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L-CARNITINE AND CARDIOMYOPATHIES OF CHILDREN: A GENERAL OVERVIEW

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Summary

Cardiomyopathy of infancy or childhood is a very serious cardiac condition. The mortality and morbidity are high and treatment options are few and limited. One year survival has variously been reported as ranging from 20% to 50%. In recent years, we have become increasingly more proficient in identifying an underlying cause of the cardiomyopathy. The etiologies fall into a diverse group of highly variable conditions: infiltrative or storage diseases, metabolic defects in energy supply, associated neurologic disease, syndromes, environmental/toxic or endocrine, arrhythmias, inflammatory/autoimmune, or due to contractile protein abnormality.
L-Carnitine has been shown to be useful for the medical treatment of pediatric cardiomyopathy due to metabolic disease, in some individuals with defects in energy metabolism, and in toxic or anthracycline cardiomyopathy. Among the defects in energy metabolism is a condition termed primary carnitine deficiency or carnitine membrane transport defect. This disease is a genetic disorder producing a severe dilated cardiomyopathy, with heart failure in infancy or childhood, severely decreased plasma and tissue levels of free and total carnitine. If the diagnosis is not established, it can lead to a fatal outcome. Reduced transport of carnitine into tissues and loss of carnitine in urine can lead to very low plasma carnitine levels and, eventually, to severe heart failure. Two siblings are described with the carnitine membrane transport defect. Diagnosed four years ago, both had severe cardiomegaly and one had cardiac decompensation.
Both had very low plasma carnitine and skeletal muscle carnitine. Oral L-carnitine supplementation led to prompt resolution of the heart failure and cardiac enlargement in both children. Additionally, their improved cardiac status has been maintained for the 4 years since treatment was begun. In these two children, L-Carnitine therapy was life-saving and efforts to identify other individuals with this medically treatable disease are warranted.
Other cardiomyopathies may also be associated with improvement or prevention with L-Carnitine. These include organic acidemias, disorders of fatty acid metabolism, anthracycline cardiomyopathy, uremic cardiomyopathy and mitochondrial disorders. Correct diagnosis of patients with varying causes of cardiomyopathy is essential to the choice of possible beneficial treatment.

Cardiomyopathy in infancy and childhood is a very serious disorder with uncertain prognosis. The mortality and morbidity of the variuos cardiomyopathies are high and the options for medical treatment of the underlying conditions are limited. One year survival of infants or children has been reported as varying from 20% to 50%. In an older classification scheme, cardiomyopathies were divided into dilated, hypertrophic and restrictive groups according to their anatomic appearance. In recent years, it has become more obvious that these classifications do not fit all cardiomyopathies, for example, those with hypertrophy and congestive heart failure together or other physiology combination.
Cardiomyopathy is a heterogeneous group of disorders due to many etiologies. If one excludes familial hypertrophic cardiomyopathy (FHC), almost 85% of the rest of the cases have no known etiology. In recent years, however, we have become increasingly able to identify underlying causes of the cardiomyopathy. Such identification of the etiology or cause is crucial to the development of improved methods of medical treatment.
Pediatric cardiomyopathies may be classified into a broader spectrum than that of the traditional anatomic classification. The following classification is useful in considering the occurrence of cardiomyopathy:

1. Infiltrative Disease
2. Defects in Energy Supply
3. Cardioneurologic Disease
4. Association with Syndromes
5. Environmental/Toxic and Endocrine Diseases
6. Arrhythmia or Conduction Anomalies
7. Inflammatory or Autoimmune Diseases
8. Contractile Protein Disease

Many of the types of cardiomyopathy from these groups are likely to be inherited, but some from categories 5, 6 and 7 may be acquired. The total number of children with a specifically defined cardiomyopathy is determined by the investigative effort of those trying to define the etiology. Each infant, child, or adult with cardiomyopathy should have a full diagnostic evaluation to determine the nature of their disease.

Each of the above categories has many possibilities for diagnosis of the different cardiomyopathies (Tables 1-8). Those conditions in which carnitine plays a role are the disorders of fatty acid metabolism, organic acidemias, anthracycline cardiomyopathy, uremic cardiomyopathy and mitochondrial disorders. In category 2 (Table 2), defects of energy supply or metabolism, carnitine plays a role in most of the diseases. Defects in fatty acid metabolism or organic acidemias or mitochondrial disease can have a secondary deficiency of carnitine. Treatment of organic acidemias such as methylmalonic acidemia with L-Carnitine has been shown by others to result in urinary excretion of large amounts of short chain fatty acids and improvement of cardiac dysfunction if present.

***Table 1** - Infiltrative Diseases Causing Cardiomyopathy*
1. Glycogenoses
2. Mucopolysaccharidoses
3. Sphingolipidoses
4. Hemochromatosis

***Table 2** - Defects in Energy Supply Causing Cardiomyopathy*
1. Fatty Acid Metabolism Defect
a. Long chain acyl CoA dehydrogenase deficiency
b. 3-OH long chain CoA dehydrogenase deficiency
c. Carnitine palmitoyltransferase II deficiency
d. Multiple acyl CoA dehydrogenase deficiency
e. Organic acidemias
2. Carnitine Deficiency
a. Membrane Transport Defect
3. Mitochondrial Diseases
a. Electron transport abnormality
b. Mitochondrial myopathy
c. Mitochondrial DNA mutations

***Table 3** - Cardioneurologic Disease and Cardiomyopathy*
1. Friedreich ataxia
2. Leigh disease
3. Congenital myopathies
4. Myotonic dystrophy
5. Other muscular dystrophies

Table 4 - Association of Cardiomyopathy with Syndromes
1. Noonan syndrome
2. Leopard syndrome
3. Marfan syndrome
4. Mulibrey nanism

Table 5 - Environmental/Toxic/Endocrine Disease and Cardiomyopathy
1. Nutritional deficiency
2. Maternal diabetes
3. Adriamycin toxicity
4. Maternal connective tissue disease
5. Selenium deficiency
6. Thyroid disease
7. Catecholamine excess
8. Diabetes
9. Uremia or renal disease

Table 6 - Arrhythmia or Conduction defects and Cardiomyopathy
1. Sudden death
2. Ventricular arrhythmias
3. Atrial arrhythmias
4. Heart block

Table 7 - Inflammatory/Autoimmune Disease and Cardiomyopathy
1. Viral myocarditis
2. Lyme disease
3. AIDS
4. Diphtheria
5. Systemic lupus erythematosus

Table 8 - Contractile Protein Disease and Cardiomyopathy
1. Duchenne muscular dystrophy
2. Becker muscular dystrophy
3. Familial hypertrophic cardiomyopathy

Among the defects in energy supply is a cardiomyopathic disease which can be treated successfully with L-Carnitine when the diagnosis is correctly made. This condition is due to primary deficiency of carnitine and is called carnitine membrane transport defect. First described in 1988 by Treem et al., carnitine membrane transport defect has a variety of clinical presentations. In the 26 known patients with this disease, the presentations include failure to thrive, generalized muscle weakness, hypoglycemia, coma, and congestive heart failure (Table 9).

Table 9 - Carnitine Membrane Transport Defect	
Presenting Clinical Features	
Hypoglycemia	4
Failure to Thrive	2
Muscular Weakness	2
Coma	3
Cardiac Failure	15
	26 patients

Despite the variable initial presenting feature of the children with menbrane transport defect, almost all of them have significant cardiac involvement. Their disorder is caused by reduced or nearly absent transport of carnitine across tissue membranes, particularly skin fibroblasts, skeletal muscle cells and kidney tubules. The reduced transport of carnitine across tissue membranes and the loss of carnitine through the renal tubules due to abnormal reabsorption of carnitine combine to produce very low total plasma carnitine levels and eventually severe congestive heart failure. Treatment of affected children with L-Carnitine has resulted in impressive resolution of cardiomegaly and alleviation of heart failure symptoms.

To illustrate this conditions, two siblings with carnitine membrane transport defect are presented. The first child (patient 1), a six and one half year old boy, developed severe congestive heart failure. He had been previously healthy except for asthma. A chest x-ray revealed severe cardiomegaly and pulmonary edema.

In comparison, a chest x-ray taken two years prior to the development had a normal cardiac size. Physical examination revealed a grade 2/6 holosystolic murmur at the cardiac apex, hepatomegaly, tachypnea and tachycardia. Left ventricular hypertrophy and tall peaked T waves were present on the ECG. An echocardiogram showed marked left ventricular dilation and severely reduced ventricular contractility.

Despite aggressive medical therapy with digoxin, diuretics, vasodilator medications and inotropic support, the condition of the child deteriorated.

Consideration was given to possible cardiac transplantation, but a plasma total carnitine was found to be 1.0 nmol/ml (normal mean total carnitine 45.8 nmol/ml). A skeletal muscle biopsy was performed and this revealed a severe lipid storage myopathy. Oral L-Carnitine was begun at a dose of 100 mg/kg/day. Within two days, there was dramatic improvement in patient 1's symptoms and intravenous medications could be discontinued. He was discharged from the hospital in one week. Echocardiographic evaluations of patient 1 while receiving L-Carnitine revealed that the left ventricular ejection fraction, which had been very low, rose to normal within 4 months. Left ventricular size (end-diastolic dimension) approached normal at 6 months of L-Carnitine therapy. Skin fibroblast studies confirmed a severely reduced carnitine transport into skin cells, yielding the diagnosis of carnitine membrane transport defect.

Patient 2, the sister of patient 1, was five and one half years old and asymptomatic. She was examined because of her brother's cardiac failure. She had a history of a cardiac murmur, but was otherwise healthy. There was a grade 2/6 holosystolic murmur at the cardiac apex suggestive of mitral regurgitation. Her chest x-ray, ECG, and echocardiogram showed the same features as were seen in her brother, namely marked cardiomegaly, left ventricular hypertrophy, and markedly reduced ventricular contractility. These features were seen despite the absence of clinical symptoms on her part. Measurement of total plasma carnitine revealed that patient 2 also had severely reduced plasma total carnitine (1.2 nmol/ml). Oral L-Carnitine was administered and patient 2 had a prompt increase in her left ventricular ejection fraction to normal in one week and decrease in the left ventricular size dimension to normal in one month.

Both patients 1 and 2 had evidence of lipid storage myopathy on skeletal muscle biopsy performed prior to their supplementation with L-Carnitine. Patient 1 also underwent a myocardial biopsy which was performed at cardiac catheterization. This revealed mildly increased levels of lipid in the myocardium, in contrast to the skeletal muscle, where lipid deposition was very extensive.

Analyses of urinary organic acids and acylglycines were normal in both children. No hypoglycemia was detected in either child. Treatment with L-Carnitine was initiated at 100 mg/kg/day. It became necessary to increase the dose of L-Carnitine to 150 mg/kg/day in order to maintain the total plasma carnitine greater than 28 nmol/ml.

These 2 children have now been followed for over 4 years since the initiation of L-Carnitine therapy. They have been healthy and well from a cardiovascular standpoint. Both children had severely reduced left ventricular ejection fractions ($<40\%$) and left ventricular shortening fractions (<0.15) prior to L-Carnitine supplementation. After 4 years of therapy, the values for left ventricular ejection fraction and shortening fraction are in the normal range ($>60\%$ and >0.25 respectively). Prior to L-Carnitine, both children had markedly enlarged left ventricles with the end-diastolic dimension exceeding 150% of normal in both. After treatment for 4 years, both children have a left ventricular end-diastolic dimension within the normal range for their body mass.

This cardiomyopathy is caused by an altered membrane transport of carnitine and, as the course

of the two children described above illustrates, it is a readily treatable disease, unlike most of the other infantile or childhood cardiomyopathies. All infants and children with cardiomyopathy, especially those with dilated left ventricles and poor ventricular function should be evaluated for this disorder. In other patients with hypoglycemia or skeletal muscle weakness, cardiac abnormalities should be screened for.

L-Carnitine treatment of the 2 siblings described above has been life-saving, and has maintained the health and cardiac stability of the two children for over four years. Other patients with the same membrane transport defect have also had resolution of their cardiac failure. Efforts to diagnose this disease are needed in order to alter the course of this potentially fatal condition. The long term prognosis of this type of cardiomyopathy associated with carnitine membrane transport defect can be changed by the therapeutic addition of L-Carnitine to the treatment plan.

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