0148-6071/87/1101-0088$02.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 11, No. 1

Printed in U.S.A.

Improvement of Liver Function Tests by Administration of L-Carnitine to a Carnitine-Deficient Patient Receiving Home Parenteral Nutrition: A Case Report

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Carnitine deficiency is a rare but often treatable cause of abnormal fatty acid metabolism. Carnitine, a quaternary amine involved in the transport of long chain fatty acids into mitochondria for oxidation and production of adenosine triphosphate (ATP), is normally synthesized in human liver and kidney from the amino acids lysine and methionine.[1] Dietary sources of carnitine include red meat and, to a lesser extent, chicken.[2] Both endogenous and exogenous carnitine are transported via the blood to skeletal and cardiac muscle. It is unclear whether biosynthesis of carnitine alone suffices to meet human requirements under normal physiologic conditions.

Primary carnitine deficiency may result from a genetic defect impairing synthesis of liver carnitine or transport of carnitine through the cell membrane.[3] More commonly, carnitine deficiency may arise secondary to an acquired disorder, eg, alcoholic cirrhosis,[4] hemodialysis,[5,6] or long-term total parenteral nutrition (TPN).[7,8] In these latter cases, carnitine may not be adequately synthesized, retained, or provided, respectively.

Due to improved iv formulations, delivery systems, and catheter care, home TPN patients have experienced greater quality and longevity of life in recent years. Because carnitine is considered an investigational new drug by the Food and Drug Administration, it is not routinely added to TPN formulations. There is growing concern among clinical nutritionists that carnitine should be considered as an essential nutrient for critical care patients receiving long-term TPN.[9] Decreased plasma carnitine levels have been observed in adult surgical patients within the first month of TPN administration.[7] More recently, a patient placed on long-term TPN developed hyperbilirubinemia and generalized skeletal muscle weakness associated with plasma carnitine deficiency.[8] The investigators postulated that transport and oxidation of fatty acids in hepatocyte mitochondria are compromised in carnitine-deficient patients, and that the resultant increase in triglyceride formation from fatty acids in the cytosol may lead to fatty infiltration and impairment of liver function.

Received for publication, March 18, 1986.
Accepted for publication, June 23, 1986.
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In this report, we describe a similar case in a home TPN patient who, in the presence of tissue and plasma carnitine deficiency, developed abnormal liver function tests. Although this patient did not respond to D,L-carnitine administered orally over a 1-week period, she did respond to L-carnitine administered intravenously over a 2-week period.

CASE REPORT

The patient was a 37-yr-old white female with a 10-yr history of peptic ulcer disease managed with cimetidine therapy. Past medications included prednisone for treatment of rheumatoid arthritis. She did not receive prednisone during the year that we followed her clinical course. In May of 1983, she underwent surgical exploration for a suspected duodenal ulcer, and at operation was found to have a thrombosis of the superior mesenteric artery necessitating resection of 50% of the small bowel. Two days later she was reexplored and the bowel was resected from 6 inches distal to the ligament of Treitz to the midtransverse colon. She was started on total parenteral nutrition. This patient continued to have abdominal pain and was transferred to the New England Deaconess Hospital where angiography confirmed continued mesenteric ischemia. At admission, she weighed 35.4 kg (75% of IBW) with a height of 155 cm. Her arm muscle circumference (AMC) was 16.2 cm (<5th percentile) and she had a triceps skinfold (TSF) of 4 mm (<5th percentile). In July 1983, a renosplenic artery bypass was successfully performed to increase the blood supply to the ischemic area. A cholecystectomy also was performed at this time. She was eventually discharged to home on August 9, 1983, on a nocturnal cycle of parenteral nutrition, containing 75 g of protein and 450 g of dextrose per day with 50 g of soybean oil emulsion (Travamulsion, Travenol Laboratories, Deerfield, IL) once per week. Her oral intake of food was less than 500 kcal/day. At this time, her liver function tests (SMAC-1, Technicon Instruments, Tarrytown, NY) were mildly elevated (Table I): total serum bilirubin = 2.2 mg/dl (normal = 0.2–1.2), direct bilirubin = 1.2 mg/dl, alkaline phosphatase = 208 mIU/ml (normal = 16–106), and aspartate amino transferase (AST) was 35 mIU/ml (normal = 10–45). The serum triglyceride level was 108 mg/dl (normal = 50–180).

TABLE I
Biochemical analyses of patient's plasma

Test (normal range)	Date							
	8/9/83	8/22/83	3/2/84	4/6/84	5/10/84	5/18/84	6/7/84	6/8/84
Total/direct bilirubin (0.2–1.2/0–0.8 mg/dl)	2.2/1.2	0.7/–	5.5/3.3	8.9/5.3	17.0/10.0	15.1/–	9.9/–	5.6/–
Alkaline phosphatase (16–106 mIU/ml)	208	110	162	232	162	125	108	
AST (SGOT) (10–45 mIU/ml)	35	58	148	270	165	167	130	
Triglycerides (50–180 mg/dl)	108		142	493		381	380	78
ALT (SGPT) (0–35 mIU/ml)				243	103	79		
Total/free carnitine (30–73/19–60 nmol/ml)				13.7/7.8		11.3/9.3	81/64	

This patient was readmitted on August 18, 1983, with Hickman catheter sepsis. After its replacement, she was given a low dose of Coumadin (1 mg/day) because of a low antithrombin III level.[10] On hospital discharge, her total bilirubin was 0.7 mg/dl, alkaline phosphatase was 110 mIU/ml, and AST was 58 mIU/ml. She remained on the same parenteral nutrient solution, except that on October 20, 1983, the lipid formula was changed to 20 g twice per week of safflower oil emulsion (Liposyn, Abbott Laboratories, N. Chicago, IL) due to complaints of nausea and abdominal pain with the lipid infusion. This abdominal pain resolved.

In November 1983, the serum bilirubin was 1.3 mg/dl, and by March 1984, had risen to 5.5 mg/dl (direct = 3.3). Other liver function tests also were elevated: alkaline phosphatase = 162 mIU/ml, AST = 148 mIU/ml, and triglycerides = 142 mg/dl. Since this patient led a relatively sedentary lifestyle, the exclusion of potentially excess calories was warranted. The dextrose was removed from the TPN and replaced with 40 g of safflower oil emulsion each night in an attempt to limit hepatic lipogenesis. In April 1984, the total bilirubin had increased to 8.9 mg/dl (direct = 5.3), alkaline phosphatase was 232 mIU/ml, AST was 270 mIU/ml, alanine aminotransferase (ALT) was 243 mIU/ml (normal = 0 –35 mIU/ml), and serum triglycerides had risen to 493 mg/dl. Liver biopsy showed early micronodular cirrhosis with moderate fatty changes and slight acute and chronic cholangitis. One hundred grams of dextrose were returned to her TPN formula, cimetidine was discontinued, and ranitidine was begun.

By May 10, 1984, her serum bilirubin had increased further to 17.0 mg/dl (direct = 10.0), although alkaline phosphatase, AST, and ALT had decreased (162, 165, and 103 mIU/ml, respectively). Plasma carnitine levels drawn in April returned showing a total carnitine of 13.7 nmol/ml (normal = 30–73) and free carnitine was 7.8 nmol/ml (normal = 19–60).[11] On May 14, 1984, the patient was started on oral D,L-carnitine elixer, 1 g/day.

On May 18, 1984, she returned to the hospital with catheter sepsis. She was maintained on TPN at the same caloric level even though her oral intake of food was approximately 1200 kcal/day. Anthropometric measurements were: weight = 36.4 kg (76% of IBW), AMC = 14.7 cm (<5th percentile), and TSF = 4 mm (<5th percentile). Liver function tests were: total bilirubin = 15.1 mg/dl, alkaline phosphatase = 125 mIU/ml, AST = 167 m IU/ml, ALT = 79 m IU/ml and triglycerides = 381 mg/dl. Plasma total carnitine was 11.3 nmol/ml and free carnitine was 9.3 nmol/ml. Her plasma glucose between May 10, 1984 and May 27, 1984 was 79 ± 14 (mean ± SD) mg/dl (normal = 60–110).

For the first week in the hospital, she received no carnitine and her bilirubin increased to 17.9 mg/dl. An abdominal ultrasound and CT scan on May 25, 1984, showed no dilation of the common bile duct. Emergency permission was obtained from the Food and Drug Administration to administer intravenous L-carnitine; on May 26th, intravenous treatment with L-carnitine (AH Robins, Richmond, VA), 1 g/day, was begun. Over the next 12 days, her liver function tests markedly improved. On June 7, the total bilirubin had decreased to 9.9 mg/dl, while alkaline phosphatase was 108 mIU/ml and AST was 130 mIU/ml. Serum triglycerides remained high (380 mg/dl). Plasma carnitine was slightly above the normal range: total = 81 nmol/ml and free = 64 nmol/ml. On this day she underwent pseudocyst gastrostomy (located in the head of the pancreas) and gastric ulcer repair. A liver biopsy taken at this time showed minimal fatty infiltration. Tissue carnitine levels were determined: total carnitine was 2.81 nmol/mg (normal = 5–20 nmol/mg) and free carnitine was 2.49 (normal = 3–14 nmol/mg). On June 8th, the serum bilirubin was 5.6 mg/dl and triglycerides were 78 mg/dl.

The patient underwent surgery on the following day for control of postoperative hemorrhage due to preexisting poorly defined coagulopathy. She continued to hemorrhage and eventually expired on June 9, 1984. Postmortem examination showed perigastric and peripancreatic abscesses. The pancreatic duct was dilated and patent throughout. Hepatomegaly (2500 g) with massive necrosis and cholestasis was noted, although there were no remarks regarding the biliary tract. There was stenosis of the superior mesenteric artery and total occlusion of the celiac and inferior mesenteric arteries. The autopsy report attributed liver dysfunction to vascular insufficiency of the liver, carnitine deficiency, and possible mechanical obstruction by the pseudocyst, although neither at laboratory evaluation prior to death nor at autopsy was this possibility documented.

DISCUSSION

A primary role of carnitine in fat metabolism is to facilitate the transfer of long chain fatty acids into the mitochondria for oxidation and generation of ATP. In the absence of carnitine, fatty acids cannot be oxidized, and the organism is totally dependent upon carbohydrates and proteins for energy. This shift in use of metabolic fuels results in two major clinical characteristics of carnitine deficiency: (1) symptomatic hypoglycemia without ketone body production once the body's carbohydrate stores are depleted, and (2) fatty infiltration of muscle, liver, and nerves as the nonutilizable fatty acids are deposited as triglycerides.[12]

Carnitine deficiency states are considered to be "primary" when they are not associated with any secondary disorder which might deplete the body's stores.[13] A primary deficiency is due to an inborn error of metabolism and could arise from: (1) a defect in the carnitine biosynthetic pathway; (2) an inability to transport carnitine into or out of cells, or (3) increased metabolism or inactivation due to increased activity of carnitine degradative pathways. When the deficiency is observed only in muscle tissue, the probable cause is a defect in carnitine transport.[14] The characteristics of this myopathic form are increased lipid accumulation in type I muscle fibers, muscle weakness, and myoglobinuria. The two mitochondrial enzymes that catalyze the formation of acylcarnitine, transport this substrate across the mitochondrial membrane, and release acyl coenzyme A are carnitine palmitoyl transferase I and II (CPTs I and II), respectively.[15] Several cases of a possible genetic defect in the formation of CPTs I and II have been reported.[3,16]

If several organs are deficient in carnitine, the disorder is "systemic." This deficiency is characterized by low plasma carnitine levels, triglyceride accumulation in hepatic, neuronal, and muscle tissues, and evidence of skeletal muscle weakness and cardiac myopathy.[17] In more severe cases, hyperammonemia, encephalopathy, hepatomegaly, hypoglycemia without ketosis, elevated liver function tests, and coma are observed.[12] In systemic deficiency, the inborn error of metabolism appears to be at the level of carnitine biosynthesis in the liver and kidney.[17]

Treatment of primary carnitine deficiency includes oral carnitine supplementation and, in some cases, prednisone administration to facilitate carnitine transport across cell membranes.[17] Diets with a high carbohydrate and low fat content should be used to prevent hypoglycemia and mobilization of adipose fat. The use of medium chain triglycerides (MCT) as a source of fat calories has been used successfully, since MCTs are not dependent upon carnitine for passage through cell membranes.[18] The use of MCTs may also be indicated as a substitute for carbohydrate calories if hepatic lipogenesis and steatosis is suspected. MCTs are not elongated or desaturated by the liver and therefore do not promote triglyceride formation and deposition.[18] High carbohydrate intakes in TPN patients may be contraindicated if liver function tests rise in the absence of other causes for hepatic dysfunction. As discussed in our case report, the patient's intake of carbohydrate was decreased to prevent lipogenesis from excess carbohydrate calories. Given her sedentary lifestyle, the total amount of nonprotein calories was lowered to better approximate her daily caloric expenditure.

Secondary states of carnitine deficiency result from an inadequate intake, increased loss or, in the case of newborn infants, inability to make carnitine due to immature development of the carnitine biosynthetic pathways.[19] Hemodialysis patients have an increased requirement for carnitine due to losses during dialysis. Plasma carnitine levels drop as much as 80% during dialysis treatment.[20] L-Carnitine supplementation with dialysis has successfully resolved postdialysis asthenia, muscle cramps, and weakness,[6] decreased hypertriglyceridemia while increasing high density lipoprotein cholesterol levels,[5] and improved the chronic anemia associated with renal failure.[21]

Carnitine deficiency may occur secondary to cirrhosis and/or malnutrition. Rudman et al[4] found low serum carnitine levels (36 nmol/ml) in cirrhotic patients who were malnourished (TSF = 23% of standard, plasma albumin = 1.4 g/dl, midarm muscle circumference = 71% of standard), whereas mildly malnourished cirrhotics (TSF = 90%, plasma albumin = 2.9 g/dl, midarm muscle circumference = 84%) had normal serum carnitine levels (66 nmol/ml). Dietary supplementation of the cirrhotic patients with lysine and methionine did not improve serum carnitine levels, indicating that cirrhotic patients may have a metabolic defect for carnitine biosynthesis. A more recent report stated that cirrhotic patients required 900 mg/day of supplemental carnitine po to attain normal serum levels.[22] Our malnourished patient may have had a similar defect with a reduced capacity to form endogenous carnitine.

Fuller and Hoppel[23] found elevated serum carnitine levels in patients with cirrhosis, in apparent contradiction to the results reported by Rudman. These differences may be resolved on the basis that Fuller's patients were not as malnourished (albumin 2.9 *vs* 1.4 g/dl, triceps skinfold 60 *vs* 23% of standard), had less liver dysfunction (bilirubin = 2.3 *vs* 6.1 mg/dl, prothrombin time = 15 *vs* 19 sec), and were consuming diets containing more carnitine. Other investigators have found that lysine administered to well-nourished subjects increased plasma carnitine levels, but undernourished subjects maintained basal carnitine levels,[24] supporting the hypothesis that carnitine biosynthesis in malnourished subjects may be impaired. Fuller's patients also had a history of alcohol abuse and had a median stay of 15 days in the hospital. Sachan et al[25] has shown that alcohol induces sequestration of carnitine in the liver. It is possible that a 2-week hospitalization period with abstinence from alcohol allowed release of sequestered carnitine from the liver, thereby accounting for the elevated plasma levels seen in Fuller's patients.

Adult patients receiving TPN who have a marginal ability to synthesize carnitine are at risk of developing carnitine deficiency.[26] During TPN, major organs other than liver have equivalent access to the nutrients, unlike the "first-pass" effect of the liver with enteral feeding. The net effect may be a decreased availability of methi-

onine and lysine for carnitine biosynthesis by the liver. Patients with short gut syndrome or Crohn's disease who are fed parenterally may not be able to absorb orally administered carnitine. It appears that our patient was unable to absorb the orally administered carnitine, since plasma levels did not change after one week. However, a complicating factor was that the carnitine used contained the metabolically inactive D-isomer form as well as the active L-form. Information regarding the proportion of each was not available. Investigators who administered D,L-carnitine intravenously reported the presence of a myasthenia-like syndrome which was resolved when L-carnitine was administered.[27] Worthley et al[8] were able to establish normal plasma carnitine levels in a patient maintained on TPN for 1 yr by intravenously administering 400 mg of L-carnitine daily. A significant rise in plasma carnitine level occurred within 4 days at this dosage. When we retested our patient after 12 days of intravenous administration of L-carnitine at 1 g/day, the plasma carnitine was slightly above the normal range. Liver tissue analysis, however, demonstrated that hepatic carnitine levels were slightly below normal at that time. Carnitine administration did improve liver morphology by decreasing hepatocyte fatty infiltration. The concomitant decrease in serum bilirubin, triglycerides, and amelioration of enzyme levels corroborated the improvement in liver function. The presence of a pancreatic pseudocyst probably was not a principal factor elevating the values of the liver function tests since: (1) the ultrasound and CT scan of the common bile duct did not reveal any dilatation, (2) the pancreatic duct was found to be patent at postmortem examination, and (3) the liver function tests improved during the 12 days of iv carnitine administration preceding the pseudocyst gastrostomy.

Hypoglycemia was not biochemically evident in our patient, primarily because her TPN schedule did not provide sufficient time for the fasting state to develop. This patient was relatively sedentary, and the amount of calories administered as TPN probably were above her actual caloric needs. Excess calories would promote glycogen storage as well as fat deposition in the liver. There was probably sufficient glycogen synthesis and release between TPN cycles to carry her through the brief fasting period each day, and thus preclude the development of hypoglycemia. In spite of her oral intake of food in addition to her TPN, this patient gained only 1 kg of weight between July 1983 and May 1984. It is not known whether her oral intake of carbohydrates had any effect on the prevention of hypoglycemia; given the small weight gain, it is unlikely that any substantial amount of nutrients, including carbohydrates, were absorbed. This attests further to the ineffectiveness of orally administered carnitine.

Based upon the postmortem examination of our patient, hepatomegaly and necrosis stemming from chronic hepatic ischemia were major factors in the etiology of this patient's coagulopathy and metabolic disturbances. Carnitine deficiency arising from reduction of exogenous and endogenous sources of this nutrient further exacerbated her liver dysfunction. The extent of the contribution of carnitine deficiency toward liver dysfunction is unknown. Hepatomegaly and elevated plasma levels of liver enzymes have been observed in other carnitine-deficient patients.[8,12] The development of hyperbilirubinemia with a high conjugated bilirubin characteristic of cholestasis in a home TPN patient with carnitine deficiency also has been reported.[8] In these cases, administration of carnitine ameliorated the liver function test results and, presumably, liver function itself.

In summary, a case is presented of a patient with short gut syndrome and vascular insufficiency of the liver who was placed on long-term TPN. Progressive liver dysfunction was associated with carnitine deficiency. Administration of 1 g of L-carnitine/day iv ameliorated liver function tests in this patient within 2 weeks. Factors considered to be important in the development of carnitine deficiency in this patient were: insufficient oral intake, reduced absorption due to short gut syndrome, prolonged parenteral feeding with a carnitine-free TPN solution, and possible impairment of carnitine biosynthesis as liver function deteriorated. Since most of these factors often are operative in home TPN patients, carnitine deficiency may be expected to develop with some degree of frequency as this feeding therapy is applied more widely.

ACKNOWLEDGMENT

This work was supported in part by Grant 35494 awarded by the National Institute of Arthritis, Metabolism, Digestive, and Kidney Diseases.

REFERENCES

1. Rebouche CJ: Comparative aspects of carnitine synthesis in man. IN Carnitine Biosynthesis, Metabolism, and Functions, Frenkel RA, McGarry JD (eds). Academic Press, New York, 1980, pp 57–67
2. Mitchell ME: Carnitine metabolism in human subjects. 1. Normal metabolism. Am J Clin Nutr 31:293–306, 1978
3. Mitchell ME: Carnitine metabolism in human subjects. 3. Metabolism in disease. Am J Clin Nutr 31:645–659, 1978
4. Rudman D, Sewell CW, Ansley JD: Deficiency of carnitine in cachectic cirrhotic patients. J Clin Invest 60:716–723, 1977
5. Vacha GM, Giorcelli MD, Siliprandi N, et al: Favorable effects of L-carnitine treatment on hypertriglyceridemia in hemodialysis patients: Decisive role of low levels of high-density lipoprotein cholesterol. Am J Clin Nutr 38:532–540, 1983
6. Bellinghieri G, Savica V, Mallamace A, et al: Correlation between increased serum and tissue L-carnitine levels and improved muscle symptoms in hemodialyzed patients. Am J Clin Nutr 38:523–531, 1983
7. Hahn P, Allardyce DB, Frohlich J: Plasma carnitine levels during total parenteral nutrition of adult surgical patients. Am J Clin Nutr 36:569–572, 1982
8. Worthley LI, Fishlock RC, Snoswell, AM: Carnitine deficiency with hyperbilirubinemia, generalized skeletal muscle weakness and reactive hypoglycemia in a patient on long-term total parenteral nutrition: Treatment with intravenous L-carnitine. JPEN 7:176–180, 1983
9. Tao RC, Yoshimura NN: Carnitine metabolism and its application in parenteral nutrition. JPEN 4:469–486, 1980
10. Bern MM, Bothe A Jr, Bistrian BR, et al: Effects of low dose warfarin on antithrombin III in morbidly obese patients. Surgery 94:78–83, 1983
11. Rebouche, CJ, Engel AJ: Carnitine metabolism and deficiency syndromes. Mayo Clin Proc 58:533–540, 1983

12. Chapoy PR, Angelini C, Brown WJ et al: Systemic carnitine deficiency: A treatable inherited lipid-storage disease presenting as Reye's syndrome. N Engl J Med 303:1389–1394, 1980
13. Rebouche CJ, Engel AG: Primary systemic carnitine deficiency: I. Carnitine biosynthesis. Neurology 31:813–818, 1981
14. Engel AG, Angelini C: Carnitine deficiency of human skeletal muscle with associated lipid storage myopathy: A new syndrome. Science 179:899–902, 1973
15. Kopec B, Fritz IB: Properties of a purified carnitine palmitoyltransferase and evidence for the existence of other carnitine acyltransferases. Can J Biochem 49:941–948, 1971
16. DiMauro S, DiMauro P: Muscle carnitine palmityl transferase deficiency and myoglobinuria. Science 182:929–931, 1973
17. McGarry JD, Foster DW: Systemic carnitine deficiency. N Engl J Med 303:1413–1415, 1980
18. Bach AC, Babayan VK: Medium chain triglycerides: An update. Am J Clin Nutr 36:950–962, 1982
19. Borum P: Possible carnitine requirement of the newborn and the effect of genetic disease on the carnitine requirement. Nutr Rev 39:385–390, 1981
20. Bartel LL, Hussey JL, Shrago E: Perturbation of serum carnitine levels in human adults by chronic renal disease and dialysis therapy. Am J Clin Nutr 34:1314–1320, 1981
21. Trovato GM, Ginardi V, DiMarco V, et al: Long term L-carnitine treatment of chronic anemia of patients with end-stage renal failure. Curr Ther Res 31:1042–1049, 1982
22. Shapira G, Rudman D, Chawla, RK: Cysteine, tyrosine, choline and carnitine supplementation during total parenteral nutrition (abstract). Clin Res 32:634A, 1984
23. Fuller RK, Hoppel CL: Elevated plasma carnitine in hepatic cirrhosis. Hepatology 3:554–558, 1983
24. Siddiqui LK, Bamji MS: Lysine-carnitine conversion in normal and undernourished adult men: Suggestion of a nonpeptidyl pathway. Am J Clin Nutr 37:93–98, 1983
25. Sachan DS, Rhew TH, Ruark RA: Ameliorating effects of carnitine and its precursors on alcohol-induced fatty liver. Am J Clin Nutr 39:738–744, 1984
26. Chawla RK, Berry CJ, Kutner MH, et al: Plasma concentrations of transsulfuration pathway products during nasoenteral and intravenous hyperalimentation of malnourished patients. Am J Clin Nutr 42:577–584, 1985
27. Bazzato G, Coli U, Landini S, et al: Myasthenia-like syndrome after D,L- but not L-carnitine. Lancet 1:1209, 1981