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Plasma carnitine status – a prognostic factor in children with dilated cardiomyopathy

M. Marx[1], **M. Skyllouriotis**[1], **E. Legenstein**[2], **E. Proll**[1], and **M. Wimmer**[1]

[1] Abteilung Pädiatrische Kardiologie, Universitätsklinik für Kinder- und Jugendheilkunde, AKH Wien, Vienna, Austria
[2] Institut für Medizinische Chemie, Universität Wien, Vienna, Austria

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Summary. *Objective* – Dilated cardiomyopathy is a rare disorder in childhood that results in a high mortality. The aim of our study was to evaluate the prognostic relevance of the individual plasma carnitine status in children with dilated cardiomyopathy.

Methods – In 26 patients plasma carnitine concentrations were determined before and after 6 and 12 months of L-carnitine treatment. According to the plasma short chain acyl-carnitine/free carnitine ratio (AC/FC) at the first presentation children were divided into two groups.

Results – In group 1 (AC/FC < 0.4) the median time from diagnosis until death was 35.8 months, the cumulative survival rate was 84% after 2 years. In group 2 (AC/FC > 0.4) median time from diagnosis until death was 8 months, the cumulative survival rate was 50% at 2 years ($p < 0.05$).

Dividing both groups into survivors and nonsurvivors in group 2 a significantly higher AC/FC ratio in the nonsurvivors could be found (survivors 0.78 v 1.3 in nonsurvivors). A significant improvement of left ventricular function 6 and 12 months after presentation and after starting L-carnitine treatment could only be documented in the surviving patients of group 2.

Conclusion – The individual plasma carnitine status in children with dilated cardiomyopathy may serve as a risk factor for survival.

Keywords: Amino acids – Dilated cardiomyopathy – Infants and children – Plasma carnitine

The cardiac muscle is capable of utilizing either free fatty acids, glucose or keton bodies as an energy source, although fatty acids, particularly long chain fatty acyl coenzyme A derivatives, provide the predominant myocardial substrates (Hütter et al., 1985). Carnitine is an essential cofactor for the beta-oxidation of free fatty acids (Opie, 1979). In the absence of carnitine, beta-oxidation ceases, glycogen is depleted, lipid accumulates and organ

dysfunction results (Engel, 1980). The naturally occuring compound L-carnitine plays an essential role in fatty acid metabolism. It is only by combining with carnitine that the activated long-chain fatty acyl CoA esters in the cytosol are able to be transported to the mitochondrial matrix where beta-oxidation occurs. Carnitine also functions in the removal of compounds that are toxic to metabolic pathways. Thus the individual carnitine status of each patient may alter specific organ functions or may be the result of alered organ metabolism, which is the case in various forms of inborn errors of metabolism, for example in disorders of organic acid metabolism. In relation to the free plasma carnitine concentration and the ratio of acyl carnitine to free carnitine a pathologic plasma carnitine status may be defined as either deficient or insufficient (Winter et al., 1987; Engel and Angelini, 1973).

In previous reports both hypertrophic and congestive cardiomyopathies have been described as being associated with carnitine deficiency. Although an unequivocal protocol has been elaborated for the treatment of primary carnitine deficiency, no guidelines are available for supplementing patients with secondary carnitine deficiency or insufficiency (Tripp and Shug, 1984). This fact made us adopt a blanket approach supplementing all our patients with dilated cardiomyopathy. The purpose of our study is to determine the individual plasma carnitine status in children presenting with dilated cardiomyopathy, to evaluate the prognostic relevance and to investigate changes in left ventricular function during oral L-carnitine treatment.

Methods and patients

In 1985 we have started to treat all children with various kinds of cardiomyopathies with L-carnitine prospectively. Up to now 29 children with dilated cardiomyopathy were recognized. Patients with congenital heart defects, valvular heart disease, chronic arrhythmias and patients with clinically obvious acute myocarditis were not included. 16 patients were male, 13 were female, ranging in age from 1 month to 15 years, the median age on admission was 38 months. All patients were subjected to a metabolic screening consisting of (urinary) organic acids, mucopolysaccharides, plasma amino acids and fatty acids. Skeletal muscle biopsy was performed in 18 out of 26 patients to reveal a metabolic disorder. Metabolic diagnoses were: one boy, age 5 years, of group "surviving" with palmitoyl-CoA dehydrogenase deficiency; one boy, age 2 months, of group "non-surviving" with palmitoyl-CoA dehydrogenase deficiency and one boy, age 2 years, cytochrome c oxidase deficiency of group "surviving". The study was designed as an open, uncontrolled prospective study and – without exception – all children presenting with DCMP entered the study. Blood samples were obtained from each patient on admission and after 6 and 12 months. Plasma free carnitine- and short-chain acylcarnitine – concentrations were determined, the ratio of short-chain acylcarnitine to free carnitine was calculated.

In order to establish normal values these three parameters were determined in 10 healthy controls ranging in age from few days to 13 years. The normal mean value for plasma free carnitine was 37 (SD 4) μmol/litre (range 28–44) and 7 (3) μmol/litre (range 3–13) short-chain acylcarnitine. The calculated normal ratio for short-chain acylcarnitine to free carnitine was 0.19 (0.09) (range 0.075–0.37).

Free plasma carnitine deficiency was defined by values below 28 μmol/l (normal value minus 2 SD's), carnitine insufficiency was diagnosed by a ratio of short-chain acylcarnitine to free carnitine $\geq$0.4 (normal value plus 2 SD's). This is in accordance to literature where

a ratio of acylcarnitine to free carnitine is considered normal when it is 0.25 and abnormal when it is greater than 0.4 (Winter et al., 1987; Battistella et al., 1980; Bohles et al., 1994).

According to the plasma short-chain acylcarnitine/free carnitine ratio at the time of first presentation the children were divided into two groups, since the comparison of surviving and nonsurviving patients showed a significant difference for the plasma short-chain acylcarnitine/free carnitine ratio. Children undergoing heart transplantation were counted as nonsurviving patients.

Group one consisted of 11 children with a short-chain acylcarnitine/free carnitine ratio below 0.4, in group two 15 children with a short-chain acylcarnitine/free carnitine ratio ≥ 0.4 were included. The echocardiographic estimation of fractional shortening as an objective parameter for left ventricular function was obtained in a standardized manner (Feigenbaum, 1986). The values at the time of admission and after 6 and 12 months were taken for statistical calculation. L-carnitine was given in 3 oral administrations per day to give a total dose of 100 mg/kg/per day. No concomitant medication was specifically contraindicated. Medication did not differ concerning digitalis, diuretics and ACE – inhibitors, regarding dosis and duration of treatment, intravenous catecholamine treatment however was necessary in 5 patients of group 1 and in 11 patients of group 2.

L-carnitine was determined radioenzymatically according to the method of Cederblad and Lindstedt (1972) with several modifications as formerly described (Lohninger et al., 1987). After deproteinisation with perchloric acid (0.1 mol/l) free L-carnitine reacts with ^{14}-C-acetylcoenzyme A to ^{14}-C-acetyl-L-carnitine, catalyzed by carnitine-acetyl-transferase. N-methyl-maleimide is added for trapping free coenzyme A. The excess of ^{14}-C-acetylcoenzyme A is bound by ion exchange resin (Dowex 1X8, chloride form 400 mesh). Residual radioactivity is proportional to the amount of ^{14}-C-acetyl-L-carnitine and measured in a liquid scintillation counter. The concentration is calculated from a calibration curve (5–50 μmol/l) considering sample dilution by pretreatment. Total L-carnitine is determined after saponification. The portion of short-chain acyl-carnitine (C_3–C_{10}) is calculated by the difference between L-carnitine content before and after saponification.

The concentrations in plasma are expressed in μmol/liter for free carnitine (FC) and short-chain acid-soluble acylcarnitines (AC).

According to the local legal requirements informed verbal consent was obtained from each patients parents participating in this study.

Statistics

Wilcoxon's rank test for comparison of the groups and the linear regression coefficient r were used in evaluating the results (SAS User's Guide, 1985). Comparison of changes in left ventricular function over time was calculated using the paired t-test.

Survival was estimated by life-table analysis using the variable interval (Kaplan-Meier) method (Kaplan and Meier, 1958). Comparison of the survival curves was carried out using unpaired one-tail Student t testing by using standard error of the life table intervals as described by Grennwood (1926) P-values of 0.05 or below were considered significant.

Results

Twenty-nine children entered the protocol. Three were eliminated from the analysis because they were missed for follow-up. 10 children died, the overall mortality rate was 38%, 4 children were heart transplanted. Median duration of follow-up for all patients was 49 months (range 2–213). Out of 26 children remaining for analysis 17 were found to have a pathologic plasma carnitine

Table 1. Plasma carnitine values at first presentation

	Overall group				
	Alive (n = 12)		Died (n = 14, 10 died, 4 HTX)		
FC	38	(6–60)	n.s.	32	(10–60)
AC	17	(2–45)	n.s.	18	(3–52)
AC/FC	0.47	(0.05–1.2)	$p < 0.05$	0.77	(0.09–2.5)
Age	26	(2–143 mo)	n.s.	48	(1–148 mo)
follow up	78	(33–213 mo)		19	(2–106 mo)
	Group 1 (AC/FC < 0.4)				
	Alive (n = 6)		Died (n = 5, 3 died, 2 HTX)		
FC	42	(27–60)	n.s.	33	(21–40)
AC	10	(2–16)	n.s.	8	(3–12)
AC/FC	0.22	(0.05–0.33)	n.s.	0.23	(0.09–0.38)
Age	19	(2–47 mo)	n.s.	37	(1–116 mo)
follow up	89	(33–213 mo)		35.8	(4–106 mo)
	Group 2 (AC/FC > 0.4)				
	Alive (n = 6)		Died (n = 9, 7 died, 2 HTX)		
FC	35	(6–54)	n.s.	31	(10–60)
AC	25	(5–45)	n.s.	27	(10–52)
AC/FC	0.78	(0.4–1.2)	$p < 0.04$	1.3	(0.47–2.5)
Age	33	(6–143 mo)	n.s.	55	(15–148 mo)
follow up	35	(2–112 mo)		8	(2–21 mo)

FC free carnitine (μmol/l); *AC* short chain acylcarnitine (μmol/l); *AC/FC* ratio short-chain acylcarnitine/free carnitine.

status (65%) at the time of first presentation. 8 were carnitine deficient, 14 insufficient and 9 had normal plasma carnitine levels. Out of the 8 children with plasma carnitine deficiency, 5 were insufficient too. 4 of these 5 children died. Concentrations of carnitine and short-chain acylcarnitine in plasma for surviving and nonsurviving patients for the overall group and the group 1 and 2 are shown in Table 1.

In the overall group a significant difference for plasma short-chain acylcarnitine/free carnitine ratio between survivors and nonsurviviors is noted (0.47 (0.36) *v* 0.77 (0.68); $p < 0.05$).

Results in group 1 (plasma short-chain acylcarnitine/free carnitine ratio below 0.4)

Out of 11 children 3 children died and 2 were heart transplanted, the median time from diagnosis until death was 35.8 months, after 24 months the cumulative survival rate was 84%. Survival analysis curves are shown in Fig. 1.

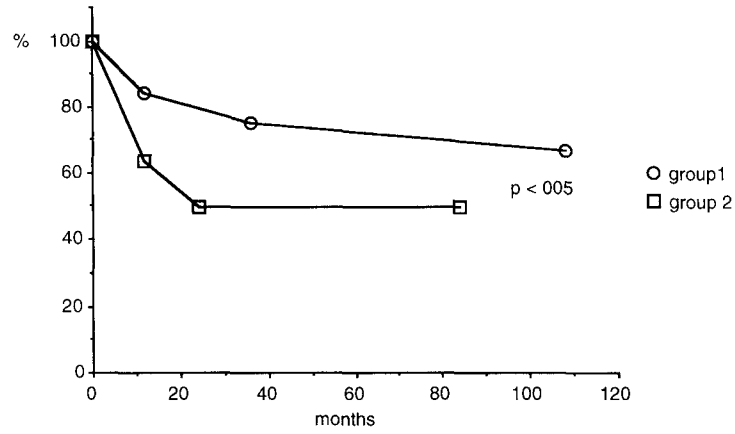

Fig. 1. Actuarial survival curves

Table 2. Plasma carnitine values before and after 6 and 12 months of L-carnitine treatment

		Group 1			Group 2	
before:						
	FC	36.7	(21–60)	n.s.	35.8	(6–54)
	AC	9.28	(3–13)	0.05	27.8	(5–45)
	AC/FC	0.25	(0.09–0.33)	0.03	0.88	(0.4–1.2)
6-months:						
	FC	54.25	(31–72)	n.s.	57	(39–82)
	AC	16.25	(3–30)	0.05	37.5	(14–62)
	AC/FC	0.26	(0.1–0.41)	0.05	0.56	(024–1.04)
12-months:						
	FC	53.6	(39–67)	n.s.	48.3	(17–57)
	AC	16.25	(3–30)	n.s.	19.8	(11–39)
	AC/FC	0.26	(0.1–0.41)	n.s.	0.47	(0.24–0.75)

FC free carnitine (μmol/l); *AC* short chain acylcarnitine (μmol/l); *AC/FC* ratio short-chain acylcarnitine/free carnitine.

Results in group 2 (plasma short-chain acylcarnitine/free carnitine ratio ≥0.4)

Out of 15 children 7 children died and 2 were transplanted, the median time from diagnosis until death was 8 months, after 24 months the cumulative survival rate was 50%. The nonsurvivors in group 2 had a significant higher short-chain acylcarnitine/free carnitine ratio (1.3 (SD 0.74) *v* 0.78 (0.31); $p < 0.04$).

Concentrations of carnitine and short-chain acylcarnitine in plasma before and after six and twelve months of L-carnitine treatment are shown in Table 2.

As listed in Table 3 a significant longer actuarial survival time in the group of children with normal plasma carnitine levels could be evaluated although

Table 3. Actuarial survival time (months) and fractional shortenings (FS %) before starting L-carnitine treatment

	Group 1			Group 2	
Survival time	35.9	(4.5–190)	$p < 0.05$	8	(3–21)
FS	9.8	(2–21)	n.s.	7.3	(2–16)

Table 4. Median values for fractional shortenings (FS %) before and 6 and 12 months after starting L-carnitine treatment

FS before	FS 6 months		FS before	FS 12 months	
Group 1 9.8 (2–21)	n.s.	14 (3–28)	9.8 (2–21)	n.s.	24 (10–32)
Group 2 7.3 (2–16)	$p < 0.01$	18.4 (3–38)	7.3 (2–16)	$p < 0.01$	24.5 (5–41)

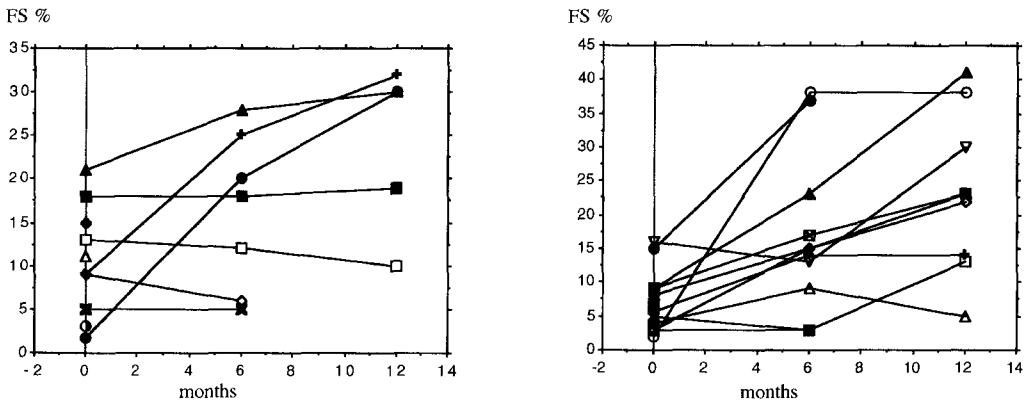

Fig. 2. Comparision of fractional shortenings (FS %) before and 6 and 12 months after starting L-carnitine treatment

the left ventricular function did not differ between the groups at the time of first presentation.

The comparison of fractional shortenings for both groups is shown in Fig. 2. Median values and ranges are listed in Table 4. A significant improvement of left ventricular function 6 and 12 months after presentation and after starting L-carnitine treatment could only be documented in the surviving patients of group 2.

Discussion

Dilated cardiomyopathy (DC) is a rare but serious disorder in childhood that results in a high mortality (Fuster et al., 1981). The natural history and the prognosis for the individual subject still remains unclear. Due to the rare incidence of DC in childhood investigators are faced with statistical problems

on the one hand and on the other hand DC remains a therapeutic challenge because in many cases it lacks specific etiologic factors.

The prognosis of infants and children with DC has varied in previous reports. Overall mortality rates between 16% after 10 year (mean follow-up 4.0 (SD 4.0) years) (Friedman et al., 1991) and 80% at 3 years (mean follow-up 15.6 (23.4) months) (Akagi et al., 1991) have been reported. According to Lewis et al. age at initial presentation did not appear to be a significant predictor of survival (Lewis and Chabot, 1991) which is in contrast to the results reported by Griffin et al. (1988). Authors reported a significant higher mortality in patients >2 years of age at onset. However, the number of patients included in their series was relatively small. There were only 12 children aged >2 years at onset. Additional risk factors of poor outcome in this study included persistent cardiomegaly and the development of significant arrhythmias by Holter electrocardiographic monitoring. Other risk factors reported in literature are elevated left ventricular end-diastolic pressure >25 Torr and complex atrial or ventricular arrhythmias (Lewis and Chabot, 1991), elevated cardiothoracic ratio, reduced left ventricular ejection fraction (Akagi et al., 1991), ST-T wave changes (Friedman et al., 1991) and family history (Griffin et al., 1988; Chen et al., 1990; Berko and Swift, 1987). Friedman et al. concluded that arrhythmias are frequently seen in children with dilated cardiomyopathy but are not predictive of outcome (Friedman et al., 1991), Ciszewski et al. reported no significant differences between survivors and nonsurvivors for any of the following parameters: incidence of severe heart failure, severe ventricular arrhythmias, relative heart volume, echocardiographic left ventricular diastolic diameter and shortening fraction and the hemodynamic parameters of cardiac index, left ventricular ejection fraction, left ventricular end-diastolic pressure, and left ventricular end-diastolic volume index (Ciszewski et al., 1994).

Our study group comprised 29 patients and we too could not obtain significant differences between survivors and nonsurvivors for any of the following parameters: degree of cardiomegaly, echocardiographic left ventricular enddiastolic diameter and shortening fraction at the time of first presentation. The only significant different parameter obtained was the individual plasma carnitine status. In the group with normal plasma short-chain acylcarnitine/free carnitine ratio (group 1) left ventricular function did not improve statistically significant during follow up but patients surviving remained stable for many years. The median time from diagnosis until death was 35.8 months in this group but only 8 months in the other one. After 24 months the cumulative survival rate was 84% in group 1, and 50% in group 2. In the group of children with the pathologic plasma short-chain acylcarnitine/free carnitine ratio (group 2) 50% of patients died within 2 years after clinical onset, the survivors in this group on the other hand showed a significant improvement in left ventricular function during follow-up. The neccessity of intravenous catecholamine treatment also was higher in patients of group 2.

Congestive heart failure is characterized by ventricular dysfunction, and neuro-hormonal and vascular changes. Reduced left ventricular function and

low cardiac output is the main mechanism for reduced tissue oxygen uptake. In this condition there is a slowing-down of intracellular oxidation of fatty acids with subsequent accumulation of acyl-CoA; this, in turn, inhibits adenine-nucleotide translocase and thus prevents the transfer of ATP and ADP from the mitochondria to the cytoplasma and vice versa (Shug, 1975). Any situation where acyl-CoA intermediates are accumulating within the mitochondria will result in a decrease in concentration of free CoA and will further diminish mitochondrial function. The block in the oxidation of acyl CoA compounds increases their esterification with free carnitine to form acylcarnitines. As long as enough free carnitine is available a change in the ratio (acylcarnitine)/(carnitine) reflects an opposite change in the ratio (acyl-CoA)/(CoA) and ensures energy supply (Brass and Hoppel, 1980). In this situation plasma levels for short chain acyl carnitine are elevated, indicating plasma carnitine insufficiency. If carnitine sources are depleted no free carnitine is available for further detoxification of acyl-CoA compounds. Thus carnitine depletion will lead to carnitine deficiency resulting in a combination of insufficiency and deficiency. Children with this combination had by far the most worst prognosis, 4 of 5 children died.

So the amount of acyl carnitine may serve – as long as enough free carnitine is available – as an indirect parameter for the reduction in tissue oxygen uptake or tissue oxygen utilisation and consequently as a parameter for the severity of congestive heart failure.

Numerous previous studies have shown intrinsic abnormalities of skeletal muscle in patients with chronic heart failure (Drexler, 1992), although the underlying mechanisms are still not clear. The work of Marcini et al. (1994) suggests that metabolic abnormalities in patients with heart failure do not result from inadequate O_2 delivery, but rather inadequate O_2 utilization by mitochondria, resulting in impaired muscular endurance related to an enhanced glycolytic metabolism due to the reduced oxidative capacity (Magnusson et al., 1994). Thus, changes in skeletal muscle metabolism may also contribute to pathologic individual plasma carnitine status in infants and children.

Up to now it is not generally accepted that there is a direct correlation between plasma carnitine levels and intramyocardial carnitine concentrations. But one can imagine that a highly increased metabolic demand due to reduced myocardial oxygen uptake may lead to intracellular carnitine depletion. Since myocardial tissue is dependent on fatty acid oxidation as a main energy source, and hence cellular carnitine availability is critical for normal cardiac function it is not surprising that just the group of children with the elevated plasma ratio of esterified to free carnitine before starting treatment had the significantly higher increase in fractional shortening during the twelve months period of L-carnitine treatment.

The benefit of L-carnitine treatment in patients with dilated cardiomyopathy is still contraversial. One of the major problems is to evaluate whether or not a specific adjuvant therapy is of benefical use in a group of children already receiving the well-known anticongestive therapy available presently. To overcome this problem our children were divided into two

groups according to their individual plasma carnitine status, while the anticongestive therapy was the same in both groups. In group one a significant increase in left ventricular function could not be obtained but survival was significantly better. According to the above mentioned mechanism tissue oxygen utilization might be normal in this group, and therefore carnitine depletion may not necessarily occur. So additional carnitine treatment is not expected to improve left ventricular function but may perhaps avoid further deterioration. Our study suggests that the individual plasma carnitine status in children with dilated cardiomyopathy may serve as a risk factor for survival and as an indirect parameter for the degree of congestive heart failure. Further prospective studies are neccessary to answer the question whether L-carnitine treatment might be indicated in children with a plasma carnitine esterified to free ratio above 0.4 to prevent the accumulation of toxic acyl-CoA compounds, to prevent carnitine deficiency and to supply energy production in heart, skeletal and smooth muscle cells.

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Authors' address: Dr. M. Marx, AKH Wien, Universitätsklinik für Kinder- und Jugendheilkunde, Währinger Gürtel 18–20, A-1090 Wien, Austria.

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