Cardiomyopathy in childhood, mitochondrial dysfunction, and the role of L-carnitine

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Cardiomyopathy in childhood is associated with high morbidity and mortality rates. Many metabolic causes have been identified, including genetic or acquired defects in mitochondrial energy production affecting β-oxidation, carnitine transport, and the electron transport chain. Combining conventional inotropic and antiarrhythmic therapy with metabolic interventions has improved overall outcome. L-carnitine, a natural substance involved in mitochondrial transport of fatty acids, is one such therapy and plays a central role in the regulation of the inner mitochondrial supply of free coenzyme A. Carnitine deficiency can be caused by both genetic and environmental causes with resultant signs and symptoms of metabolic disease, including cardiomyopathy. Administration of L-carnitine can result in improvement or resolution of the cardiomyopathy. (Am Heart J 2000;139:S63-S69.)

Cardiomyopathy is a serious disease associated with a poor prognosis and a high mortality rate. The World Health Organization/International Society and Federation of Cardiologists task force defines idiopathic cardiomyopathy as a disease of heart muscle of unknown cause that does not represent a response to coexisting or preexisting diseases of the heart or circulation such as acquired or congenital heart disease.[1] Three pathophysiologic forms of cardiomyopathy are recognized: dilated, hypertrophic, and restrictive. Dilated cardiomyopathy accounts for more than 90% of all reported cases.[1,2]

In 1990, 43,000 patients were admitted to US hospitals with the diagnosis of cardiomyopathy; 40,000 of these were older than 45 years of age. The incidence in children is low, but exact figures are lacking. Based on statistics from California, the reported prevalence of cardiomyopathy in children is 1 in 54,000. Survival rates are poor, with up to 80% 5-year mortality in some studies.[3-5] In a recent Finnish study with 62 pediatric patients, the mortality rate was 50%; 6.4% of the patients were undergoing a heart transplant, 27% were living with residual disease, and only 16% were disease free.[6]

In most cases of cardiomyopathy in children, no specific cause is identified. Known acquired causes include vitamin and/or trace mineral deficiencies, electrolyte disturbances, endocrine disorders, toxins, drug toxicity, collagen vascular diseases, immunologic disease, malignancy, morbid obesity, pulmonary disease, Kawasaki disease, infection, radiation, congenital heart disease, and anoxic damage from coronary artery atherosclerosis.

Genetic disorders are estimated to account for at least 20% to 30% of cardiomyopathy in children. A few are caused by malformation syndromes, such as Noonan's syndrome, and primary defects affecting cardiac muscle proteins, such as the β-myosin defects.[5-32] Many of the remainder are caused by inborn errors of energy metabolism.

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Muscle energy metabolism

Muscular energy production depends on genetic factors such as normal mitochondrial function, including enzyme activity and cofactor availability, and on environmental factors, including availability of fuels (sugars, fats, and proteins) and oxygen. Fat is the primary energy source for all muscle tissue, including heart muscle. Any condition that affects the energy cascade can lead to a decrease in muscular energy supply with a resulting myopathy, or in heart muscle, cardiomyopathy.[5-32]

Inborn errors of metabolism

Inborn errors of metabolism and inherited muscle disorders make up the largest group of genetic causes of cardiomyopathy. Because these disorders are genetic and generally affect several organ systems, the patients often have multisystem disease.[7] The diseases include the lysosomal and glycogen storage disorders, carbohydrate-deficient glycoprotein syndromes, organic acidurias, mitochondrial dysfunctions, and fatty acid oxidation defects. In the disorders of fat oxidation and mitochondrial function, diminished energy production is a common pathologic factor.[7,28] The clinical presentation depends on the specific genetic defect involved.

The best known inborn error of metabolism, though not the most common, is Pompe's disease, a lysosomal glycogen storage disease caused by a recessively inherited deficiency of α-1,4-glucosidase (acid maltase). In the severe infantile variety, the onset is in the first few months of life with both generalized muscle weakness and hypertrophic cardiomyopathy; death by 1 year of age

is the rule. No current therapy is available, but trials of enzyme replacement are expected to begin soon.[7,29,30]

Disorders affecting the catabolism of amino acids and organic acids can also cause myopathy and cardiomyopathy. One example is the autosomal recessive disorder of propionyl coenzyme A (CoA) carboxylase deficiency, which causes propionic aciduria. These patients often have life-threatening acidosis, myopathy, failure to thrive, and occasionally cardiomyopathy. Treatment is aimed at reducing the amount of flux through the propionic acid pathway through dietary restriction of amino acid precursors and the removal of accumulated propionate with L-carnitine, an amino acid derivative.[7,31]

Muscle, including cardiac muscle, derives most of its energy from mitochondrial fatty acid oxidation. Fatty acid oxidation is a complex process that includes the uptake of fatty acids, their transport into the mitochondria through the carnitine cycle, β-oxidation, the tricarboxylic acid cycle, and oxidative phosphorylation to adenosine triphosphate (ATP). Patients with genetic defects of β-oxidation often have myopathy, including cardiomyopathy. Very long-chain 3 hydroxy fatty acyl CoA dehydrogenase deficiency (VLCHAD) is one such defect. Patients with this recessively inherited defect in enzymatic activity often have either dilated or hypertrophic cardiomyopathy.[32]

Disorders involving mitochondrial energy production have been increasingly identified during the last decade. The generation of ATP is controlled by both maternally inherited mitochondrial DNA (mtDNA) and nuclear DNA. There are 5 complexes in the mitochondrial electron transport chain, which are made up of at least 64 polypeptides (of which 13 are encoded by mitochondrial DNA). Any defect in these complexes can result in a decrease in energy production. Although any tissue can be involved, skeletal muscle and cardiac muscle are affected most frequently. Therapy of these disorders is still empirical but usually treatment involves the use of nutritional agents in pharmacologic doses.[32]

The carnitine cycle

L-carnitine is a trimethylated amino acid derived from the diet and from endogenous sources. The main dietary sources of L-carnitine include red meats and dairy products, including human breast milk. Infants, with a low body protein mass, generally depend on dietary sources for their carnitine supply, whereas adults are more capable of endogenous synthesis. Synthesis depends on available endogenous protein sources with the conversion of trimethylated lysine derivatives liberated during muscle protein catabolism. The lysine derivatives undergo enzymatic conversion to L-carnitine through an initial synthetic pathway in the muscle and undergo a final conversion step in the liver.

Carnitine exists in a free form (nonesterified) or bound, as acylated (esterified) derivatives. Normally the predominant acylcarnitine is acetylcarnitine from acetyl-CoA, but carnitine can also be esterified with many bound CoA derivatives, including the intermediates of β-oxidation and some amino acid intermediates. Carnitine is excreted mainly through the urine, although some is lost through bile. Ninety-five percent of the filtered free carnitine is reabsorbed by the renal tubules, and the majority of the esterified carnitine is excreted in the urine, thus permitting excretion of the abnormal metabolites that accumulate in many inborn errors of fatty acid and amino acid metabolism.[33] Carnitine itself is not catabolized, and its only metabolic conversion involves the formation of such esters.

Esterification of carnitine is under the control of several enzymes, including carnitine palmitoyl transferase I (CPT I) on the outer (cytosolic) surface of the inner mitochondrial membrane and carnitine palmitoyl transferase II (CPT II) on the inner surface of the mitochondrial membrane. Fatty acyl CoA molecules are converted by CPT I to fatty acyl carnitines and cross the membrane into the inner mitochondrial surface through a mitochondrial membrane carnitine acyl translocase. Once inside the mitochondria, CPT II reesterifies the fatty acyl carnitine to generate a fatty acyl CoA and a free carnitine. The CPT I and CPT II enzymatic steps are reversible. Therefore the acyl groups can be transported out of the mitochondria through reversal of the carnitine transport pathway.[33,34]

Carnitine deficiency from a genetic defect in carnitine synthesis has not been described in any patients to date. The only primary defect in carnitine metabolism that has been identified is the absence of the muscle membrane carnitine transporter, which is inherited as an autosomal recessive defect. Inherited defects in activity of CPT I, CPT II, and carnitine membrane translocase have all been described. All these disorders of carnitine transport and transfer can result in muscle dysfunction, including cardiomyopathy.[33,34]

In its role of transporter, L-carnitine modulates the availability of free CoA for mitochondrial metabolic processes. Because the inner mitochondrial membrane is impermeable to CoA, the availability of free CoA within the mitochondria requires the rapid removal of organic acids esterified to CoA. If the amount of available free CoA falls because of accumulation of acyl CoA derivatives for any reason, metabolic steps requiring free CoA can be compromised. This can result in a rapid shutdown of mitochondrial energy output and deterioration in multiple cellular functions. Some of the steps affected by such a decrease in the free CoA/acyl CoA ratio include conversion of pyruvate to acetyl CoA, α-ketoglutarate to succinate, conversion of succinyl CoA to oxaloacetate, and β-oxidation. These disruptions

of metabolism can result in lactic acidosis, hypoglycemia, and decreased ATP production.[33,34] Therefore, any genetic defect of mitochondrial metabolism and any metabolic or acquired defect resulting in carnitine deficiency can result in a severe compromise to mitochondrial energy production, which may involve the heart.

In propionic aciduria, propionyl CoA accumulates within the mitochondria in massive quantities; free carnitine is then esterified, creating propionyl carnitine, which is then excreted in the urine. Because the supply of carnitine in the diet and from synthesis is limited, such patients readily develop carnitine deficiency as a result of the increased loss of acylcarnitine derivatives. This condition demands supplementation of free carnitine above the normal dietary intake to continue to remove (detoxify) the accumulating organic acids.[35] A similar mechanism can occur with valproic acid, which is metabolized through CoA derivatives.[36]

Secondary carnitine deficiencies

Carnitine deficiency can also be attributed to other causes. Dietary deficiency was identified in otherwise normal infants fed infant soy formulas unsupplemented with L-carnitine. Subsequent identification of this problem, and supplementation of all infant formulas with adequate amounts of L-carnitine, has essentially eliminated this cause of secondary deficiency. However, deficiency is still being identified because of the use of total parenteral nutrition unsupplemented in L-carnitine. This deficiency is reported to occur more readily in children younger than age 2 years, possibly attributable to a decrease in muscle protein available for carnitine synthesis, decreased carnitine synthesis in the young child, or other yet to be described factors.[33,37,38]

Other causes for secondary carnitine deficiency may also be present. If the diet is adequate, poor absorption of carnitine can also result in a secondary deficiency, which may occur with chronic malabsorption, such as cystic fibrosis, and chronic or acute diarrhea illnesses. Renal tubular dysfunction can result in decreased reabsorption of L-carnitine and in total carnitine deficiency, as occurs in patients with the renal Fanconi syndrome. Loss of carnitine can also occur from either hemodialysis or peritoneal dialysis.[37]

Diagnostic considerations and therapeutic options

Diagnostic considerations

The identification of abnormal cardiac muscle function should lead clinicians to consider all possible causes, including genetic and acquired disorders of energy metabolism. All too often, the diagnosis of cardiomyopathy is made with little consideration of the primary cause and consequently of potential therapeutic approaches. In some cases, muscle membrane is affected and can result in nonspecific elevation of muscle-related enzymes, such as creatine phosphokinase, alanine aminotransferase, and aspartate aminotransferase.

Table I. Metabolic testing for cardiomyopathy

- General
  - Blood
    - Gases
    - Electrolytes
    - Glucose
    - Ketones
    - Enzymes (AST, ALT, CK, and isozymes)
    - Ammonia
    - Lactate
    - Carnitine (total, free, and acyl/ester)
    - Amino acids
  - Urine
    - Ketones
    - Quantitative organic acids
- Specialized*
  - Blood
    - Plasma acylcarnitine derivatives
    - Pyruvate
    - Mitochondrial DNA studies
    - Transferrin electrophoresis
    - Lysosomal enzymes
  - Urine
    - Acyl-glycine derivatives
- Tissue biopsies
    - Skeletal muscle†
    - Cardiac muscle
    - Liver
    - Skin for fibroblast culture

AST, Aspartate aminotransferase; *ALT,* alanine aminotransferase; *CK,* creatine kinase.
*As indicated by results from the general assays.
†Studies should include routine histology, electron microscopy, mitochondrial electron transport studies, mitochondrial DNA, carnitine, with sufficient samples frozen for future studies.

Although more than 95% of total body carnitine is found in muscle, because plasma is more readily available for quantitation, most patients with carnitine deficiency are initially identified by low plasma levels. A plasma free carnitine level of 20 mmol/L or less is the accepted value for deficiency and an acyl/free carnitine ratio of 0.4 or greater represents a situation in which an increased load of acyl CoA derivatives depletes available free stores, a situation commonly referred to as carnitine insufficiency.[33,34,37,39]

In all cases of cardiomyopathy, investigations should include studies for metabolic disorders (Table I). Urine studies are indicated for quantitative organic acids and acyl-glycine derivatives. Enzyme studies for certain lysosomal storage disorders might also be indicated. Tissue biopsy is often indicated for establishment of a metabolic diagnosis. Consultation with a metabolic specialist before biopsy is strongly recommended if a muscle

biopsy is to be performed because some of the critical assays are very sensitive to adverse handling. For example, mitochondrial disorders are best diagnosed on isolated mitochondrial preparations made from fresh muscle, which can only be done in a few centers; if improperly handled, frozen specimens can lead to equivocal results. Establishment of skin fibroblast cultures in addition to tissue sampling might also prove useful because this tissue can be used for future enzymatic or DNA studies. DNA banking with white blood cells might also be valuable.

Signs, symptoms, and therapeutic approaches

In childhood, cardiomyopathy typically presents with exercise intolerance leading to signs and symptoms of congestive heart failure, including sudden onset of respiratory distress in a previously well child; lethargy; decreased appetite; signs of an infectious component, including fever, vomiting, diarrhea, and/or irritability. Pallor, tachycardia, hypotension, and occasionally shock are also seen. Other physical signs may include hepatomegaly, cyanosis, encephalopathy, and/or cardiac murmurs. Often, severe cardiomegaly is seen on chest radiographs, while echocardiogram shows depressed systolic function with decreased fractional shortening and ejection fraction and left atrial enlargement.[7,15-17]

Treatment of pediatric cardiomyopathy includes clinical resuscitation and stabilization and the use of traditional pharmacologic therapy. Digitalis provides inotropic benefit; diuretics reduce vascular volume. Afterload-reducing agents, such as the angiotensin-converting enzyme inhibitors and direct-acting vasodilators, such as captopril and lisinopril and (less often) hydralazine, are also commonly used. In addition, coenzyme Q10 and antioxidants are often part of the strategy. β-Adrenergic agents have been found to improve hemodynamic function in some patients, and anticoagulants are used in patients with a thrombus. In recent years, therapies aimed at improving mitochondrial energy metabolism have been introduced, often with the addition of L-carnitine to the therapeutic regimen, even in the absence of demonstrated carnitine deficiency.[7,16,39]

Experience with L-carnitine

Since 1980, many authors have noted a relation between certain inborn errors of metabolism and plasma carnitine deficiency.[31-35,37,39-50] In 1984, Tripp and Shug[42] reported abnormal plasma carnitine values in pediatric patients with cardiomyopathy. A poor prognosis was noted in patients with elevated total carnitine (free + acyl carnitine) levels in plasma. In a review of 51 children with plasma carnitine deficiency, Winter et al[37] reported that 10 patients had cardiomyopathy. Five of the 10 patients were premature infants receiving total parenteral nutrition that was not supplemented with carnitine. Therapy with L-carnitine in all 10 patients resulted in improvement in cardiac function.

Ino et al[43] reported on 11 children with cardiomyopathy, 8 of whom had abnormal plasma carnitine values. Of these 8, 6 showed improvement in cardiac function with L-carnitine therapy. In 1990, Spevak[44] reviewed the treatment of children with cardiomyopathy, including intravenous electrolyte and glucose solutions, inotropic agents, antiarrhythmic agents, and specific nutrients such as selenium, thiamine, or L-carnitine. More than 75% of the cases treated with L-carnitine for an identified carnitine deficiency showed a beneficial effect.

Regitz et al[45] reported on myocardial carnitine values in patients with cardiomyopathy in 1990. They found low levels in patients with dilated cardiomyopathy and postulated that defects in myocardial energy metabolism, such as inborn errors of metabolism, may result in a secondary carnitine deficiency. The term “primary carnitine responsive cardiomyopathy” was originally applied to 4 unrelated children who were later studied by Tein et al,[47] all of whom were shown to have decreased L-carnitine uptake in fibroblasts. These patients had negligible uptake versus intermediate rates of uptake found in their parents, indicating an autosomal recessive carnitine membrane transporter defect. Serum carnitine levels were low because of diminished renal reabsorption, and all the children showed dramatic response to L-carnitine therapy.

Pierpont[46] reported 2 cases of L-carnitine responsive cardiomyopathy in siblings with a confirmed carnitine membrane transporter defect. Both children had a lipid storage myopathy and, despite conventional therapy, showed deterioration in cardiac function. Institution of L-carnitine therapy resulted in a rapid resolution of the cardiomyopathy. Pierpont suggests that a trial of L-carnitine is warranted in all cases of cardiomyopathy. Diagnostic efforts are crucial because the long-term prognosis of the carnitine membrane transport defect is vastly altered by this treatment. Bennett et al[48] reported in 1996 on an infant with endocardial fibroelastosis and severe carnitine deficiency in muscle in whom the primary defect was also found to be a carnitine membrane transporter defect.

In 1997, Yano et al[49] reported a case of L-carnitine responsive cardiomyopathy from malonyl CoA decarboxylase deficiency. Kothari and Sharma[50] reported in 1998 on the treatment of 13 children with idiopathic cardiomyopathy. L-carnitine therapy resulted in modest improvement in left ventricular function. In 1998, Cox et al[32] reported on the reversal of a severe hypertrophic cardiomyopathy in a patient with VLCHAD by dietary restriction of very long-chain fats and L-carnitine therapy.

Table II. Retrospective review of pediatric patient demographics

Population*
50 (26 F, 24 M)
Number and classification of myopathy
48 dilated; 2 hypertrophic
Age
<1 month (n = 14)
1-12 months (n = 19)
12-24 months (n = 7)
>24 months (n = 10)
Cause of cardiomyopathy
Idiopathic (n = 22 [44%])
Carnitine deficiency (sole cause, 11 [22%])
Organic aciduria (n = 10 [20%])
Familial (n = 2 [4%])
Maternal diabetes (n = 2 [4%])
Mitochondrial myopathy (n = 1 [2%])
Duchenne muscular dystrophy (n = 1 [2%])
Associated with Stickler's syndrome (n = 1 [2%])

*Pediatric patients treated with L-carnitine for cardiomyopathy unassociated with congenital heart defect at Valley Children's Hospital, Madera, Calif. Data from summary for the basis of approval for Carnitor for the treatment of carnitine deficiency secondary to inborn errors of metabolism. NDA submitted for FDA submitted for FDA approval by sigma-tau Pharmaceuticals, Inc.

A retrospective chart review of 50 children with cardiomyopathy not associated with a congenital heart defect and treated with L-carnitine between May 1984 and September 1998 at Valley Children's Hospital in Madera, Calif, was recently reported. The results are summarized in Table II.[51]

A retrospective, multicenter study of 221 pediatric patients up to 18 years of age (120 female, 101 male) with cardiomyopathy was undertaken to evaluate the course and outcome in patients treated with and without L-carnitine (the control group). The study was conducted at 7 centers in the United States between July 1983 and July 1994. Patients were excluded if there was an underlying structural cardiac defect or a known β-myosin defect. Charts were reviewed to gather data on demographics, echocardiograms, electrocardiograms, chest roentgenograms, clinical outcome, intercurrent illnesses, concomitant medications, L-carnitine dosing characteristics, survival, and a clinical assessment of both severity of illness and functioning ability. There were 87 patients treated with L-carnitine; 76 received therapy for more than 2 weeks and were included in the study (Table III).

Outcome was similar in both groups, with 71% of the L-carnitine–treated patients alive at the end of the study and 63% of the control group alive at the end. Nine percent of the L-carnitine group received cardiac transplants versus 14% of the controls. Death occurred in 20% of the L-carnitine group versus 23% in the control group. The mean ejection fraction was significantly lower ($P < .001$) in the L-carnitine–treated group versus the controls before therapy, indicating a sicker population. Improvement in mean ejection fraction was seen with both groups, but the change from baseline in the L-carnitine group showed a greater degree of improvement than in the control group by study end ($P < .001$). The criteria used for calculating the adjusted severity for comparing the carnitine-treated group to the control group were based on 3 separate factors: ejection fraction, signs and symptoms (weighted according to severity), and a clinical functional score ranging from normal eating and activity at one end to hospitalization for chronic illness at the other end. Overall, the L-carnitine–treated patients had a greater degree of clinical severity based on reported symptoms and were less functional at the beginning of the study than the control group. For example, in the carnitine-treated group, 48 (63.2%) of 76 were hospitalized for chronic illness versus 35 (25.7%) of 136 for the control group. Conversely, 12 (15.8%) of 76 in the carnitine-treated group ate normally with age-appropriate activity versus 62 (45.6%) of 136 for the control group. Again, the degree of change in both clinical severity and functional score for the L-carnitine group, from the baseline to end point of the study, was significantly greater than the change for these parameters in the control group ($P < .001$). By the end of the study, both groups had similar clinical severity and functional scores, thus reflecting that patients treated with L-carnitine were more severely affected at the time of diagnosis. Although not significantly different, survival in the L-carnitine group was slightly better than in the control group (Helton E et al, personal communication) (Table III).

Table III. Outcome of 221 patients with cardiomyopathy

	Carnitine-treated	Control	Total	*P* value
Died	15 (20%)	33 (23%)	48 (22%)	>.05
Alive	54 (71%)	91 (63%)	145 (66%)	>.05
Transplant	7 (9%)	21 (14%)	28 (12%)	>.05
Total	76 (34%)	145 (66%)*	221	

*Clinical function score was not available on 9 controls.

Discussion

By offering a route for removal of accumulating toxic intramitochondrial acyl CoA derivatives, L-carnitine offers the possibility of improving overall mitochondrial energy metabolism. L-carnitine therapy in acutely ill children with cardiomyopathy, even if they are awaiting diagnostic testing results, should be considered. Use of 50 to 300 mg/kg per day orally or intravenously has been shown to be safe and efficacious for the treatment of inborn errors of metabolism in children.[52] In such patients, treatment may be lifesaving, and delay in treatment may result in death or irre-

versible disease. Theoretical concerns about L-carnitine inducing arrhythmias in patients with VLCHAD have been inferred from animal models of cardiac ischemia in which increased levels of long-chain acylcarnitines are associated with ischemic damage; these effects are inhibited by CPT I inhibitors. However, there are several case reports of clinical improvement with L-carnitine in such patients without serious side effects.[32,48] Madden et al[53] have suggested that the ischemic changes observed are a result of inhibition of β-oxidation and decreased ATP production. They postulate that the CAT I inhibitors improve the clinical outcome by their known stimulation of glucose oxidation. Obviously, in severely ill patients with cardiomyopathy, arrhythmia is a common complication. Details regarding anecdotal reports of any kind need to be analyzed in light of the clinical situation, concomitant medications, and comparison with controls before such side effects are assigned to L-carnitine. Because patients with VLCHAD represent few of the metabolic patients, and the benefit of L-carnitine therapy for many metabolic disorders has been proven, it would seem prudent that all patients be considered for this potentially lifesaving drug.[32,48]

Conclusions

The diagnosis of cardiomyopathy should automatically lead to a search for underlying metabolic causes. Clinicians need to consider both genetic and environmental factors. Diagnostic metabolic testing of mitochondrial metabolism should be done in all cases (Table I). Among the information to consider obtaining is detailed family history; blood studies, including pH, bicarbonate, electrolytes, glucose, ammonia, lactate, pyruvate, alanine and other amino acids, creatine kinase, and liver function; mitochondrial DNA studies; plasma or tissue carnitine (total, free, and acyl); acylcarnitine derivatives in blood; and urine studies of acylglycine derivatives and quantitative organic acids. Tissue biopsy is often indicated for establishment of a metabolic diagnosis. If a muscle biopsy is to be performed, consultation with a metabolic specialist before biopsy is important because proper handling of the tissue at surgery is critical. Establishment of skin fibroblast cultures in addition to tissue sampling may also prove useful, as this tissue can be used for future enzymatic or DNA studies. DNA banking with white blood cells may also be useful.

With increasing knowledge of the mechanisms of cardiac muscle dysfunction, additional approaches to therapy have emerged. In patients with a primary metabolic cardiomyopathy, specific treatment of the metabolic disorder often results in a reversal of the cardiac disease. For the organic acidurias, fatty acid oxidation defects, and mitochondrial disorders, the use of specific dietary modification and pharmacological doses of several cofactors, including L-carnitine, is worth consideration and may be lifesaving.

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