Carnitine Deficiency in Surgical Neonates Receiving Total Parenteral Nutrition

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● **Carnitine plays a key role in the oxidation of fatty acids. Most solutions for parenteral nutrition do not contain carnitine. Because endogeneous carnitine synthesis is insufficient in newborns, they are prone to developing a carnitine deficiency when they are dependent on total parenteral nutrition (TPN). Stimulated by the clinical observation of manifest clinical symptoms of carnitine deficiency in one patient, a study of 13 consecutive neonates who received TPN for over 2 weeks was begun. Their plasma carnitine levels before and during carnitine supplementation were determined. All patients had a carnitine intake far below the recommended minimal need of 11 μmol/kg per day. Although only three of them clearly showed clinical symptoms described as carnitine deficiency, carnitine supplementation for all neonates receiving TPN for over 2 weeks is recommended.**

INDEX WORDS: Total parenteral nutrition; carnitine.

CARNITINE IS PRESENT in the diet, notably in milk and meat, and can be synthesized from lysine and methionine in the liver and kidneys when dietary carnitine is low. Carnitine is essential to the intracellular mitochondrial oxidation of long-chain fatty acids, and is necessary for the transfer of fatty acids across the inner mitochondrial membrane.[1]

Neonates, in particular, are dependent on exogenous carnitine supplementation to maintain adequate carnitine concentrations, because of their much higher requirement.[2] The minimal carnitine requirement of the infant has been calculated at 11 μmol/kg per day.[3] Most infant formulas contain carnitine,[4,5] but most solutions for parenteral nutrition do not. Infants receiving total parenteral nutrition (TPN) have lower carnitine concentrations in plasma[6-8] and tissues.[9,10]

The clinical observation of secondary carnitine deficiency on a nutritional basis in one neonate on TPN, initiated a study in 13 infants who received TPN for over 2 weeks. The relationship between plasma carnitine levels and the composition of the nutrition given to these patients was studied. This study included the observation and detection of clinical signs of carnitine deficiency.

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MATERIALS AND METHODS

In a 22-month period (April 1986 to February 1988), plasma carnitine levels were determined in 13 neonates who required TPN for at least 2 weeks postoperatively. At the time of admission, 12 of the 13 patients were less than 4 days old, one patient (G) was 15 days old. The mean duration of gestation was 36 weeks (SD, ±2.7), and mean birth weight was 2,360 g (SD, ±515). Diagnoses at the time of admission included: jejunal atresia (3), necrotizing enterocolitis (3), diaphragmatic hernia (2), gastroschisis (1), VACTERL-syndrome (1), teratoma (1), intrathoracic stomach and pulmonary hypoplasia (1), and diaphragm paralysis following birth trauma (1). Carnitine levels were determined at varying intervals, in combination with routine blood sampling for the determination of liver function, and vitamin and trace element (zinc, copper) levels.

Nutritional Scheme

In this institution, TPN consists of (1) glucose, 5% to 10%, (2) 10% amino acid solution (Aminovenös; Fresenius, Hamburg, West Germany), and (3) lipid solution, 10% (Intralipid; Kabivitrum, Amsterdam, The Netherlands), plus trace elements and vitamins (Pedel, Soluvit, and Vitalipid; Kabivitrum). None of these ingredients contains carnitine.

When a central venous catheter (pediatric Broviac) was used, 15% to 20% glucose and 20% Intralipid were given. The time of introduction as well as the choice of the infant formula (elemental diet) was determined for each child individually. For each child, the energetic value of the given nutrition was calculated (per kilogram body weight per 24 hours), as well as the protein, fat, and carbohydrate intake (in grams per kilogram per day). The carnitine intake was calculated in milligrams per kilogram per day. The contribution of blood transfusions and fresh frozen plasma to the carnitine intake was also determined (plasma, packed cells, and whole blood contain approximately 43, 32, and 38 nmol/mL, respectively.[11]

All infants on TPN routinely receive fresh frozen plasma once a week.

Clinical Observation

Clinical observation was focused on the following symptoms of carnitine deficiency[12-14]: (1) hypotonia; (2) cardiomyopathy in the absence of structural abnormalities on echocardiography; (3) hepatomegaly and abnormal liver function (hypoalbuminemia, coagulation disturbances, and increased liver-specific enzymes, after the exclusion of other causes of cholestatic jaundice); (4) encephalopathy; (5) hypoglycemia (blood glucose level less than 2 mmol/L); (6) dicarboxylic aciduria; (7) failure to thrive; and (8) recurrent infections (sepsis, diarrhea, respiratory infections).

The symptoms were considered to be the result of carnitine deficiency if they could not be explained in any other way, and if they clearly improved after carnitine supplementation.

Investigative Periods

In the study period three stages were distinguished. The first starts on the day of admission and ends on the day of the first plasma carnitine assay (mean, 21 days; range, 16 to 83 days). All plasma carnitine assays are performed as described by Barth et al.[15] In the second stage, the patients have decreased plasma carnitine levels but do not yet receive supplementary carnitine (mean, 28 days; range, 10 to 66 days). In the third stage, carnitine supplementation is given (mean, 25 days; range, 6 to 93 days) after the start of supplementation. In eight of the 13 patients, a second carnitine assay was done at least 1 week after carnitine supplementation.

Supplementation

L-carnitine supplementation (Sigma, Hamburg, West Germany) was given in random doses of 50 and 100 mg/kg per day. Patients in whom partial oral nutrition was started were given carnitine orally as well.

CASE REPORT

Patient A (Excluded From Study)

A boy (37.5 weeks' gestation; birth weight, 3,260 g) presented with a distended abdomen and was admitted with a diagnosis of meconium peritonitis. Laparotomy showed ileal atresia as well. The atretic segment was resected and ileostomies were made. Parenteral nutrion was started postoperatively.

In the second week, his clinical condition deteriorated and he developed generalized hypotonia, hyperbilirubinemia, and cardiac failure.

Thoracic x-rays showed an increased cardiothoracic ratio of 0.7. Electrocardiography showed signs of biventricular hypertrophy, and echocardiography demonstrated diminished ventricular contractility. Supplementary laboratory investigations showed only a slight increase in serum transaminases. Because of the suspicion of sepsis, broad spectrum antibiotics were started in combination with cardiotonic drugs. However, his clinical condition did not improve. Metabolic urinalysis by means of gaschromatography showed an increased excretion of dicarboxylic acids (C6-C8-C10).

In the 4th week of life, L-carnitine suppletion (100 mg/kg per day) was started. The clinical condition improved quickly. Hypotonia disappeared, and reevaluation of chest x-rays, ECG, and echocardiography showed normal findings. In the 7th week, the plasma-free carnitine concentration was 23.6 μmol/L, which is a low-to-normal level. In the following week, closure of his ileostomies was performed without problems and the patient was discharged from the hospital at 11 weeks of age. Now 4 years of age, he is doing well. His height follows the 50th percentile, and his weight follows the 3rd percentile.

RESULTS

The results of the caloric intake and carnitine levels of all 13 patients under study are summarized in Tables 1, 2, and 3.

Table 1. Calculated Energetic Value and Intake of Carbohydrates, Fat, and Carnitine of the Nutrition Before (Period 1) and During (Period 2) Proven Carnitine Deficiency

Patient	Duration (days)	Type of Feeding	Energy (kCal/kg/day)	Carbohydrates (g/kg/day)	Fat (g/kg/day)	Carnatine (mg/kg/day)
			Period 1			
B	19	(TPN/IF)	54.4	7.23	2.08	0.79
C	35	(TPN)	70.9	11.70	1.92	0.01
D	83	(TPN/IF)	59.1	9.27	3.09	1.25
E	20	(TPN)	78.0	13.80	1.79	0.03
F	16	(TPN)	65.5	11.44	1.37	0.07
G	17	(TPN)	42.5	6.02	1.11	0.13
H	64	(TPN/IF)	99.6	10.71	5.27	2.96
I	37	(TPN)	61.7	8.26	1.89	0.26
J	48	(TPN/IF)	92.7	12.15	3.77	1.08
K	20	(TPN)	59.9	9.35	1.73	0.02
L	21	(TPN)	91.9	15.37	2.27	0.06
M	35	(TPN/IF)	99.2	11.80	4.80	1.29
N	21	(TPN)	71.0	11.16	2.80	0.06
			Period 2			
B	19	(IF)	100.3	13.59	4.30	2.51
C	12	(IF)	111.9	12.80	5.53	1.72
D	31	(TPN/IF)	71.0	9.38	2.78	0.25
E	35	(TPN)	86.6	15.56	1.97	0.02
F	12	(TPN/IF)	116.3	15.59	3.27	0.58
G	11	(TPN/IF)	108.4	19.97	2.28	0.25
H	10	(TPN)	91.1	16.75	1.86	0.03
I	43	(TPN/IF)	99.2	12.75	4.35	1.43
J	66	(TPN/IF)	93.8	12.94	3.72	1.05
K	36	(TPN)	74.1	12.92	1.73	0.03
L	21	(IF)	98.1	10.38	5.20	1.43
M	42	(TPN/IF)	139.5	18.83	5.38	1.29
N	28	(TPN/IF)	117.3	13.52	4.62	1.43

Abbreviations: TPN, total parenteral nutrition; IF, infant formula.

Table 2. Plasma Carnitine Levels in Patients Without Supplementation

Patient	Carnitine Assay		
	Day	TC	FC
B	19	13.0	8.5
F	16	14.3	10.7
J	45	11.2	8.5
M	35	7.8	5.8
N	21	13.3	6.6

NOTE. Carnitine concentrations are expressed in μmol/L.
Abbreviations: TC, total carnitine; FC, free carnitine.

The mean caloric intake in period 1 was 72.8 kilocalories per kilogram per day (±18.3) and in period 2, 100.6 kilocalories per kilogram per day (±18.6). Four to five patients received hypocaloric intake in the immediate postoperative phase (period 1). The mean carnitine intake both in period 1 and period 2 was far below the minimal need of 11 μmol/kg per day.[3] The mean plasma total carnitine concentration was 11.5 μmol/L (±3.6). The mean free carnitine concentration in plasma was 7.9 μmol/L (±2.2) (Table 1).

Clinical Symptoms

Hypotonia was found in three patients (B, H, and I). In patient B, hypotonia was part of a double-sided pyramidal syndrome following postnatal asphyxia. In patient H, myopathy persisted after carnitine therapy. In this patient, the persistent myopathy is still unexplained. Muscle biopsy showed a low-to-normal carnitine concentration. Only in patient I could the hypotonia be attributed to a carnitine deficiency. Repeated ultrasounds and electroencephalography did not show intracranial abnormalities, and no signs of other metabolic derangements were found. The patient suffered from liver dysfunction, which disappeared after carnitine supplementation.

Patients J and N both developed cardiomegaly; however, both had a ventricular septal defect with left-to-right shunting. In patient K, a heart enlargement was observed on x-ray. No structural abnormalities nor other metabolic diseases were found. The dilatation of the heart disappeared after supplementation with carnitine.

Hypoglycemia was never found in our patients. In seven of the 13 patients, the excretion of organic acids was investigated by gaschromatography; no abnormalities were found.

Failure to thrive and recurrent infections were frequent in the patients studied, due to central venous lines, abdominal wounds, and/or immunosuppression. In none of the patients could these symptoms be attributed to carnitine deficiency.

Supplementation

In patients B, F, J, M, and N, no second carnitine assay was performed (Table 2). These patients were discharged from the hospital before the result of the first assay was known, but they had no symptoms of carnitine deficiency that would have prevented their discharge. Table 3 shows a strong correlation between the second carnitine assay and the dosage of the supplementation ($r = .871$, $P = .005$; Pearson test).

DISCUSSION

Carnitine deficiency can be divided into two groups, (1) a primary systemic carnitine deficiency of yet undetermined cause,[1] and (2) a secondary nutritional carnitine deficiency following protein-calorie malnutrition and malabsorption in infants receiving carnitine-free TPN.[16] The normal total carnitine plasma concentration in the newborn is 30.7 μmol/L (±2.6).[16] All 13 neonates who received TPN for more than 2 weeks had a plasma carnitine deficiency. With a total carnitine in plasma under 20 μmol/L, a tissue deficiency may be assumed.[17] Although the carnitine level in this case report is unknown before substitution, the diagnosis of a clinical manifestation of carnitine deficiency was considered justified in view of the clinical picture and its disappearance after treatment with carnitine.

Identification of symptoms that could be considered

Table 3. Plasma Carnitine Concentrations and Supplementation

Patient	First Carnitine Assay (μmol/L)			Supplementation (mg/kg/day)		Second Carnitine Assay (μmol/L)	
	Day	TC	FC	Day	Dose	Day	FC
C	35	10.6	7.9	47	100	70	66.9
D	83	12.6	9.2	114	100	207	74.8
E	20	5.9	4.2	55	50	80	34.0
G	17	20.7	12.9	38	50	66	29.6
H	64	11.1	8.2	74	100	80	47.8
I	37	8.1	6.3	80	100	99	46.5
K	20	11.7	7.1	56	50	89	34.6
L	21	11.5	8.9	35	50	42	24.0

Abbreviations: TC, total carnitine; FC, free carnitine.

characteristic for carnitine deficiency was attempted. Applying this method, it was found that two other patients had symptoms that could be ascribed to carnitine deficiency as well: patient I had generalized hypotonia and liver dysfunction, and patient K had cardiomegaly.

The lack of clinical symptoms during TPN, with plasma carnitine deficiency, can partly be explained by a continuous supply of carbohydrate,[18] either by infusion or by a later frequent feeding regimen (continuous drip feeding). For this reason, no hypoglycemia was found. In addition, there was no increase in urinary dicarboxylic acids as a sign of defective mitochondrial beta oxidation of fatty acids.

Enteral feeding was generally started using a formula containing peptides and fat, consisting of 50% of medium chain triglycerides (Pepti Jr; Nutricia, Zoetermur, The Netherlands). The oxidation of medium chain fatty acids is carnitine-independent.[19]

Neonates who receive TPN for more than 15 days will develop carnitine deficiency.[3] Two of the 13 carnitine deficient patients in this study showed symptoms of carnitine insufficiency. Patient A is also considered to be an example of carnitine defficiency. Therefore, to prevent any possible occurrence of this serious syndrome, giving a supply of carnitine (3 to 10 mg/kg per day) to all neonates receiving TPN for more than 2 weeks is recommended.

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