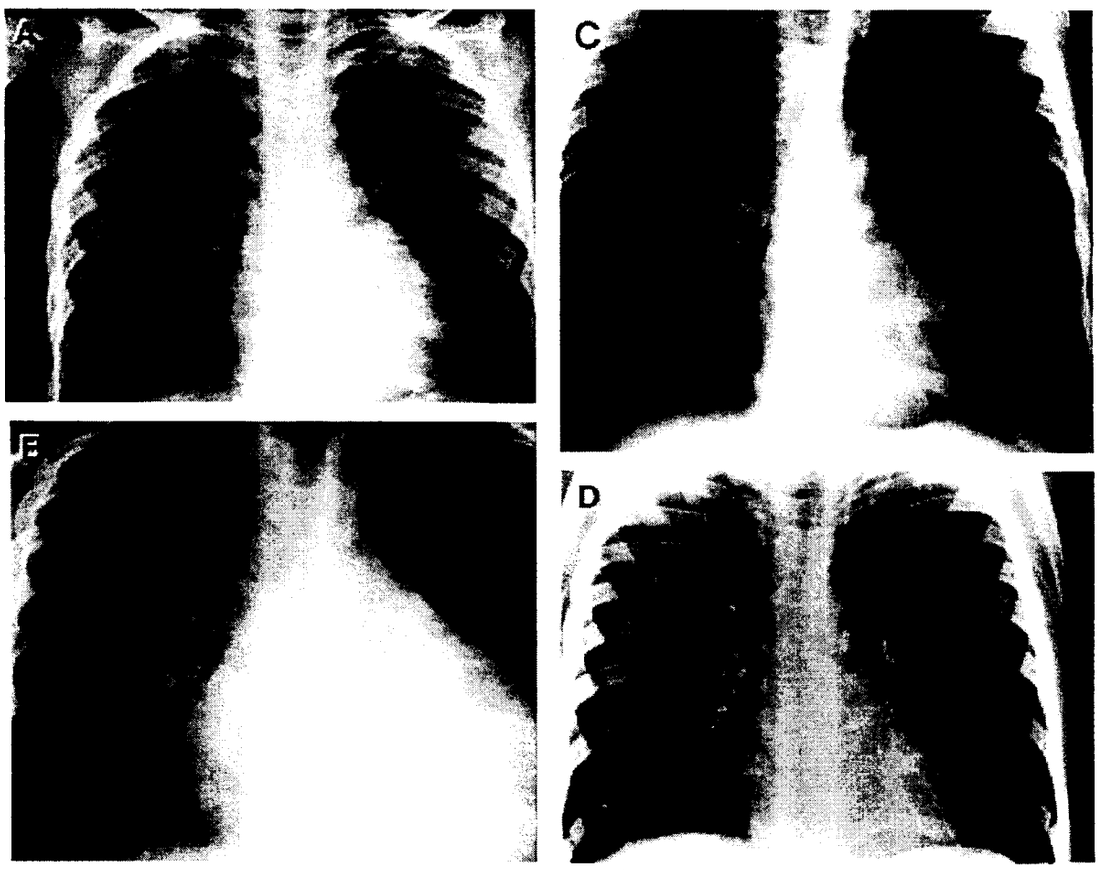
Figure 1



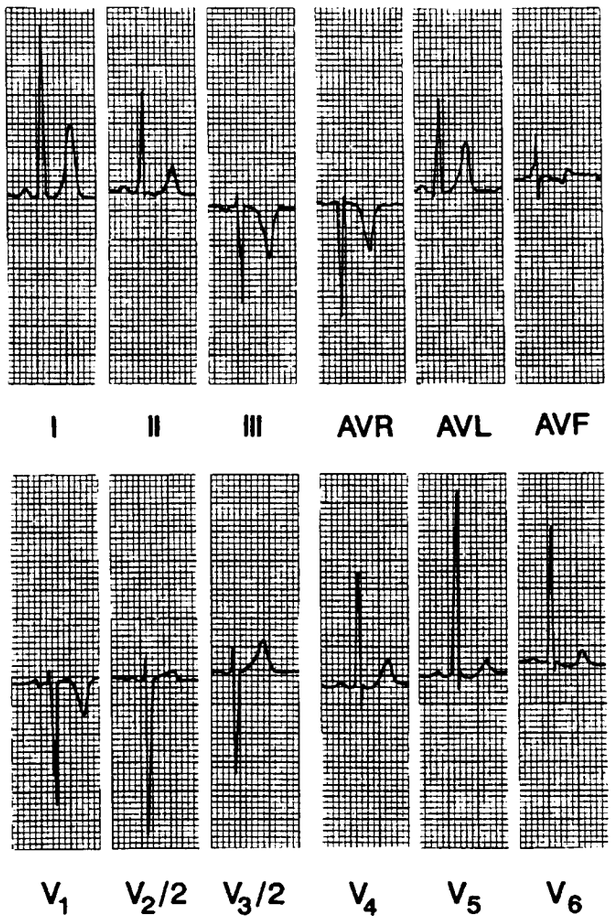
Chest radiographs of patient 1 at 4 years **(A)**, 6.5 years **(B)**, 8.5 years **(C)**, and 10.5 years **(D)**.

was present at the cardiac apex. The liver was palpable 5 cm below the right costal margin and there was mild proximal muscle weakness. An electrocardiogram revealed left ventricular hypertrophy with peaked T waves in the left precordial leads. Echocardiographic findings reflected a dilated cardiomyopathy with cardiac hypokinesis and severely reduced left ventricular ejection fraction (LVEF). Therapy with digoxin, furosemide, nitroprusside, captopril, dopamine, and dobutamine was initiated. Cardiac catheterization and angiography revealed marked dilation of the left ventricle with poor contractility and mild mitral regurgitation. An endomyocardial biopsy was obtained. There was continued deterioration of the patient's cardiac status over the next 3 weeks despite aggressive medical therapy. The patient was being considered for cardiac transplantation. At that time, a plasma total carnitine level was found to be extremely low (1.0 nmol/mL; normal 45.8 ± 9.1 nmol/mL). A skeletal muscle biopsy was obtained, as were skin fibroblasts for carnitine transport studies. Oral L-carnitine supplementation at a dosage of 100 mg/kg per day was initiated, with dramatic improvement in cardiac function over 2 to 4 days. His exercise tolerance was greatly improved by 1 week and he had normal activity by 1 month. The cardiac size decreased to normal by 6 months (Figure 1, *C*) and has remained normal for more than 5 years with L-carnitine therapy (Figure 1, *D*).

Patient 2

Patient 2 is a 5-and-a-half-year-oldgirl, the sister of patient 1. She was found to have a systolic heart mur-

Figure 2



Electrocardiogram of patient 2 demonstrating tall peaked T waves and left ventricular hypertrophy.

mur at the same time that her brother developed congestive heart failure. She had previously been considered healthy and had no cardiac symptoms. At examination, her heart rate was 100 beats/min with readily palpable pulses. Blood pressure was 90/60 mm Hg. A grade 2/6 systolic murmur of mitral regurgitation was present at the cardiac apex. A chest radiograph showed marked cardiomegaly with a left ventricular enlargement configuration. An electrocardiogram showed left ventricular hypertrophy with peaked T waves (Figure 2). Echocardiographic findings reflected dilated cardiomyopathy with cardiac hypokinesis, which was similar to her brother's. Therapy with digoxin was initiated. The plasma total carnitine level was markedly decreased (Table I). A skeletal muscle biopsy was obtained, as were skin fibroblasts for carnitine transport studies. Oral L-carnitine supplementation at a dosage of 100 mg/kg per day was initiated, with prompt resolution of cardiac dilation. The patient's cardiac function has remained normal for more than 5 years.

Special studies of patients 1 and 2: Biochemical tests

Patients 1 and 2 had normal electrolytes, blood urea nitrogen, and creatine levels. There was no hyperammonemia or hypoglycemia. Viral cultures and serologic studies in patient 1 were negative. Urinary organic acid

Table I. Plasma and skeletal muscle carnitine measurements

	Free carnitine	Short-chain acylcarnitine	Long-chain acylcarnitine	Total carnitine
Plasma (nmol/mL)				
Patient 1				
Before L-carnitine	0.7	0.1	0.3	1.0
After L-carnitine				
1 w	16.7	9.0	1.4	26.6
1 mo	17.2	19.1	1.2	38.6
11 mo	20.7	10.6	1.7	31.1
2 y	19.8	10.5	1.4	32.4
4 y	29.8	14.8	0.5	45.1
5 y	20.5	13.6	0.6	34.7
Patient 2				
Before L-carnitine	0.4	0.8	0.3	1.2
After L-carnitine				
1 w	31.6	14.5	1.4	46.5
1 mo	21.7	7.4	1.7	31.0
11 mo	20.3	12.9	1.9	34.6
2 y	14.4	7.2	1.7	24.3
4 y	27.3	11.4	1.6	38.3
5 y	19.0	19.6	0.8	39.4
Mother of patients 1 & 2	28.1	5.0	1.3	33.7
Father of patients 1 & 2	28.8	6.6	1.8	37.7
Patient 3				
Before L-carnitine	1.0	–	–	1.0
After L-carnitine	15.8	–	–	21.6
2 y	23.0	9.0	–	32.0
Controls (mean ± SD, n = 36)	35.8 ± 9.1	8.0 ± 2.2	2.4 ± 0.5	45.8 ± 9.1
Skeletal muscle (nmol/mg NCP)				
Patient 1	<0.01	<0.01	0.01	0.02
Patient 2	<0.01	<0.01	<0.01	0.01
Controls (mean ± SD, n = 9)	15.8 ± 5.0	2.8 ± 1.0	0.7 ± 0.4	19.4 ± 5.9

NCP, noncollagenous protein.

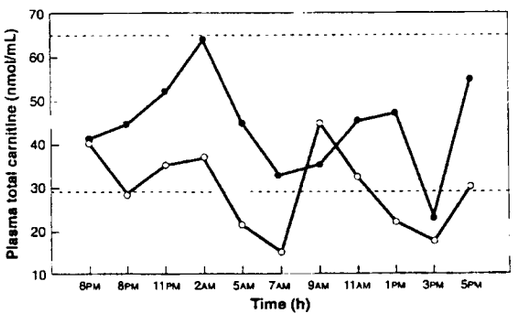
levels and acylglycine excretion were normal in both children, and urinary acylcarnitine analysis after an oral L-carnitine load (100 mg/kg) revealed a normal excretion pattern in both children. Patients 1 and 2 were severely deficient in both plasma free carnitine and plasma total carnitine before supplementation with L-carnitine (Table I). Measurements of plasma carnitine levels from both the mother and the father yielded free and total carnitine levels that were borderline low compared with controls, a finding that has been described in other heterozygotes for the carnitine transporter deficiency (Table I).[9]

After patients 1 and 2 had been on a regimen of supplemental carnitine, the plasma free and total carnitine increased to nearly normal levels (Table I). However, it has been difficult to maintain the free carnitine above 20 nmol/mL despite the use of 150 mg/kg per day of L-carnitine. Measurements of carnitine levels from skeletal muscle, before supplementation, revealed that the total carnitine was less than 0.1% of expected normal levels in both children. Fractional urinary excretion of free carnitine was also measured in both patients 1 and 2 while they were taking a regimen of supplemental L-carnitine of 100 mg/kg per day. For both children, the urinary fractional excretion of free carnitine exceeded 100% of the filtered load (159% for patient 1 and 134% for patient 2).

Table II depicts studies of fibroblast carnitine transport in patients 1 and 2 and that of both of their parents. Fibroblast carnitine transport was measured by the method of Stanley et al.[7] Patients 1 and 2 had an extremely low velocity of carnitine transport at 5 μmol/L of L-carnitine. Both parents had fibroblast carnitine transport approximately one half of the normal transport velocity, as would be expected for people who are heterozygotes for the carnitine transport deficiency.

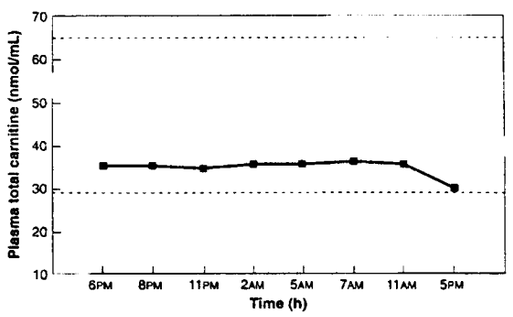
When both siblings had been receiving L-carnitine treatment for 3 years, a 24-hour evaluation of plasma total carnitine levels was obtained (Figure 3). This test revealed wide variation in plasma total carnitine levels over the 24-hour period for both patients. Patient 1 had total plasma carnitine levels that were somewhat lower on the average than patient 2. There were 2 time periods when his plasma total carnitine fell considerably below the normal range. In contrast, measurements of plasma total carnitine in his mother remained at very constant levels at the lower end of normal and did not fall below the normal range in the 24-hour period (Figure 4).

Figure 3



Plasma total carnitine measurements over a 24-hour period in 2 children with carnitine transporter defect. Wide variation in plasma levels of 2 patients, both receiving 150 mg/kg L-carnitine in 3 divided doses. Normal plasma total carnitine range 29 to 64 nmol/mL. *Open circles,* patient 1; *solid circles,* patient 2.

Figure 4



Plasma total carnitine measurements over a 24-hour period in mother of patients 1 and 2 who is a heterozygote for carnitine transporter defect. Minimal variation of plasma total carnitine levels. Normal plasma total carnitine range 29 to 64 nmol/mL

Table II. Fibroblast carnitine transport

	V at 5 μmol/L (pmol/min/ mg protein)	Vmax (pmol/min/ mg protein)	Km (μmol/L)
Patient 1	0.016	*	*
Patient 2	0.019	*	*
Mother of patients 1 & 2	0.49	1.04	2.25
Father of patients 1 & 2	0.51	0.99	5.64
Patient 3	0.090	*	*
Controls (n = 18)	0.93 ± 0.13	1.69 ± 0.32	2.67 ± 0.55

V at 5 μmol/L, transport velocity at 5 μmol/L L-carnitine; *Vmax,* maximum transport velocity.
*Could not be measured because of very low transport.

Skeletal muscle and cardiac pathology

Figure 5 is a photomicrograph of the skeletal muscle biopsy for patient 1. There is widespread deposition of lipid throughout all sections of the biopsy. Cardiac muscle histologic sections from patient 1 have mildly increased levels of lipid but no extensive lipid infiltration such as in the skeletal muscle (Figure 6). There is mild hypertrophy of the myocardial cells.

Echocardiographic monitoring of treatment

When patient 1 was begun on L-carnitine supplementation, echocardiography was used to measure LVEF and left ventricular internal dimension in diastole (LVED). For patient 1, the initial LVEF was <37%, with normal values ranging from 56% to 78%.[10] The LVED was >170% of predicted normal for body surface area of patient 1 (Figures 7 and 8). After 3 months of therapy, the LVED of patient 1 had fallen to 135% of normal, and by 7 months of therapy it had fallen to 110% of normal, with a corresponding LVEF of 65% (Figures 7 and 8).

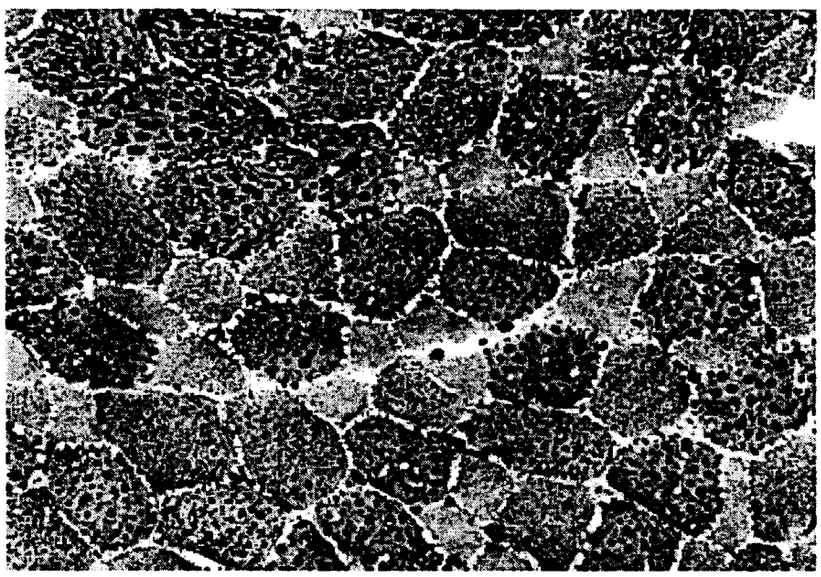
Patient 2 also had severely reduced LVEF (31%) and increased LVED (>150%), although these measurements indicate that her heart was not as dilated as her brother's. After 1 week of L-carnitine supplementation, the LVEF had doubled in patient 2 and increased in patient 1. After 1 month of therapy, patient 2 demonstrated a marked reduction in size of the left ventricle, but patient 1 was slower to resolve his ventricular dilation (Figure 8).

Both children have maintained a nearly normal LVED and a normal LVEF for more than 5 years of L-carnitine therapy.

Patient 3

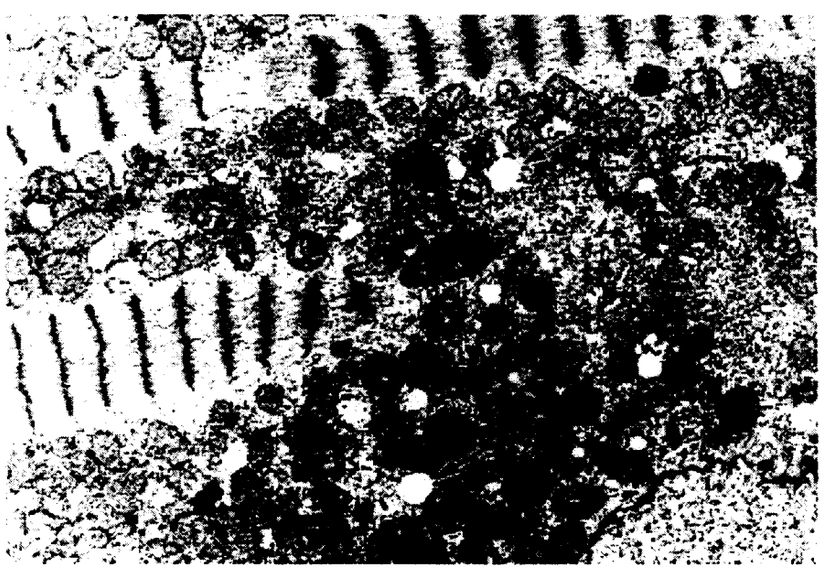
Patient 3 is a 45-month-old boy who was evaluated 2 months after presenting with hypoglycemia and coma. These episodes had followed an extended period of lethargy and poor responsiveness. He is reported to have had several episodes of hypoglycemia before the recent presentation. On examination, he had mild macrocephaly and bilateral esotropias. Blood pressure was 107/40 mm Hg, the lungs were clear, and no cardiac murmur was present. A chest radiograph showed the heart size at the top limits of normal, and an electrocardiogram showed borderline left ventricular hypertrophy. An echocardiogram revealed mild left ventricular hypertrophy with normal LVEF and LVED. He was started on a regimen of 100 mg/kg per day of L-carnitine and has had no further episodes of hypoglycemia for 2 years.

Figure 5



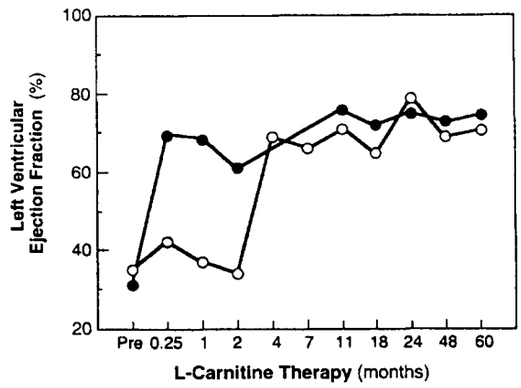
Photomicrograph (×200) of skeletal muscle biopsy of patient 1. Oil red 0 stain reveals widespread lipid deposition. (Courtesy of Stephen Smith, MD, University of Minnesota.)

Figure 6



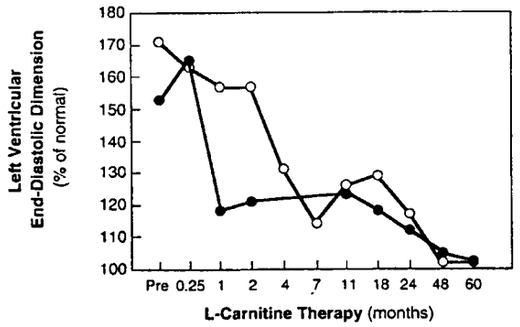
Electron micrograph (×3400) of endomyocardial biopsy from patient 1. *Arrows* indicate lipid droplets. (Courtesy of Nancy Staley, MD, University of Minnesota.)

Figure 7



Changes in LVEF (%) during 5 years of L-carnitine therapy. Normal LVEF is 56% to 78%. *Open circles*, patient 1; *solid circles*, patient 2.

Figure 8



Changes in left ventricular end-diastolic dimension (percent of normal values) during 5 years of L-carnitine therapy. Percent of normal value for left ventricular and diastolic dimension is calculated with 95th percentile for body surface area. *Open circles*, patient 1; *solid circles*, patient 2.

Special studies on patient 3

Liver enzymes (including aspartate aminotransferase 192 U/L, normal 0 to 5 U/L) were elevated, as was ammonia (58 μmol/L, normal 10 to 35 μmol/L). Plasma free and total carnitine values were very low (Table I). A liver biopsy revealed extensive lipid deposition within hepatocytes. Urinary organic acid measurements and urinary acylcarnitine excretion pattern were found to be normal. Total plasma carnitine was markedly decreased at 5.0 nmol/mL. Fibroblast carnitine transport was similar to patients 1 and 2, with very low velocity (Table II).

Discussion

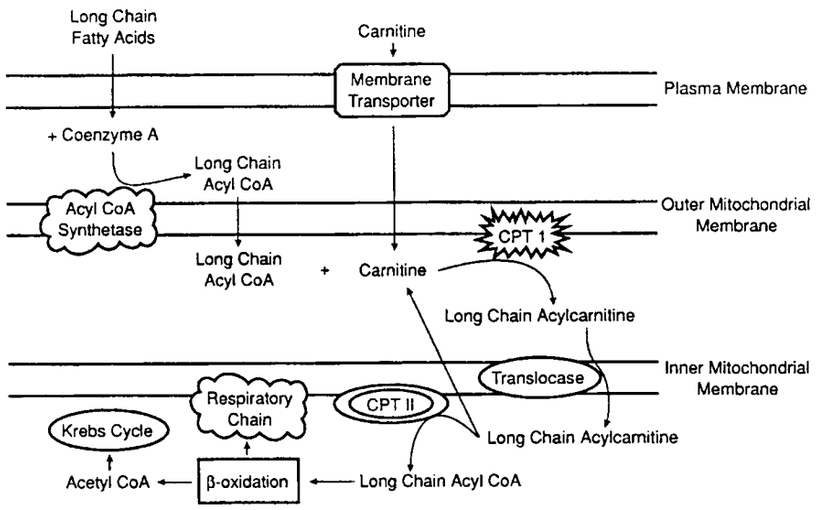
Long-chain fatty acids are an important energy substrate for the myocardium and other muscle tissue. Long-chain fatty acid metabolism depends on carnitine availability. Carnitine forms acylcarnitine esters with long-chain fatty acids and facilitates their transport across the inner mitochondrial membrane (Figure 9). Once inside the mitochondria, the long-chain fatty acids can undergo β-oxidation, thereby providing a critical source of energy for cardiac and skeletal muscle.[3,11]

Carnitine deficiency syndromes can present as metabolic encephalopathy, hypoglycemia, lipid storage myopathy, or cardiomyopathy.[6,7] More frequently, plasma carnitine deficiency occurs as a result of metabolic errors such as defects in fatty acid oxidation, organic acidurias, or mitochondriopathies. From 1979 to 1988 there were 6 reports documenting 7 children with severe plasma and muscle carnitine deficiency.[12-17] A carnitine transport abnormality was suspected in all these patients. In 2 of the 7 children, renal carnitine loss was documented, suggesting an associated defect in tubular reabsorption of carnitine.[16,17] All these children had some evidence of myocardial dysfunction, with 5 of the 7 having congestive heart failure. In 1 patient, the diagnosis of carnitine deficiency was made by measurements on postmortem tissues, and no carnitine supplementation was possible.[14] The other 6 patients had improvement in their clinical status and cardiac function in response to L-carnitine therapy.

In 1988, Treem et al[4] and Eriksson et al[5] documented hereditary defects of carnitine transport in skin fibroblasts, muscle, and renal tubular cells (Table III). These 2 reports were followed by others.[18-24] In all, there are 14 literature reports, along with 3 children described in this article, that illustrate cardiac involvement as one manifestation of the carnitine transporter defect in 33 children (Table III). Heterogeneity is present in the initial clinical presentation of these 33 children: 2 had failure to thrive, 2 had muscle weakness, 5 had coma, 4 had hypoglycemia, 1 had sudden neonatal death, and 19 had cardiac failure. All patients had low levels of plasma free and total carnitine or very low tissue carnitine. All but 2 had very low fibroblast carnitine transport. Twenty of 33 patients had measurements of muscle carnitine levels, with 17 of the 20 lower than 6.4% of control values.[14,22] Nineteen of the 33 patients had significant lipid deposition in skeletal muscle. Improvement in cardiac function occurred with institution of L-carnitine therapy in 30 of 33 patients (2 patients died before therapy and the outcome is unknown in 1 patient).

Of the 33 children with carnitine membrane transporter defect, 5 had repeat muscle sampling to determine if there was an increase in muscle carnitine con-

Figure 9



Mitochondrial fatty acid transport facilitated by action of carnitine. Long-chain fatty acids are activated by acyl coenzyme A (CoA) synthetase to long-chain acyl-CoA esters, which pass through outer mitochondrial membrane. Long-chain acyl-CoA esters are then converted to long-chain acylcarnitine by carnitine palmitoyltransferase (CPT 1). Long-chain acylcarnitine passes through inner mitochondrial membrane through a translocase enzyme. Once inside, long-chain acylcarnitine is reconverted to a long-chain acyl-CoA ester by carnitine palmitoyltransferase II (CPT II). Long-chain acyl-CoA then enters β-oxidation cycle for conversion to acetyl CoA, which in turn enters Krebs cycle and respiratory chain.

tent that occurred concomitantly with normalization of plasma carnitine levels. In 1 patient, muscle carnitine concentration remained low, and there were minimal increases in the other patients, with resultant total carnitine muscle concentrations of 0.5% to 3% of normal.[5,12,19] This finding suggests that the muscle carnitine remains low despite observed improvement of muscle strength during L-carnitine supplementation. It is possible that only a modest increase in muscle carnitine level is sufficient to produce functional improvement in the children with carnitine transporter defect. With respect to the heart, little is known about myocardial carnitine levels before or after treatment with L-carnitine except in 3 patients who died before treatment and whose myocardial levels were low at autopsy.[14,21,22]

The other patients with cardiac involvement have shown vast improvement in cardiac function on L-carnitine. This course is similar to the experience of patients 1 and 2. Such improvement in cardiac function may be caused by increases in myocardial carnitine above a critical level at which cardiac decompensation eventually occurs. The mechanism whereby cardiac decompensation is delayed, often for many years in some of these patients, is not well understood. The nature of the carnitine transporter defect implies that myocardial carnitine levels are chronically low. It is also possible that progression of the cardiac involvement may be caused by a gradual impairment in cardiac metabolism that leads to slow deterioration in heart function and eventually congestive heart failure. Treatment with L-carnitine may increase the availability of carnitine until there is no longer a limitation of cardiac metabolism.

The most outstanding features of the 2 siblings described in this report are the prompt resolution of their cardiac symptoms after L-carnitine supplementation and the maintenance of normal cardiac function for longer than 5 years. In the evaluation of patient 1, a chest radiograph taken 2 years before his presentation in heart failure revealed a nearly normal heart size (Figure 1, *A*). Over the ensuing 2 years, he had severe cardiomegaly, and cardiac failure symptoms developed. This suggests, at least in patient 1, that he was able to maintain adequate cardiac function for a number of years despite the carnitine transporter defect until symptoms of overt heart failure eventually ensued. It can also be seen (Figures 7 and 8) that patient 1 took longer to improve than patient 2, largely because he was in very significant cardiac distress with severe congestive heart failure when his condition was diagnosed.

Table III. Characteristics of literature patients with carnitine transporter defect

Patient	Reference	Age (mo)	Sex	Major clinical feature	Total plasma carnitine (nmol/mL)	Lipid storage in muscle	% Normal muscle total carnitine
1	Chapoy et al[12]	3	M	Coma	4.8	+	1.5
2	Tripp et al[14]	11	F	Cardiac failure	4.8	+	0
3	Tripp et al[14]	26	M	Cardiac failure	4.5	ND	1.0
4	Rodrigues-Pereira et al[17]	18	M	Cardiac failure	1.8	ND	1.5
5	Treem et al[4]	3.5	F	Coma	0-2.2	+	0.5
6	Eriksson et al[5]	48	F	Cardiac failure	<3%	+	1.0
7	Tein et al[6]	1	F	Cardiac failure	19	+	4.7
8	Tein et al[6]	17	M	Failure to thrive	1.2	+	5.5
9	Tein et al[6]	30	F	Coma	0	+	ND
10	Tein et al[6]	2	F	Failure to thrive	9	+	4.7
11	Stanley et al[7]	12	M	Cardiac failure	2.1	ND	ND
12	Stanley et al[7]	13	F	Cardiac failure	1.5	+	20.8
13	Stanley et al[7,16]	18	F	Cardiac failure	4.2	+	6.4
14	Stanley et al[7,13]	20	F	Cardiac failure	9	+	10.8
15	Stanley et al[7]	36	F	Cardiac failure	0.3	ND	ND
16	Stanley et al[7,15]	40	M	Cardiac failure	4.2	+	2.0
17	Stanley et al[7]	84	M	Cardiac failure	4	ND	ND
18	Stanley et al[7]	20	M	Weakness	1.4	+	0.1
19	Stanley et al[7]	8	M	Hypoglycemia	4.0	ND	ND
20	Stanley et al[7]	11	M	Hypoglycemia	1.4	ND	ND
21	Stanley et al[7]	18	F	Hypoglycemia	0	ND	6.4
22	Stanley et al[7]	24	M	Hypoglycemia	1.8	ND	ND
23	Garavaglia et al[18]	26	M	Cardiac failure	4.4	+	1.6
24	Garavaglia et al[18]	24	M	Weakness	4.0	ND	ND
25	Christensen et al[19]	8	M	Cardiac failure	0.97	ND	ND
26	Briones et al[20]	45	M	Cardiac failure	10.8	+	10
27	Bennett et al[21]	8	F	Cardiac failure	ND	+	0.3
28	Rinaldo et al[22]	0.16	M	Sudden death	ND	ND	ND
29	Pons et al[23]	90	F	Cardiac failure	8.2	+	ND
30	Shoji et al[24]	96	F	Coma	4.6	ND	ND
31	Patient 1 (this report)	78	M	Cardiac failure	1.0	+	0.1
32	Patient 2 (this report)	66	F	Cardiac failure	1.2	+	0.05
33	Patient 3 (this report)	45	M	Coma	5.0	ND	ND

ND, Not determined.

His sister, patient 2, had no symptoms when diagnosed, and her LVEF normalized with 1 week of L-carnitine supplementation, compared with nearly 7 months for her brother. Patient 3 had no cardiac symptoms and mild left ventricular hypertrophy as detected by echocardiograms. It is likely that cardiac failure eventually would have developed if his disorder had not been detected until he was older and if treatment with L-carnitine had been delayed.

The causes of dilated cardiomyopathy are heterogeneous.[25] The development of dilated cardiomyopathy in children generally carries a poor prognosis.[19,26-30] Several studies of the natural history of pediatric cardiomyopathy include a 1-year mortality rate of 10% to 58% and 16% to 80% at 5 years. If persistent congestive heart failure was present despite therapy, the long-term survival rate was low.[30] In one study, a group of children older than 2 years at the time of development of dilated cardiomyopathy were found to have an 80% mortality rate after 2 years.[27] In a combined analysis of the 2 studies, the cumulative mortality rate at long-term follow-up of such children revealed a survival rate of less than 5%.[26-28] Not all studies have found such a poor survival rate in older children (>2 years of age at diagnosis), and one study found the 2-year mortality rate of this group to be approximately 30%, similar to children presenting at a younger age. Other contributing factors besides age at presentation may include familial disease, endocardial fibroelastosis, and left ventricular end-diastolic pressures greater than 25 mm Hg.[29,31]

Conclusions

The low survival rate of children with dilated cardiomyopathy suggests that pediatricians and pediatric cardiologists need to take active measures to identify underlying causes so that appropriate treatment can be instituted. In the case of patients 1 and 2, the identification of their severe plasma and muscle carnitine defi-

ciency was essential to the selection of L-carnitine therapy. For patient 1, the L-carnitine therapy was lifesaving and produced dramatic resolution of his severe congestive heart failure within a few days. For both patients 1 and 2, continued L-carnitine therapy led to resolution of all evidence of cardiomyopathy and maintenance of normal cardiac function for more than 5 years. This study provides new data on the long-term (5-year) efficacy of treating carnitine membrane transporter defect with L-carnitine supplementation. Continued follow-up will be necessary to see if their cardiac function remains normal. All children with dilated cardiomyopathy need to be rapidly evaluated for carnitine deficiency and carnitine transporter defect. Treatment with L-carnitine on a long-term basis can alter the natural history of the disease and reduce or eliminate signs of cardiomyopathy.

Research is currently focusing on the specific genetic abnormality in carnitine transporter defect. A murine model of primary carnitine deficiency, the juvenile visceral steatosis (jvs) mouse, has been under investigation since 1988.[32,33] These mice have systemic carnitine deficiency that originates from a recessive mutant gene jvs on murine chromosome 11. This information has led to studies in human beings in which a locus on chromosome 5q has been found to be syntenic with the jvs locus of mice and appears to be the locus for the transporter defect in human beings.[24] OCTN2, an organic cation/carnitine transporter, maps to this same region. Mutations within the gene for OCTN2 have recently been found in patients with carnitine transporter defect.[34,35] Further studies are needed to determine whether different mutations in OCTN2 are responsible for the variability in clinical presentation of children with carnitine transporter defect.

References

1. Kelly DP, Strauss AW. Inherited cardiomyopathies. N Engl J Med 1994;330:913-9.
2. Winter SC, Jue K, Prochazka J, Francis P, Hamilton W, Linn L, et al. The role of L-carnitine in pediatric cardiomyopathy. J Child Neurol 1995;10 Suppl 2:S45-2S51.
3. Bremer J. Carnitine-metabolism and functions. Physiol Rev 1983;63:1420-80.
4. Treem WR, Stanley CA, Finegold DA, Hale DE, Coates PM. Primary carnitine deficiency due to a failure of carnitine transport in kidney, muscle and fibroblasts. N Engl J Med 1988;319: 1331-6.
5. Eriksson BO, Lindstedt S, Nordin I. Hereditary defect in carnitine transport is expressed in skin fibroblasts. Pediatr Res 1990;28: 247-55.
6. Tein I, DeVivo DC, Bierman F, Pulver P, DeMierleir LJ, Cvitanovic-Sojat L, et al. Impaired skin fibroblasts carnitine uptake in primary systemic carnitine deficiency manifested by childhood carnitine-responsive cardiomyopathy. Pediatr Res 1990;28:247-55.
7. Stanley CA, DeLeeuw S, Coates PM, Viany-Liaud C, Divry P, Bonnefont JP, et al. Chronic cardiomyopathy and weakness or acute coma in children with a defect in carnitine uptake. Ann Neurol 1991;30:709-16.
8. Breningstall GN. Carnitine deficiency syndromes. Pediatr Neurol 1990;6:75-81.
9. Scaglia F, Wang Y, Singh RH, Dembure PP, Pasquali M, Fernhoff PM, et al. Defective urinary carnitine transport in heterozygotes for primary carnitine deficiency. Genet Med 1998;1:34-9.
10. Silverman NH. Pediatric echocardiography. Baltimore: Williams & Wilkins; 1993.
11. Wood JM, Bush B, Pitts BJR, Schwartz A. Inhibition of bovine heart Na^+K^+-ATPase by palmityl carnitine and palmityl CoA. Biochim Biophys Res Commun 1977;74:677-84.
12. Chapoy PR, Angelini C, Brown WJ, Stiff JE, Shug AL, Cederbaum SD. Systemic carnitine deficiency: a treatable inherited lipid storage disease presenting as Reye's syndrome. N Engl J Med 1980; 303:1389-94.
13. Morand P, Despert F, Carrier HN, Sudubray BM, Fardeau M, Romieux B, et al. Myopathie lipidique avec cardiomyopathie severe par deficit generalise en carnitine. Arch Mal Coeur 1979;5: 536-44.
14. Tripp ME, Katcher ML, Peters HA, Gilbert EF, Arya S, Hodach RJ, et al. Systemic carnitine deficiency presenting as familial fibroelastosis: a treatable cardiomyopathy. N Engl J Med 1981;305:385-90.
15. Waber LJ, Valle D, Neill C, Di Mauro S, Shug A. Carnitine deficiency presenting as familial cardiomyopathy, a treatable defect in carnitine transport. J Pediatr 1982;101:70-5.
16. Sansaricq CM, Rutkowski SF, Snyderman F, et al. Reye-like syndrome in a young girl with carnitine spillage [abstract]. Fed Proc 1987;46:1341.
17. Rodrigues-Pereira R, Scholte HR, Luyt-Houwen IEM, Vaandrager-Verduin MHM. Cardiomyopathy associated with carnitine loss in kidney and small intestine. Eur J Pediatr 1988;148:193-7.
18. Garavaglia MS, Uziel G, Dworzak F, Carrara F, DiDonato S. Primary carnitine deficiency: heterozygote and intrafamilial phenotypic variation. Neurology 1991;41:1691-3.
19. Christensen E, Vikre-Jorgensen J. Six years' experience with carnitine supplementation in a patient with an inherited defective carnitine transport system. J Inherit Metab Dis 1995;18:233-6.
20. Briones P, Garavaglia B, Ribes A, Yoldi ME, Rodes M, Romen C, et al. Clinical and biochemical findings in a Spanish boy with primary carnitine deficiency. J Inherit Metab Dis 1995;18:237-40.
21. Bennett MJ, Hall DE, Pottlitt RJ, Stanley CA, Variend S. Endocardial fibroelastosis and primary carnitine deficiency due to a defect in the plasma membrane carnitine transporter. Clin Cardiol 1996; 19:243-6.
22. Rinaldo P, Stanley CA, Hsu BYL, Sabchez LA, Stern HJ. Sudden neonatal death in carnitine transporter deficiency. J Pediatr 1997;131:304-5.
23. Pons R, Carrozzo R, Tein I, Walker WF, Addonizo LJ, Takahashi T, et al. Deficient muscle carnitine transport in primary carnitine deficiency. Pediatr Res 1997;42:583-7.
24. Shoji Y, Koizumi A, Kayo T, Korson MS, Perez-Atayde A, Lacro RV, et al. Evidence for linkage of human primary systemic carnitine deficiency with D5S436: a novel gene locus on chromosome 5q. Am J Hum Genet 1998;63:101-8.
25. Schwartz ML, Cox GF, Lin AE, Fisher LD, Gersh BJ, Tajik AJ, et al. Clinical approach to genetic cardiomyopathy in children. Circulation 1996;94:2021-38.
26. Taliercio CP, Seward JB, Driscoll DJ, Fisher LD, Gersh BJ, Tajik AJ, et al. Idiopathic dilated cardiomyopathy in the young: clinical profile and natural history. J Am Coll Cardiol 1985;6:1126-31.

27. Taliercio CP. Dilated cardiomyopathy in children. J Am Coll Cardiol 1988;11:145-6.
28. Griffin ML, Hernandez A, Martin TC, Goldring D, Bolman RM, Spray TL, et al. Dilated cardiomyopathy in infants and children. J Am Coll Cardiol 1988;11:139-44.
29. Lewis AB, Chabot M. Outcome of infants and children with dilated cardiomyopathy. Am J Cardiol 1991;68:365-9.
30. Friedman RA, Moak JP, Garson A. Clinical course of idiopathic dilated cardiomyopathy in children. J Am Coll Cardiol 1991;18:152-6.
31. Chen SC, Nouri S, Balfour I, Jureidini S, Appleton RS. Clinical profile of congestive cardiomyopathy in children. J Am Coll Cardiol 1990;15:189-93.
32. Kaido M, Fujimura H, Ono A, Toyooka K, Yoshikawa H, Nishinura T, et al. Mitochondrial abnormalities in a murine model of primary carnitine deficiency. Eur Neurol 1997;38:302-9.
33. Hashimoto N, Suzuki F, Tamai I, Nikaido H, Kuwajima M, Hayakawa J, et al. Gene-dose effect on carnitine transport activity in embryonic fibroblasts of JVS mice as a model of human carnitine transporter deficiency. Biochem Pharmacol 1998;55:1729-32.
34. Lamhonwah AM, Tein I. Carnitine uptake defect: frameshift mutations in the human plasmalemmal carnitine transport gene. Biochem Biophys Res Commun 1998;252:396-401.
35. Wang Y, Ye J, Ganapathy V, Longo N. Mutations in the organic cation/carnitine transporter OCTN2 in primary carnitine deficiency. Proc Natl Acad Sci USA 1999;96:2356-60.