

L-carnitine for treatment of cardiomyopathies

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(CARDIOLOGIA 1998; 43 (Suppl 2): 685-686)

Introduction

Cardiomyopathy is a serious disease with an often poor prognosis and high mortality. Estimates of incidence range between 2 to 8 per 100 000¹ to 17.2 per 100 000² among all age groups (43 000 hospital admissions were reported for ICD Code 425.4 in 1990). The incidence in the first year of life has been estimated at 1 in 10 000 live births³ while reports for the pediatric population inclusive cite approximately 5000 cases annually. Survival rates in children remain dismal; despite even the most aggressive therapeutic efforts with 5-year mortality reported up to 80%. In a recent Finnish study, the outcome in 62 pediatric patients showed a mortality rate of 50%, 6.4% undergoing heart transplant, 16% recovered and 27% with residual disease⁴.

Advances in molecular biology and metabolism and the acquisition and evaluation of genetic data have begun to provide substantial insights into these often intractable disorders. Over 100 specific disease conditions have been identified resulting in cardiomyopathy including viral infection, deficiencies of specific vitamins or minerals, electrolyte disturbances, endocrinopathies, anoxic damage, drug toxicities, genetic defects of the cytoskeleton, and genetic inborn errors of metabolism⁵.

Inborn errors of energy metabolism, including fatty acid oxidation defects and mitochondrial disorders,

often present with skeletal muscle weakness and cardiomyopathy. Pathology reveals lipid storage and associated deficiency of carnitine.

Carnitine's role is to transport long chain fatty acids across the inner mitochondrial membrane for delivery for beta oxidation. In addition, carnitine removes accumulate products of metabolism (toxic intermediates) from the mitochondria and these compounds are excreted in the urine attached to carnitine. Dietary sources and endogenous synthesis provide ample carnitine for normal metabolic functioning. However, a genetic block in mitochondrial fat metabolism can result in massive accumulation of these toxic organic acids requiring carnitine supplementation to prevent deficiency. Measurement of plasma carnitine in these patients will reveal a low free carnitine (< 20 μ M/l) and an increased bound (acyl) carnitine reflected as an increased acyl/free carnitine level (> 0.4). In addition to carnitine deficiency secondary to an inborn error of metabolism, tissue carnitine deficiency can occur due to a genetic defect in the carnitine membrane transporter.

Symptoms of deficiency include failure to thrive, muscle weakness, cardiomyopathy, encephalopathy and hepatic dysfunction. Treatment with L-carnitine can restore metabolism to a more normal state with improvement in muscle tone and strength and myocardial contractility⁶⁻¹².

Methods

A retrospective chart review of cases of childhood cardiomyopathy treated with L-carnitine was conducted. Patients were selected based on the echocardiographic finding of cardiomyopathy and treatment with L-carnitine. Patients with congenital heart defects were excluded.

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Results

Fifty pediatric aged patients were identified who were treated with L-carnitine for cardiomyopathy between May of 1984 and September of 1998 (172 months). There were 26 females and 24 males. Fourteen patients (28%) had onset under 1 month of age, 19 (38%) between 2 and 12 months of age, 7 (14%) between 12 and 24 months of age and 10 (20%) over 24 months of age. Forty-eight patients had dilated cardiomyopathy and 2 had hypertrophic cardiomyopathy.

All patients were treated with L-carnitine both intravenous during the acute illness and oral therapy after. Usual dosage used was 300 mg/kg/day for intravenous carnitine and 100-200 mg/kg/day for oral carnitine. Side effects were minimal with most frequent being gastrointestinal dysfunction (diarrhea and increased cramping) and body odor. Length of follow-up ranged from 1 month to 172 months with an average of 32.7 months.

The etiology of the cardiomyopathy was idiopathic in 22 (44%), associated with plasma free carnitine deficiency in 11 (22%), organic aciduria in 10 (20%), Stickler syndrome in 1 (2%), Duchenne dystrophy in 1 (2%), mitochondrial myopathy in 1 (2%), and a familial disorder in 2 (4%). A total of 33 patients had some abnormality of plasma carnitine: 22 with a low free plasma carnitine and 27 having an elevation of carnitine acyl/free levels.

Overall outcome showed 6 patients died (12%), 2 had cardiac transplants (4%), 6 had persistent disease (12%), and 36 showed complete resolution of cardiomyopathy (72%). As in other studies, survival in the older onset patients (> 24 months) was the poorest with 30% dying and 10% undergoing transplant, 20% with persistent disease and 40% completely resolving their cardiomyopathy. Of the 33 patients with an abnormality of plasma carnitine level (deficiency or insufficiency or both), 4 died (12%) and 2 (6%) had persistent disease.

Of the 6 patients that died and 2 that went for cardiac transplant, etiology was unknown in 3, Duchenne dystrophy in 1, Stickler syndrome in 1, glutaric aciduria II in 1, 2-ketoadipic aciduria in 1 and an undefined mitochondrial disorder (based on muscle biopsy) in 1.

Discussion

The overall survival (84%) of our patients is exceedingly high with 72% showing complete resolution of cardiomyopathy. Interestingly, the survival rate in those patients with deficiency or insufficiency of car-

nitine was the same (12% mortality). The patients were treated with conventional therapies (ACE-inhibitors, digoxin and diuretic) and the only consistent difference between our group and those reported in the literature is the treatment with L-carnitine.

In a previous multicenter study we compared the survival of 76 pediatric aged cardiomyopathy patients to 145 patients treated with conventional therapies without carnitine. In this study the treated patients had significantly poorer baseline morbidity and by the end of the study they were similar to the untreated cohort giving a statistically significant rate of improvement with L-carnitine therapy.

L-carnitine therapy is safe with few side effects. The findings in this study and others strongly suggest that carnitine therapy improves the outcome of cardiomyopathy even in the absence of carnitine deficiency or insufficiency.

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