Original Article

The Role of L-Carnitine in Pediatric Cardiomyopathy

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ABSTRACT

Metabolic and genetic factors underlie some forms of cardiomyopathy in childhood. A variety of inborn errors of metabolism can impair mitochondrial energy production, or β-oxidation, in the heart and lead to myocardial dysfunction. L-Carnitine, an essential element of β-oxidation, transports fatty acids across the mitochondrial membrane for energy production. L-Carnitine deficiency syndromes are now well described as secondary to a variety of inborn errors of metabolism and often include cardiomyopathy in the clinical picture. Despite traditional therapies for cardiomyopathy, mortality for this disorder remains at well over 50%. Review of reports of L-carnitine supplementation studies and results from our own trial underscore the importance of its role in cardiac function and demonstrates that there is likely a subpopulation of patients with cardiomyopathy responsive to L-carnitine treatment. (*J Child Neurol* 1995;10(Suppl):2S45–2S51).

There has been much interest in elucidating the determinants of cardiomyopathy in the pediatric population. Efforts directed at investigating the metabolic basis for myocardial dysfunction have been particularly active. Some forms of cardiomyopathy, known for their high mortality and resistance to intervention, are now being better understood as outcomes of genetic defects and metabolic disturbances. One area that has yielded significant insights into the pathogenesis of pediatric cardiomyopathy has been the examination of defects in mitochondrial energy production; impairments of the mechanism of the myocardium's primary source of energy, the oxidation of fatty acids, may eventuate into these life-threatening clinical syndromes. Here, we review the clinical background and course of cardiomyopathy, its incidence and prognosis, and the role that L-carnitine, the primary transport molecule of mitochondrial energy production, plays in the pathogenesis of this disease. In addition, we provide case studies that exemplify a variety of circumstances in which genetic and metabolic defects can occur and outline their characteristic clinical sequelae. We also provide our own findings from a two-center trial investigating the effect of carnitine supplementation in this group of patients.

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FEATURES OF CARDIOMYOPATHY

Cardiomyopathy refers to a group of disorders in children and adults characterized by primary involvement of the ventricular myocardium. The World Health Organization/International Society and Federation of Cardiologists task force on the classification of cardiomyopathies has defined this condition as a heart muscle disease of unknown cause that is not secondary to an acquired or congenital heart disease.[1,2] It is an important cause of morbidity and mortality; a total of 43,000 patients were hospitalized in 1990 for this disorder in the United States during the 1st year of life, and the incidence is approximately one in 10,000 live births.[3] The survival of patients with cardiomyopathy is dismal, in the range of 50% to 60% after 2 years.[4]

The three pathophysiologic classifications of cardiomyopathy currently recognized are hypertrophic, restrictive, and dilated. Hypertrophic cardiomyopathy is hypertrophy of the ventricular myocardium without an identifiable cause. Dilated cardiomyopathy, accounting for over 90% of all reported cardiomyopathies and by far the most common cardiomyopathy in individuals less than 19 years old, is a primary disease of the ventricular myocardium characterized by increased left ventricular or biventricular volumes without an appropriate increase in ventricular septal or free wall thickness. The essential

physiologic derangement is decreased myocardial contractility (systolic dysfunction) accompanied by a variable degree of impairment of diastolic function.

Clinical Features

Pediatric cardiomyopathy typically presents with normal prenatal and postnatal health followed by a sudden onset of respiratory distress, decreased appetite, lethargy, and occasionally, vomiting, irritability, or fever. The illness often begins during or after a mild upper respiratory tract infection. Children are generally pale with a rapid pulse and may have signs of shock. The liver is enlarged, and peripheral cyanosis is frequent. Cardiac murmurs may be present. Marked cardiomegaly is evident on radiograph, with pulmonary venous congestion. The electrocardiogram often shows extreme left ventricular hypertrophy but may reveal low voltage in some cases. The echocardiogram reveals depressed systolic function with decreased fractional shortening and ejection fraction. Left atrial enlargement is noted, and global left ventricular dysfunction without major regional wall abnormalities may be seen. Intracavitary thrombus may also be detected.[5,6]

Histopathology

Typical ultrastructural features of dilated cardiomyopathy include myocyte hypertrophy and degeneration, including mitochondrial hyperplasia, abnormal Z bands, dilated and disorganized sarcoplasmic and transverse tubular systems, loss of myofibrils, increased lipid droplets, myelin figures, increased phagolysosomes, and increased glycogen. A study of five pairs of twins with dilated cardiomyopathy revealed abnormal mitochondria with circular and stacked cristae. This particular pathology has also been described in several inborn errors of mitochondrial fat metabolism with resultant secondary carnitine deficiency or carnitine insufficiency.[7]

Etiology

Multiple etiologies for cardiomyopathy have been identified,[8–32] but in the majority of cases, the etiology remains obscure. It has been estimated that 20% of cardiomyopathies may be inherited. In addition, the molecular basis of these disorders as they relate to muscle function provide valuable clues to the pathophysiology of cardiomyopathy and to potential therapeutic strategies.[4] Cardiomyopathy has been described as secondary to inborn errors of metabolism, primary and secondary carnitine deficiency or carnitine insufficiency, vitamin deficiencies, electrolyte disturbances, endocrine disease, drug toxicities, collagen vascular diseases, trace mineral deficiency or toxicities, single gene or mitochondrial genetic diseases, and anoxic damage.[33] Idiopathic cardiomyopathy, cardiomyopathy with no identifiable cause, may in part be a consequence of a poorly understood and as-yet-undiagnosable metabolic defect or a defect in mitochondrial functioning.

Treatment and Prognosis

The cornerstones of traditional pharmacologic therapy for the congestive heart failure associated with progressive cardiomyopathy have been digitalis, diuretics, and afterload reducing agents. Although review of the literature reveals somewhat discrepant mortality statistics (possibly due to the effects of maternal disease in early infancy*), despite traditional therapies, mortality has been reported as high as 58% at 1 year and 80% at 5 years in patients with dilated congestive cardiomyopathy, the most common cardiomyopathy in pediatric patients.[34–44] Cardiac transplantation remains the only alternative for patients with nonresponding disease.

L-CARNITINE, METABOLISM, AND CARDIOMYOPATHY

Levocarnitine (L-carnitine), 3-hydroxy-4-*N*-trimethylaminobutyric acid, is a quaternary ammonium compound present in all tissues and is an essential cofactor in the system that transports long-chain fatty acids across the inner mitochondrial membrane, where they undergo energy production. Carnitine is obtained from the diet, the major sources being red meat and dairy products. Carnitine is also synthesized from lysine and methionine, the final synthetic step occurring in the liver. It is not metabolically altered by the body and is excreted in the urine as either free carnitine or acylcarnitine. Free carnitine is largely reabsorbed in the renal tubule, and acylcarnitine is excreted.[45]

Once absorbed from the diet, carnitine enters the circulation and actively crosses muscle membrane. The same transport mechanism in muscle membrane is proposed for the renal transport of carnitine.[11]

Carnitine plays a central role in the shuttle of fatty acids across the inner mitochondrial membrane, and defects in carnitine metabolism can lead to disturbances in mitochondrial energy metabolism. Disturbances include poor dietary intake or malabsorption of carnitine, excessive loss of carnitine in the urine from impaired renal tubular function, and inborn errors of metabolism.[46]

Clearly, defects in many of the steps of mitochondrial fat metabolism result in decreased adenosine triphosphate (ATP) production; these defects have been and are continuing to be described. Impairments of energy production have foremost consequences for myocardial functioning. The heart relies chiefly on the aerobic breakdown of fat for its energy supply. Known as β-oxidation, this complex, multiple-enzyme process occurs in the mitochondria. Each enzyme-controlled step is consequently vulnerable to genetic defects that may partially or completely impair subsequent metabolic steps.

Normally, long-chain fatty acids are released by lipolysis and cross into the mitochondria in a series of steps. The initial step is the activation of the fatty acid to coenzyme A (CoA) in the cytosol to form fatty acyl-CoA. Once activated, the fatty acyl-CoA cannot cross into the mitochondria until transferred by carnitine. This step occurs via the enzyme carnitine acyltransferase I. Once the fatty

*In February 1993, a consensus of the National Pediatric Cardiology Study Group meeting at Jackson Hole, WY.

acylcarnitine molecule is formed, the molecule is transported across the mitochondrial membrane via carnitine acyltranslocase. Once the fatty acylcarnitine molecule reaches the mitochondrial matrix, it is again transferred to CoA via carnitine acyltransferase II. The fatty acyl-CoA molecule that is formed is then ready to undergo β-oxidation. Coupling of β-oxidation with the electron transport pathway within the mitochondria leads to the formation of chemical energy, ATP.[47]

The carnitine released in the matrix of the mitochondria can return to the cytosol via carnitine acyltranslocase. In addition, carnitine may also form an ester with an acyl-CoA molecule within the mitochondria via the enzyme carnitine acyltransferase II, and this acylcarnitine molecule may then leave the mitochondria via the translocase. This mechanism provides a route for removal of acyl derivatives that accumulate during normal metabolism and for large amounts occurring during states of abnormal metabolism. Thus, carnitine can also play a detoxifying or scavenging role.[47]

GENETIC DEFECTS AND INBORN ERRORS OF METABOLISM

Treem et al[11] described an autosomal recessive disorder of carnitine membrane transport resulting in low muscle carnitine levels, as well as low plasma levels due to altered renal reabsorption. Patients can develop cardiomyopathy with this disorder, which was found to be reversible with carnitine supplementation.[11] Carnitine acyltransferase I and II and translocase defects have also been reported. All are inherited as autosomal recessive disorders and can have an associated cardiomyopathy.[4]

Defects of fatty acid oxidation, such as long-chain fatty acyl-CoA dehydrogenase deficiency and long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, have been reported associated with cardiomyopathy. Carnitine supplementation in these disorders remains controversial, but restriction of long-chain fats in the diet has been reported to be helpful.[4,48,49]

Electron transport defects result in decreased ATP production and both skeletal myopathy and cardiomyopathy. Historically, these disorders have been named according to their symptom complexes, such as MELAS for myoclonic epilepsy, lactic acidosis, strokelike syndrome and MERRF for myoclonic epilepsy, ragged red fiber disease. More recently, these disorders are being differentiated via the molecular defects in maternally inherited mitochondrial DNA. Many of these disorders are associated with cardiomyopathy.[4,48–50]

Secondary carnitine deficiency states have now been well described in association with inborn errors of metabolism in which acyl-CoA derivatives accumulate within the mitochondria. These disorders result in low levels of free carnitine and increased acylcarnitines. Such disorders include many of the organic acidurias: propionic aciduria, methylmalonic aciduria, isovaleric aciduria, and glutaric aciduria II are examples.[48,51–53]

In addition, in several inherited disorders of fatty acid metabolism, dicarboxylic acids accumulate, such as deficiencies of medium-chain acyl-CoA dehydrogenase, long-chain acyl-CoA dehydrogenase, and very long chain acyl-CoA dehydrogenase.[49] The alteration of tissue carnitine in these disorders can result in general muscle weakness and cardiomyopathy.

Cardiomyopathy can also be a symptom in multiple acyl-CoA dehydrogenase deficiency (glutaric acidemia type II),[53] which is characterized as a deficiency of cofactors for several different enzymes, with resulting accumulation of carboxylic acids derived from the breakdown of fatty acids and amino acids, as well as an accumulation of dicarboxylic acid.[33,53] The literature reports that carnitine can promote the excretion of excess organic or fatty acids in patients with defects in fatty acid metabolism or specific organic acidopathies that bioaccumulate acyl-CoA esters.[32,33] Carnitine supplementation, although not correcting the primary metabolic error, has been found to relieve many of the symptoms associated with these disorders.[46]

Carnitine deficiency has also been associated with diabetes mellitus. Dietary deficiency of carnitine was described in infants receiving unsupplemented soy formulas and those on total parenteral nutrition. Infants appear particularly susceptible to nutritional carnitine deficiency.[54] Renal loss of carnitine occurs in patients with renal tubular dysfunction disorders, such as renal tubular acidosis and renal Fanconi syndromes. Long-term renal dialysis can also lead to carnitine deficiency.[41]

REVIEW OF CARNITINE SUPPLEMENTATION STUDIES

Much of the interest in examining the role of carnitine in cardiomyopathy has centered on investigating carnitine levels in these disorders. Enough evidence has been accumulated to indicate that at least a subset of cardiomyopathies are accompanied by a carnitine deficiency[55,56] or carnitine insufficiency.[57,58] Carnitine insufficiency is described as an abnormal ratio of plasma acylcarnitine to free carnitine (greater than 0.4) and is an indicator of metabolic disturbance. Each of these reports documents cases responding with clinical improvements to carnitine supplementation and normalization of their cardiac functioning.

Similarly, cases in which a specific inherited defect has been identified have been shown to have a responsive carnitine deficiency. In 1988, Ino et al[59] reported two cases of X-linked recessive dilated cardiomyopathy and three cases with an enzymatic defect of fatty acid oxidation. These patients had low free and elevated esterified carnitine and showed improvement in cardiac function (by echocardiography) with combined therapies of digitalis, diuretics, and carnitine supplementation. Also, two reports describe two patients with Duchenne muscular dystrophy who also had low muscle carnitine levels, suggesting that carnitine deficiency might play a role in the cardiomyopathy that develops consequent to Duchenne muscular dystrophy.[60]

Pierpont[44] has described two cases of carnitine transport defect–associated cardiomyopathy in siblings. One

patient, in spite of 2 years of therapy with digoxin, diuretics, and vasodilators, experienced a steady deterioration of cardiac function and was considered a candidate for cardiac transplantation. Skeletal muscle biopsy on both patients revealed a lipid storage myopathy, and examination of plasma and muscle carnitine levels revealed a severe deficiency; carnitine therapy was subsequently initiated in the symptomatic sibling. The resultant improvement in cardiac functioning permitted removal from intravenous medication within 2 days and discharge from the hospital in 1 week. Cardiac function and size returned to normal after 6 months of carnitine therapy.

The asymptomatic younger sibling was found to have mitral regurgitation and a cardiac condition similar to her brother's, with a low plasma level of free carnitine. Supplementation was thought to be life saving in both of these patients. The transport of carnitine from supplementation in these transport defect cases was attributed to passive diffusion of the carnitine across the mitochondrial membrane.

Waber et al[61] reported a similar case of lipid myopathy in a boy who presented at age 3 plus years with cardiomegaly, distinctive electrocardiogram, and history of a brother dying of cardiomyopathy. Muscle and plasma carnitine were reduced to 2% to 10% of normal. After a year of carnitine supplementation, the cardiac disease resolved, and muscle strength became normal. Although the plasma carnitine concentration was in the low-normal range, the urinary concentration of carnitine was 30 times normal, suggesting a distinct form of deficiency; defective renal or gastrointestinal carnitine transport was the likely cause of this patient's disorder.

Tein et al[62] described four unrelated children with primary carnitine-responsive cardiomyopathy demonstrated by carnitine uptake fibroblast cultures. Each child was noted to have negligible uptake of carnitine (2% of control values), and their parents showed intermediate uptake rates. Serum carnitine levels were low in all four children before carnitine supplementation. Cardiac dysfunction improved within 1 month of therapy. Left ventricular parameters showed marked positive changes, accompanied by improved clinical outcome in their failure to thrive, school performance, and motor function. It was thought that carnitine played an important role in sequestering the toxic long-chain acyl-CoA metabolites that had accumulated and promoted sarcolemmal membrane damage and arrhythmias.[53]

Bohles et al[63] reported 68 patients with myocardial ischemia undergoing aortocoronary bypass operation who were assigned to either carnitine or control therapy. Biopsy of the right atrial appendage was analyzed for carnitine fractions, ATP, and lactate. Analyses of biopsies from patients receiving carnitine treatment showed relatively higher ATP concentration and lower lactate concentrations than control-treated patients. Carnitine-treated patients also needed less inotropic medication postoperatively.

Patients undergoing long-term hemodialysis develop cardiomyopathy and cardiac disease as one of the most important causes of death. Hemodialysis results in a progressive and substantial loss of carnitine from muscle, and the ratio of free to total carnitine becomes abnormally low. Similarly, Kudoh et al[64] reported markedly reduced plasma carnitine levels and an inversely correlated cardiothoracic ratio in chronic hemodialysis.

In an attempt to further evaluate the role of carnitine in patients with cardiomyopathy, we conducted a retrospective review of data collected on carnitine supplemented patients from two medical centers. A total of 35 patients were selected for inclusion and evaluation.

METHODS

Thirty-five patients were identified from two centers from a 10-year period who had their cardiomyopathy treated with oral carnitine. These centers were Geisinger Medical Center in Danville, Pennsylvania, and Valley Children's Hospital in Fresno, California. The following inclusion and exclusion criteria were applied to each patient case: (1) Patients were diagnosed with cardiomyopathy, supported by echocardiography, chest radiograph, physical examination, or history. (2) Patients had received oral carnitine. (3) At least one posttherapy follow-up assessment was available with adequate data to assess efficacy. (4) Patients with an acquired metabolic disorder not due to an inborn error of metabolism were excluded from the study.

There were 21 males and 14 females with a mean age at the start of carnitine therapy of 34.5 months (SD, 65 months) and a range of birth to 23.9 years. Therapy was most commonly begun by age 2 years. The mean duration of carnitine therapy was 25.3 months, ranging from 1.5 to 84.1 months from the date carnitine was begun to the last recorded visit. The average carnitine dose given was 96 mg/kg and ranged from 14 to 455 mg/kg daily.

Cardiomyopathy type was classified as dilated (23 patients), hypertrophic (six patients), or restrictive (one patient). A metabolic etiology for cardiomyopathy was suspected in 12 patients based on organic acid analysis, skeletal muscle myopathy, or enzymatic analysis. Table 1 shows the distribution of diagnoses. Twelve of the 35 patients had a proven or suspected inborn error of metabolism. All proven or suspected metabolic disorders involved mitochondrial fat oxidation.

Data Collection

Markers of treatment efficacy included echocardiogram results (shortening fraction), plasma carnitine levels, and mortality. These data were collected both before and after the administration of carnitine, where available.

Table 1. Distribution of Diagnoses

Diagnostic Category	*Specific Diagnosis*	*Patients, n (%)*
Fatty acid defect	Skeletal muscle myopathy	6 (75.0)
	Long-chain fatty acyl-CoA dehydrogenase deficiency	2 (25.0)
	Total (% of all patients)	8 (22.9)
Organic and amino aciduria	Glutaric aciduria type 2	4 (100.0)
	Total (% of all patients)	4 (11.4)
Unknown	Unknown diagnosis	23 (100.0)
	Total (% of all patients)	23 (65.7)
Total patients	—	35 (100.0)

Table 2. Patient Deaths

Patient	*Type of Cardiomyopathy*	*Diagnosis*	*Age at Death, mo*	*Cause of Death*	*Time on Carnitine, mo*
1	Dilated	Muscle myopathy (FAO)	35.6	Cardiac arrest	11.6
7	Dilated	Muscle myopathy (FAO)	21.3	Arrythmia	4.0
9	Dilated	Unknown	25.0	Cardiac arrest	16.6
22	Dilated	Muscle myopathy (FAO)	197.8	Cardiac arrest	28.2
27	Hypertrophic	Unknown	76.2	Arrythmia	6.3
28	Hypertrophic	LCAD	NA	NA	NA
29	Restrictive	Muscle myopathy	292.2	CHF	5.6
33	Hypertrophic	Unknown	20.5	Cardiac arrest	8.9

FAO = fatty acid oxidation defect; LCAD = long-chain acyl-CoA dehydrogenase deficiency; NA = not available; CHF = congestive heart failure.

Analysis

The echocardiogram shortening fraction values before and after carnitine administration were compared using a paired *t*-test procedure in patients who had both values available (23 patients). In cases in which there were multiple posttreatment shortening fractions, the last echocardiogram value was used. The observed mortality rate was compared with literature values.

Carnitine Status

Carnitine deficiency was defined as a plasma free carnitine level less than 20 μmol/L, and plasma ester to free carnitine ratios of more than 0.4 were considered abnormally high. Twenty-four patients had pretreatment carnitine levels available. Of these, 10 (42%) had levels below 20 μmol/L and were considered carnitine deficient (mean, 29.59 μmol/L; SD, 18.5 μmol/L). Of 23 patients measured after therapy, all had free carnitine levels above 20 μmol/L (mean, 59.2 μmol/L; SD, 29.2 μmol/L).

RESULTS

Eight (23%) of 35 patients died from their cardiomyopathy (Table 2). Five of these had a suspected or proven inborn error of metabolism. Three of the expired patients had carnitine deficiency before therapy.

Twenty-three patients had both baseline and posttreatment echocardiograms available. Pretreatment and posttreatment echocardiogram values are presented in Table 3. The difference between the mean pretreatment fractional shortening value and the mean posttreatment fractional shortening value (0.25 versus 0.30) was statistically significant ($P = .043$).

Laboratory values, including complete blood counts, serum chemistry, and urine analysis, were collected and reviewed by one of the investigators for changes attributable to carnitine therapy. All laboratory values could be explained by the patients' underlying disorder, and no unexpected changes were noted.

DISCUSSION

Twelve of the 35 patients had either a proven or suspected inborn error of metabolism as the primary etiology for their cardiomyopathy. This was a surprisingly high proportion of patients with a metabolic disorder because metabolic etiologies of cardiomyopathy are generally thought to be rare. The metabolic disorders suspected as a cause of cardiomyopathy in these 12 patients fell into three categories: long-chain fatty acyl-CoA dehydrogenase deficiency, electron transport flavoprotein deficiency (glutaric aciduria II), and disorders of mitochondrial electron transport or metabolism. The finding of cardiomyopathy in such defects is not surprising considering the known dependency of cardiac muscle metabolism on fatty acid oxidation as an energy source. Because all three types of metabolic disorder are associated with an accumulation of acyl-CoA derivatives within the mitochondria, carnitine therapy would be expected to improve the metabolic dysfunction, with removal of acylcarnitine derivatives.

Currently, cardiologists would not expect to find a high percentage of patients with cardiomyopathy to have an underlying inborn error of metabolism as the etiology. In addition, the finding of only three categories of metabolic defects (long-chain fatty acyl-CoA dehydrogenase deficiency, glutaric aciduria II, and mitochondrial defects) as the cause is even more surprising.

Overall, eight (23%) of 35 patients died from their cardiomyopathy, and five (62.5%) of these had a suspected or proven inborn error of metabolism. Because overall there were 12 patients in this study with a suspected or proven inborn error of metabolism, their mortality rate was five (42%) of 12.

We postulate that carnitine administration results in improved excretion of toxic acyl-CoA intermediates that accumulate due to aberrant fatty acid catabolism and may have contributed to the improvement in cardiac function. Treatment with pharmacologic levels of carnitine needs to be considered in patients presenting with life-threatening cardiomyopathy. Measurement of tissue and plasma carnitine levels of both free and acylcarnitines and proper investigations into mitochondrial disorders are imperative. Studies should include evaluation for organic acidopathies, fatty acid oxidation defects,

Table 3. Mean Echocardiogram Fractional Shortening Values Before and After Carnitine Treatment

	Pretreatment	*Posttreatment**	*P*
n	23	23	—
Mean FS	0.254	0.304	.043
SD	0.14	0.13	—
Minimum	0.080	0.10	—
Maximum	0.660	0.54	—

*Mean elapsed time from treatment start was 23.8 months (range, 3 to 68 months).
FS = fractional shortening; SD = standard deviation.

defects in mitochondrial electron transport, carnitine membrane transport defects, and defects of carnitine acyltransferases I and II and translocase. Carnitine deficiency secondary to dietary deficiency, malabsorption, increased renal loss, dialysis, or pharmacologic agents needs to be evaluated.

Studies to consider include: organic acids; amino acids; plasma, urine, or tissue carnitine levels; muscle biopsy for mitochondrial enzymes and muscle carnitine membrane transport; mitochondrial DNA studies; and assessment of renal tubular function. Carnitine treatment of some of the specific defects remains controversial, but in most of the defects, including the organic acidopathies and carnitine membrane transport defects, carnitine therapy can be life saving.

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