Clinical Nutrition (1992) **11**: 368–372

CASE REPORT

Late onset primary systemic carnitine deficiency exacerbated by carnitine-free parenteral nutrition

A. L. BUCHMAN*, H. V. VINTERS†, S. DIETHELM‡, M. E. AMENT* and M. A. VERITY†

Division of Pediatric Gastroenterolgy/Nutrition, †Division of Neuropathology, ‡Division of Anatomic Pathology, UCLA Medical Center, Los Angeles, CA, USA (Correspondence and reprint requests to A. L. Buchman, Division of Digestive Diseases, Emory University School of Medicine, P. O. Drawer AL, Atlanta, GA 30322, USA)

ABSTRACT — We describe a 21-year-old male with previously normal plasma total and free carnitine levels who developed a deficiency manifest by decreased plasma and muscle total and free carnitine, decreased urine carnitine, severe hepatic steatosis, mediastinal lipomatosis, progressively impaired triglyceride clearance, myopathy and intermittent hypoglycemia. This case demonstrates that systemic carnitine deficiency may occur in some patients receiving long term carnitine-free TPN. Carnitine may be an essential element of the diet in this patient population.

Case report

The patient was a 21-year-old male who developed progressive ataxia with limb incoordination starting at the age of 13. By the age of 16 his muscle strength had become diffusely and mildly weakened. There was no consanguity or family history of neuromuscular or hepatic disease. An initial electromyogram (EMG) was normal although nerve conduction studies showed markedly reduced amplitudes of lower extremity axon potentials. Plasma carnitine levels are shown in the Table. In July 1987, valproic acid, which had been started 3 months previously because of a seizure disorder, was discontinued because of encephalopathy and hepatic toxicity. At this time no volatile or nonvolatile organic acids or methylmalonic acid were detected in the urine. Carnitine levels were determined in October 1988 and April 1989 (Table 1).

In 1988 chronic abdominal pseudoobstruction was diagnosed on the basis of a delayed ^{99}Tc gastric emptying study, delayed intestinal transit with a dilated duodenum seen on a gastrointestinal radiographic series, and his clinical symptoms. Because of frequent exacerbations, the patient was started on nightly total parenteral nutrition (TPN) in May 1989 although he continued to eat when the pseudobstruction was in remission. TPN supplied 100% of his daily caloric and protein requirements. This consisted of 2 l of a 20% dextrose solution, 3.5% amino acids including 1.4g methionine and 2.03g lysine/l (Travasol, Baxter Travanol, Deerfield IL, USA), electrolytes, trace elements and multivitamins including 4 mg pyridoxine, 40 mg niacin and 100 mg ascorbate per day. 250 cc of Intralipid 20% (Kabi Vitrum, Alameda CA, USA) was infused 3 times weekly. The patient was unable to walk by this time because of weakness and ataxia.

In June 1989 an EMG showed increased irritability, abundant spontaneous fibrillation potentials, positive

Table 1 Plasma carnitine and triglyceride levels

	Total Carnitine nmo/ml Normal 55–103	Free Carnitine nmo/ml Normal 31–82	Esterified Carnitine nmo/ml	Triglyceride (mg/dl)
May, 1987	65.3	65.3	0	N/A
Oct, 1988	58.0	48.8	9.2	N/A
Apr, 1989	30.0	28.0	2.0	N/A
Sept, 1989	N/A	N/A	N/A	148
Early Aug, 1990	22.0	21.0	1.0	183
Late Aug, 1990	17.0	14.0	3.0	210

sharp waves and an absence of motor unit potentials in all muscles tested in the lower extremities.

A sample of blood for fasting triglyceride level was drawn on a day he was to receive Intralipid (i.e. not on days following the night time infusion) (Table 1). TSH and whole blood vitamin B6 (pyridoxal phosphate) were normal. In November 1989 an abdominal CT scan showed an apparently normal liver. Because of recurrent aspiration pneumonia the patient was no longer given anything to eat.

In January 1990 an echocardiogram showed normal left ventricular size but inferoapical hypokinesis to akinesis with an estimated left ventricular ejection fraction (LVEF) of 50–55%. In January 1990 AST was 76 u/l, ALT 144 u/l, Alk phos 279 u/l and total bilirubin 18.8 mmol/l. In May 1990 the AST was 102 u/l, ALT 211 u/l, Alk phos 321 u/l and total bilirubin 17.1 mmol/l. However, the later tests were obtained following copper supplementation for low serum copper before it was determined that the patient had a defect in ceruloplasmin – copper binding and copper deposition in the liver resulted (unpublished observations). Plasma methionine and lysine levels were normal in August 1990. Two episodes of nonketotic hypoglycemia were noted 4 h after TPN had been tapered off. The blood sugar was as low as 44 mg/dl; the serum insulin level was normal.

A percutaneous liver biopsy (Fig. 1A) in August 1990 revealed severe steatosis and hepatocellular swelling. The biopsy was also notable for mild portal lymphocytic infiltration and fibrosis with extension into the lobules. Cholestasis was minimal. In a previous liver biopsy in August 1987 (Fig. 1B) no hepatic steatosis had been evident. The hepatic copper concentration was normal. The patient had never received a blood transfusion and had never used intravenous drugs. Serological tests for hepatitis A and B were negative. A chest CT showed mediastinal lipomatosis. Urine free carnitine was 7 nmol/g creatinine (normal 11–91). Oil red staining of a muscle biopsy showed marked fiber size variation with necrotic, regenerating and split fibers (Fig. 2). An increased amount of lipid was noted in several fibers, especially those which were hypertrophic. Total muscle carnitine, measured by radioisotopic assay (1) was 12.3 nmol/mg NCP (53% of normal control) and the free carnitine 10.0 nmol/mg NCP (55% of normal control). Muscle carnitine palmityl transferase measured spectrophometrically (2) was 77 nmol/min/100 mg NCP (controls 68–100). A sural nerve biopsy showed profound demyelination. Plasma thiobarbituric acid reactive substances (TBARS), an index of lipid peroxidation, were measured using a fluorometric assay (3) and were slightly supranormal (9.37 nmol/MDA m vs normal 7.83 ± .30). Corneal fatty acid deposition was noted by an Ophthalmology consultant. The patient died following complications of a cardiac arrest before intravenous carnitine could be administered. Permission for autopsy was refused by the family.

Discussion

We have described a patient who developed carnitine deficiency while receiving TPN. Although the patient was at risk for carnitine insufficiency at the time of valproic acid toxicity, his hepatic function, hepatic transaminases and plasma carnitine levels remained normal for nearly 2 years thereafter. The manifestations of carnitine deficiency appeared only after his oral intake had diminished, and became profound once oral intake ceased and TPN was begun. The carnitine deficiency occurred in spite of an adequate supply of methionine and lysine, the two precursors of carnitine. The patient's carnitine deficiency was indicated by low plasma and muscle total and free carnitine with progressive decrease in the plasma carnitine over a relatively short period of time in association with low urine carnitine and corneal fat deposition in the absence of a mitochondrial encephalopathy. The carnitine deficiency was manifested by a progressive inability to clear triglycerides from the serum, severe hepatic steatosis and mediastinal lipomatosis. Although carnitine deficiency may have contributed to the patient's muscle weakness, it seems more likely that denervation atrophy played a more significant role.

Low plasma carnitine levels have been described previously in long term TPN patients, (4) although the significance of this finding has been questioned (5, 6). In rats, a prolonged carnitine-free diet results in a 50% depletion not only in serum but also in muscle and hepatic carnitine (7). Endogenous carnitine synthesis therefore is insufficient to compensate for dietary deficiency in spite of the provision of adequate amounts of carnitine precursors. Berner et al (2) found that low carnitine levels were caused by a deficiency in the carnitine precursor lysine. Our patient had a normal plasma lysine concentration. Although our patient also appeared to be choline deficient, the plasma carnitine failed to increase with (8) normalization of the plasma free choline level from lecithin supplementation.

Some of the hepatic fat deposition in this case may be due in part to a disturbance in patient's copper metabolism. This included eventual hepatic copper 'overload' when he was unable to bind supplemental copper to correct a deficiency. However, such

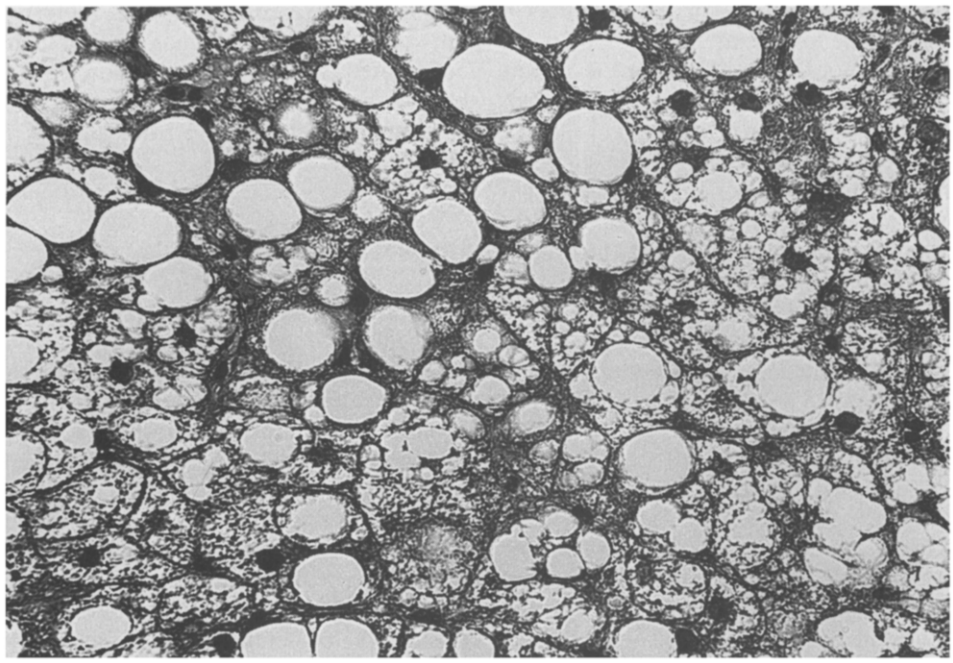

Fig. 1A. Liver biopsy from August 1990 showing severe steatosis and hepatocellular swelling (Mag. × 25).

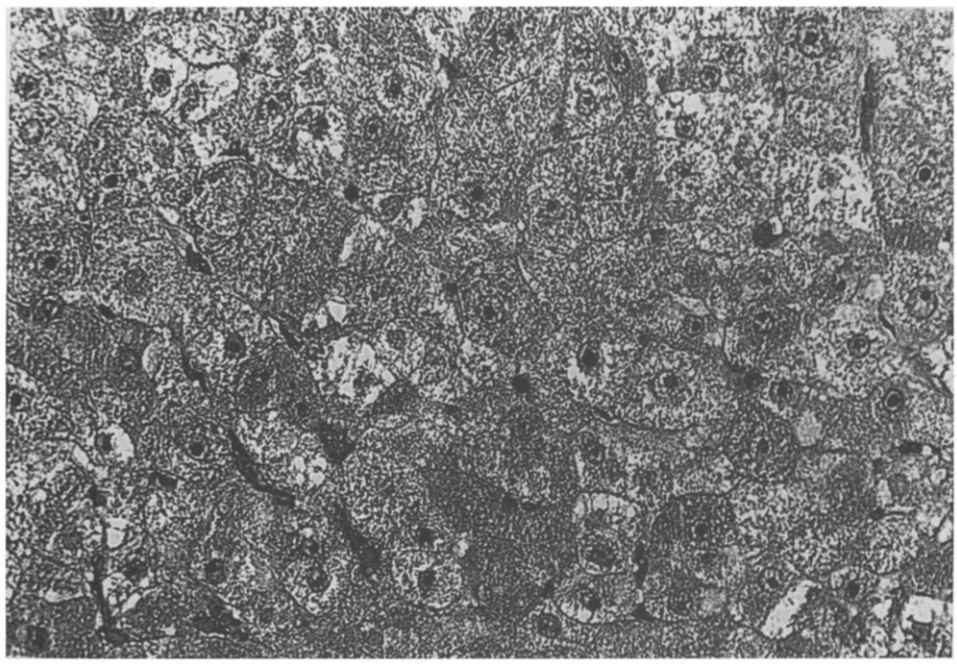

Fig. 1B. Liver biopsy from August 1987 showing no steatosis.

widespread signs of deficient lipid oxidation suggest that the low levels of carnitine are indicative of a primary deficiency. Although we suspect that copper has a role in lipid oxidation we cannot speculate on the specificity of that role.

Selenium and copper deficiency are both associated with cardiomyopathy (9, 10) but carnitine deficiency may also have contributed to the wall

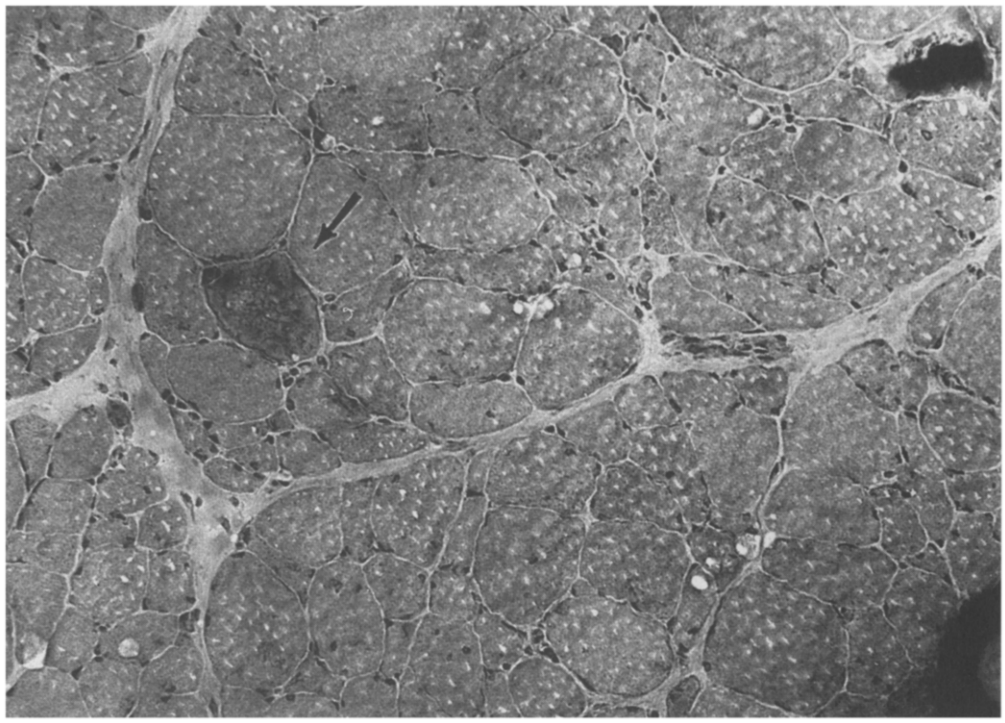

Fig. 2A. Cryostat cut transverse section of skeletal muscle (modified Gomori trichrome stain) shows marked fiber size variation and a rare fiber resembling a 'ragged-red' fiber (arrow) (Mag. × 245). The mitochondria show no abnormal patterns or cristae.

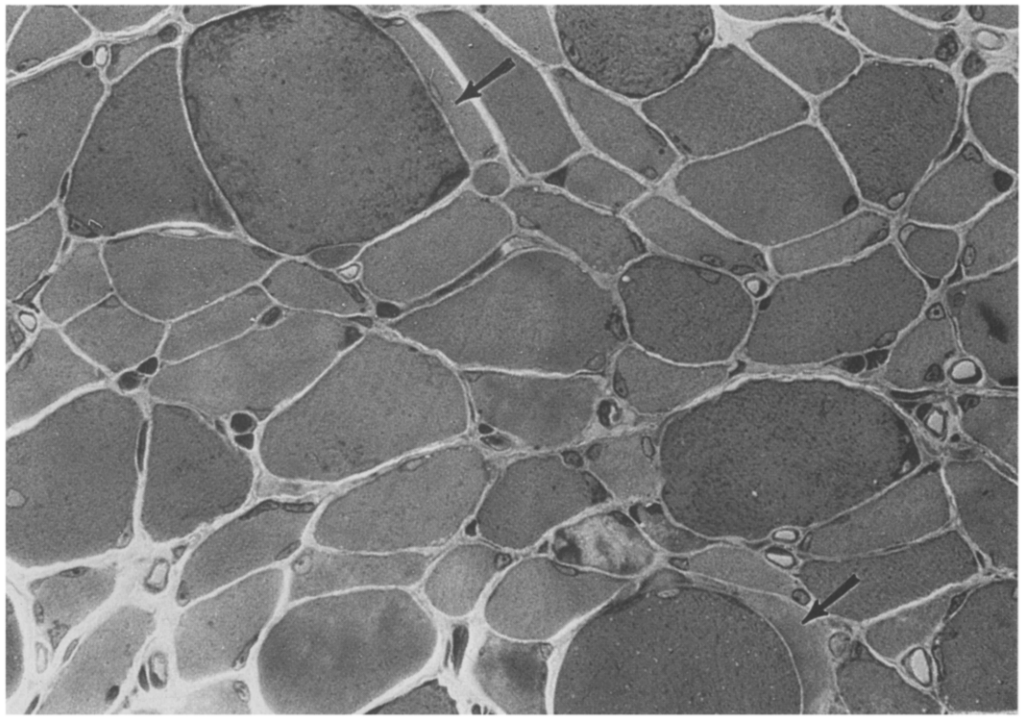

Fig. 2B. Plastic embedded section of skeletal muscle (toluidine blue stain) shows marked fiber size variation with scattered hypertrophic fibers (arrows), several of which contained increased lipid on appropriate histochemical stains (Mag. × 625).

motion abnormalities and borderline LVEF seen on echocardiogram in our patient (11, 12, 13).

Because carnitine facilitates transfer of long chain fatty acids into the mitochondria for oxidation, a deficiency of carnitine would lead to fat deposition in muscle and in liver as demonstrated in this case. Nerve dysfunction may also result from carnitine deficiency. Snyder et al (14) have suggested that the denervation changes seen on EMG in carnitine deficiency are a result of muscle membrane instability. In our patient the peripheral nerve demyelination was probably a result of copper deficiency which occurred before the low plasma carnitine levels were detected. However, a role for carnitine deficiency in promoting more rapid demyelination cannot be excluded. Although our patient manifested some signs found in Kearns-Sayre syndrome such as blindness and episodic vomiting, these were more likely related to the copper deficiency in our patient causing retinal nerve atrophy and neurogenic intestinal pseudo-obstruction, although carnitine deficiency may also have contributed via nerve demyelination. He lacked the other characteristic findings of Kearns-Sayr syndrome including dementia, lactic acidosis, short stature or the ECG findings of the syndrome.

In conclusion, we have described a patient with primary carnitine deficiency exacerbated by carnitine-free TPN. This case suggests that carnitine may be a conditionally essential nutrient in selected patients, especially those receiving long term TPN.

References

1. McGarry J D, Foster D W 1976 An improved and simplified radioisotopic assay for the determination of free and esterifeid carnitine. Journal of Lipid Research 17: 277–81
2. Bieber L L, Abraham T, Helmrath T 1972 A rapid spectrophotometric assay for carnitine palmityl transferase. Analytical Biochemistry 50: 509–18
3. Yag I K 1976 A simple fluorometric assay for lipoperoxides in blood plasma. Biochemical Medicine 15: 212–6
4. Berner Y N, Larchian W A, Lowry S F 1990 Low plasma carnitine in patients on prolonged total parenteral nutrition: association with low plasma lysine. Journal of Parenteral and Enteral Nutrition 14: 255–8
5. Bowyer B A, Fleming C R, Ilstrup D et al 1986 Plasma carnitine levels in patients receiving home parenteral nutrition. American Journal of Clinical Nutrition 43: 85–91
6. Bowyer B A, Miles J M, Haymond M W, Fleming C R 1988 L-carnitine therapy in home parenteral nutrition patients with abnormal liver tests and low plasma carnitine concentrations. Gastroenterology 94: 434–8
7. Heinonen O J, Takala J 1991 Experimental carnitine depletion in rats. Clinical Nutrition 10: 91–6
8. Buchman A L, Dubin M, Jenden D et al 1992 Lecithin increases plasma free choline and decreases hepatic steatosis in long-term total parenteral nutrition patients. Gastroenterology 102: 1363–70
9. Fleming C R, Lie J T, McCall J T et al 1982 Selenium deficiency and fatal cardiomyopathy in a patient on home parenteral nutrition. Gastroenterology 83: 689–93
10. Prohaska J R, Heller L J 1982 Mechanical properties of the copper deficient rat heart. Journal of Nutrition 112: 2140–50
11. McGarry J D, Foster D W 1980 Systemic carnitine deficiency. New England Journal of Medicine 303: 1413–5
12. Levitan M D, Murphy J T, Sherwood W G et al 1987 Adult onset systemic carnitine deficiency: favorable response to L-carnitine supplementation. Canadian Journal of Neurological Sciences 14: 50–4
13. Stanley C A, DeLeeuw S, Coates P M et al 1991 Chronic cardiomyopathy and weakness or acute coma in children with a defect in carnitine uptake. Annals of Neurology 30: 709–16
14. Synder T M, Little B W, Roman-Campos et al 1982 Successful treatment of familial idiopathic lipid storage myopathy with L-carnitine and modified lipid diet. Neurology 32: 1106–15
15. DiPaulo R V, Newberne P M 1992 Copper deficiency and meylination in the newborn rat (Abst). Federal Proceedings 31: 699
16. DiPaulo R V, Kanfer J N, Newberne P M 1974 Copper deficiency and the central nervous system. Myelination in the rat: morphological and biochemical studies. Journal of Neuropathology and Experimental Neurology 33: 221–36
17. Yajima K, Suzuki K 1979 Neuronal degeneration in the brain of the bridled mouse a light microscopic study. Journal of Neuropathology and Experimental Neurology 38: 35–46
18. DiMauro S, Bonilla E, Zeviani M et al 1985 Mitochondrial myopathies. Annals of Neurology 17: 521–38

Submission date: 30 December 1991; *Acceptance date*: 24 July 1992