Hyperammonemic Encephalopathy Caused by Carnitine Deficiency

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Carnitine is an essential co-factor in fatty acid metabolism. Carnitine deficiency can impair fatty acid oxidation, rarely leading to hyperammonemia and encephalopathy. We present the case of a 35-year-old woman who developed acute mental status changes, asterixis, and diffuse muscle weakness. Her ammonia level was elevated at 276 μg/dL. Traditional ammonia-reducing therapies were initiated, but proved ineffective. Pharmacologic, microbial, and autoimmune causes for the hyperammonemia were excluded. The patient was severely malnourished and her carnitine level was found to be extremely low. After carnitine supplementation, ammonia levels normalized and the patient's mental status returned to baseline. In the setting of refractory hyperammonemia, this case illustrates how careful investigation may reveal a treatable condition.

KEY WORDS: carnitine deficiency; hyperammonemia; encephalopathy; malnutrition.
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INTRODUCTION

Carnitine deficiency is an uncommon metabolic disorder that can lead to cardiac, hepatic, myopathic, and neurologic sequelae.[1–4] Primary carnitine deficiency caused by hereditary transport defects generally manifests in the neonatal period, afflicting roughly 1 in 40,000 live births.[1,5] Although primary carnitine deficiency may rarely manifest later in life, secondary deficiencies are most commonly encountered in adults. Because of a lack of awareness, the diagnosis of secondary hypocarnitinemia is frequently overlooked. We present a patient with multiple surgical complications that contributed to the development of severe malnutrition and carnitine deficiency, manifesting as hyperammonemic encephalopathy. This case report describes an uncommon cause of elevated serum ammonia levels and highlights the importance of carefully evaluating malnourished patients with hyperammonemia for carnitine deficiency.

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CASE REPORT

A 35-year-old woman was admitted to the hospital with acute onset confusion and lethargy. The patient had undergone a Roux-en-Y gastric bypass 6 years earlier for treatment of morbid obesity, and had a prior lateral pancreaticojejunostomy 4 years ago for management of complications stemming from hereditary pancreatitis. Four months before admission, she underwent a pancreatic head resection because of recurrent episodes of pancreatitis. The patient subsequently developed persistent nausea, vomiting, and abdominal pain necessitating several hospitalizations for rehydration. An upper G.I. series demonstrated a fixed narrowing at the gastrojejunal anastomosis, and subsequent EGD revealed a stricture (Fig. 1), which was dilated with an 18-mm balloon to modest clinical benefit. Her medications on presentation included promethazine, pantoprazole, oxycodone, pancreatic enzyme supplements, methylcellulose, and a multiple vitamin; however, recent compliance had been poor because of nausea and vomiting. There was no history of alcohol or illicit substance use. On examination, the patient was afebrile with normal vital signs. Her weight was 43.6 kg, corresponding to a body mass index (BMI) of 17.3, a decline of 26 kg over the prior 6 months. She was somnolent yet arousable, oriented only to person, and could follow simple commands. Ophthalmoplegia was not observed. Asterixis was present. Other pertinent physical findings included temporal wasting, hepatomegaly, diffuse muscle weakness, and bilateral lower extremity edema.

A complete blood count revealed a hemoglobin of 9.5 g/dL (normal 11.7–15.5), a platelet count of 204 thousand/μL (normal 140–400), and a white blood cell count of 5.4 thousand/μL (normal 4.5–11.0), with a normal differential (50.2% neutrophils, 44.3% lymphocytes, 5.0% monocytes, 0.2% eosinophils, 0.3% basophils). Serum glucose, electrolytes, including serum bicarbonate (28 mmol/L; normal 21–33), and lactic acid levels were normal. The patient's renal function (BUN 13 mg/dL, creatinine 0.5 mg/dL) and urine output were also normal. A spot urine for ketones and a urine acetest for ketone bodies were negative. An hepatic profile, ALT 26 U/L (normal 3–45), AST 36 U/L (normal 3–35), alkaline phosphatase 144 U/L (normal 44–160), bilirubin total 1.0 mg/dL (normal 0.2–1.0), bilirubin direct 0.3 mg/dL (normal 0.0–0.3), was unremarkable, as were the serum amylase 11 U/L (normal 28–100), and lipase 19 U/L (normal 10–71). Serum albumin was low (1.6 g/dL; normal 3.5–5.5) and INR was mildly elevated (1.3; normal 0.9–1.1). A CK level (42 U/L; normal 10–160) and echocardiogram were normal. Serum and urine toxicology screening was negative. The serum thiamine concentration was mildly decreased (74 nmol/L; normal 87–280). A fasting

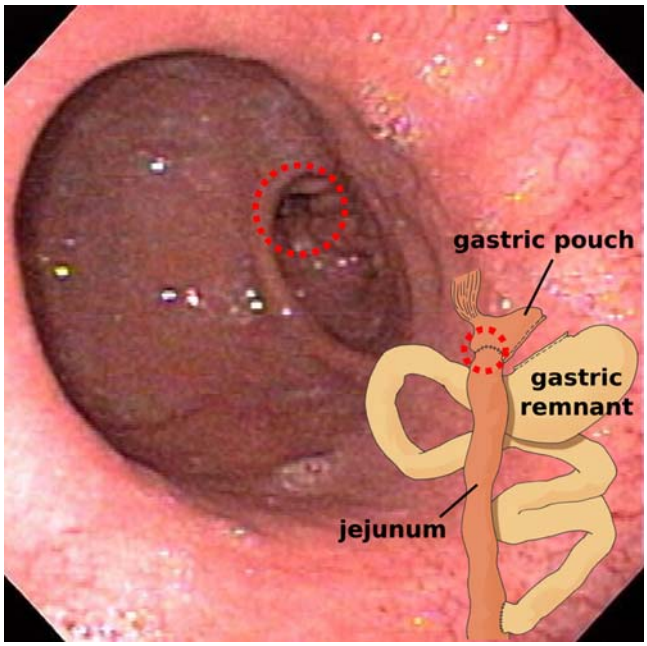

Figure 1. Stricture at the site of gastrojejunal anastomosis. An endoscopic view from the patient's esophagus into the gastric remnant is shown. Marked narrowing of the gastrojejunal anastomosis (dotted circle) was noted at the time of endoscopy. The *inset* depicts a rendition of the patient's surgical anatomy following gastric bypass

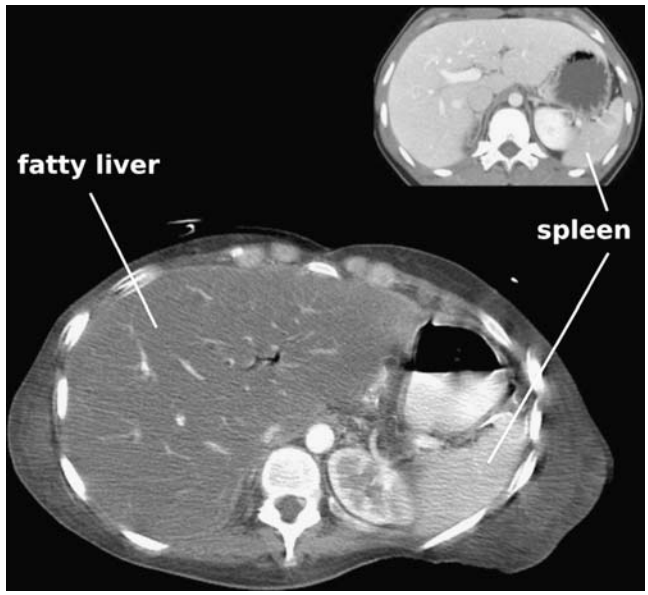

Figure 2. Contrast-enhanced abdominal CT. Shown is a cross-sectional image from the patient's abdominal CT. The decreased attenuation of the liver in comparison with the spleen is characteristic of diffuse fatty infiltration. The *inset* displays an example of normal hepatic attenuation

serum ammonia level was markedly elevated at 276 μg/dL (normal: 40–80). Computed tomography (CT) of the head was unremarkable.

The patient was administered thiamine, lactulose, and neomycin. Because of a deteriorating mental status and a continued rise in the fasting serum ammonia (which peaked at 582 μg/dL), the patient was intubated for airway protection and hemodialysis was initiated. Abdominal CT scan revealed fatty infiltration of the liver and findings consistent with her prior surgeries (Fig. 2). Hepatitis A, B, and C serologies were negative. Iron studies and a serum α_1-antitrypsin level were normal. Antinuclear, antimitochondrial, and antismooth muscle antibodies were negative. The serum ceruloplasmin was low at 7.2 mg/dL (normal 20–60); however, a 24-hour urinary copper level was normal (46 μg/dL; normal 3–50) and slit-lamp examination did not reveal Kayser–Fleischer rings. Plasma concentrations of ornithine (89 μM), citrulline (19 μM), and arginine (39 μM) were normal, and blood and urine cultures were negative.

The patient's muscle wasting, marked weight loss, and abnormal serologic analyses, including albumin, ceruloplasmin, prealbumin 8.2 mg/dL (normal 17–34), transferrin 55 mg/dL (normal 200–374), and retinol binding protein 1.1 mg/dL (normal 2.8–6.9), all suggested severe malnutrition. Total parenteral nutrition (TPN) utilizing a calorically dense formula containing an amino acid profile rich in branched-chain amino acids and low in aromatic and ammonogenic amino acid was initiated. The diagnosis of carnitine deficiency was entertained, and serum total carnitine 22 mM (normal 33.8–77.5), free carnitine 19 μmol/L (normal 25–55), and acylcarnitine ester 3.0 μmol/L (normal 3.8–19) levels were subsequently found to be low. Oral levocarnitine (330 mg three times daily) was initiated and ammonia levels progressively declined to normal (Fig. 3). The patient was extubated, hemodialysis was discontinued, and her mental status returned to baseline. She continues to do well 11 months after hospital discharge.

DISCUSSION

Hyperammonemia is a well-established cause of encephalopathy. Disorders commonly associated with increased serum

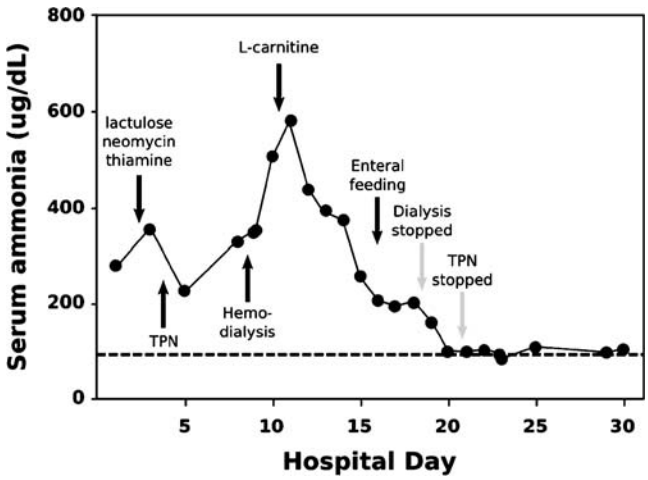

Figure 3. Time course of serum ammonia levels. This graph depicts the patient's serum ammonia concentration over the course of her hospitalization, with the upper limit of normal indicated by the dotted line. The onset (dark arrows) and termination (light arrows) of relevant clinical interventions are indicated. *TPN*: total parenteral nutrition

ammonia levels include hepatic failure, urea cycle defects, organic acidemias, and Reye's syndrome.[6] Infections with urea-splitting organisms, such as *Proteus mirabilis*, also have rarely been implicated.[7] Iatrogenic etiologies include transjugular intrahepatic portosystemic shunting (TIPS),[8,9] total parenteral nutrition,[10] and adverse drug effects (e.g., valproic acid).[11–14] In the present case, there was no evidence of underlying liver disease or acute hepatitis. Cultures were negative and the patient's medical regimen did not contain any drugs that have been implicated as a cause of hyperammonemia. A serum amino acid analysis effectively excluded the presence of a urea cycle defect. Although Reye's syndrome remains a possibility, it is rare in adults,[15] and there was no viral prodrome or history of aspirin ingestion to support this diagnosis. In the absence of other identifiable etiologies of hyperammonemia, and in light of the patient's severely malnourished state, a diagnosis of carnitine deficiency was entertained.

The first reports implicating a role for carnitine (β-hydroxy-γ-trimethylaminobutyrate) in the regulation of serum ammonia followed observations of a Reye-like syndrome in carnitine-deficient children.[16–19] Similar observations have been made in patients receiving valproic acid, although the concomitant finding of hypocarnitinemia and hyperammonemia were initially thought to be independent consequences of the medication.[14,20,21] Subsequent studies raised the possibility that valproic acid-induced encephalopathy is mediated by carnitine deficiency.[12,13] Evidence in support of an association between serum carnitine and ammonia is derived from findings in individuals with congenital defects in carnitine transport. Primary systemic carnitine deficiency is an autosomal recessive disorder caused by mutations in the OCTN2 (organic cation transporter) gene, resulting in decreased renal tubular reabsorption of carnitine.[1,22] Homozygotes typically manifest hyperammonemia, hypoglycemia, and both cardiac and skeletal myopathies.[23] A similar presentation has been described in individuals possessing defects in enzymes involved in mitochondrial carnitine transport (i.e., carnitine palmitoyl transferases, carnitine acylcarnitine translocase).[24,25] Notably, carnitine supplementation has been demonstrated to reverse hepatic encephalopathy in these patients.[26,27]

Carnitine is an essential co-factor in the metabolism of long-chain fatty acids (Fig. 4). It binds fatty acyl-CoA residues and promotes their translocation from the cytoplasm into the mitochondrial matrix, where β-oxidation and generation of energy occur.[28] Disruption of the carnitine transport system results in the cytosolic accumulation of unoxidized fatty acyl-CoA molecules. These metabolites are believed to inhibit the urea cycle,[29,30] thereby impairing an important mechanism of ammonia excretion. Defective transport of long-chain acyl-CoA into the mitochondria may additionally compromise biosynthesis of *N*-acetylglutamate, an allosteric activator involved in the urea cycle.[31] Diminished acetyl-CoA reserves further inhibit ureogenesis, ketogenesis, and gluconeogenesis.[30] Other clinical consequences of impaired fatty acid oxidation include hepatic steatosis, hepatomegaly, and myopathy. Although the hepatic enlargement and steatosis observed on CT in this case are consistent with carnitine deficiency, it is unknown whether these changes may have predated the presentation. Evidence of myopathy was limited to muscle weakness on physical examination, as serum CK levels and echocardiogram were normal. As short- and medium-chain fatty acids do not require

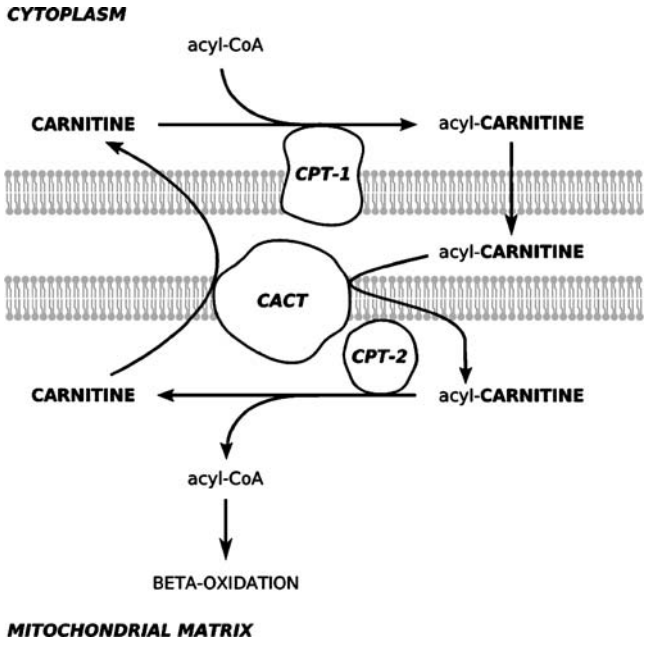

Figure 4. The mitochondrial carnitine transport system. This diagram details the process of carnitine transport from the cytosol to the mitochondrial matrix. Carnitine binds cytosolic fatty acyl-CoA to form acylcarnitine, which is transported into the mitochondrial matrix via the carnitine acylcarnitine translocase (CACT) protein. In the mitochondrial matrix, acyl-CoA undergoes subsequent beta-oxidation, while carnitine is recycled to the cytoplasm. *CPT-1*: carnitine palmitoyl transferase 1; *CPT-2*: carnitine palmitoyl transferase 2

the carnitine shuttle to enter mitochondria, therapy for primary defects in carnitine transport often includes a low-fat diet supplemented with medium-chain triglycerides.[3]

Our patient exhibited signs of severe malnutrition, likely because of chronic pancreatitis (which can lead to protein malabsorption and a generalized catabolic state), with an additional contribution from her prior gastric bypass, poor oral intake secondary to gastric outlet obstruction, and recent abdominal surgery. We postulate that hypocarnitinemia resulted from the combination of reduced oral intake and impaired carnitine biosynthesis. Normally, 75% of body carnitine is derived from dietary protein; however, in the absence of exogenous ingestion, over 90% of carnitine is synthesized by the liver from lysine and methionine.[32] Methionine levels are preferentially reduced in malnourished states because of its relatively low content in foods[33] and increased consumption by competing metabolic pathways.[34,35] In our patient, methionine levels were extremely low (6 mM; normal 37–136), likely resulting in impaired carnitine biosynthesis and in elevated levels of unmetabolized lysine. Although there are a number of potential exacerbating factors that may have contributed to the mental status changes observed in this patient, including thiamine deficiency, micronutrient insufficiencies (e.g., zinc), and occult liver dysfunction, the manifestation of refractory hyperammonemia in the setting of low-serum carnitine, free carnitine, and acylcarnitine ester levels, in conjunction with the temporal response to L-carnitine administration, support our contention that carnitine deficiency was the primary abnormality. Correction of the underlying carnitine deficiency

restored hepatic excretion of ammonia and facilitated resolution of the encephalopathy.

Carnitine deficiency is infrequently encountered in malnourished patients. Whether this is because an underlying predilection (such as a polymorphism or heterozygosity for one of the genes involved in carnitine transport) is a necessary precondition,[36] or because the problem is underrecognized, remains conjectural. In the absence of an obvious cause of hyperammonemia, it is prudent to measure serum carnitine levels, particularly in the setting of malnutrition. The present case illustrates how the careful workup of hyperammonemia may reveal a treatable condition, leading to an improved clinical outcome.

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